Table of Contents

Planning Committees

Abstracts

<table>
<thead>
<tr>
<th>Page Numbers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 4</td>
<td>Plenary Session</td>
</tr>
<tr>
<td>LB1</td>
<td>Late-Breaking (LB) Abstract</td>
</tr>
<tr>
<td>5 – 12</td>
<td>Oral Abstract Session</td>
</tr>
<tr>
<td>100 – 358</td>
<td>Poster Presentations</td>
</tr>
<tr>
<td>100 – 202</td>
<td>Definitive Management of Head and Neck Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>203 – 217</td>
<td>Epidemiology and Prevention</td>
</tr>
<tr>
<td>218 – 247</td>
<td>Imaging</td>
</tr>
<tr>
<td>248 – 250</td>
<td>Immunology and Immunotherapy</td>
</tr>
<tr>
<td>251 – 265</td>
<td>Management of Recurrent Head and Neck Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>266 – 293</td>
<td>Molecular Biology and Therapeutics</td>
</tr>
<tr>
<td>294 – 321</td>
<td>Nonsquamous Cell Malignancies of the Head and Neck: Thyroid, Skin, Salivary Gland, and Sinus Cancers</td>
</tr>
<tr>
<td>322 – 358</td>
<td>Survivorship</td>
</tr>
</tbody>
</table>

Index of Presenting Authors

Pages 110-111

All abstracts accepted for presentation at the 2016 Multidisciplinary Head and Neck Cancer Symposium are embargoed until the opening ceremony of the symposium, Thursday, February 18, 2016, at 8:00 a.m. Mountain Time.

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CONTENT ADVISOR

Oral Oncologist
Betsy K. Davis, DMD, MS, Medical University of South Carolina
1 Molecular Profile of Human Papillomavirus–Positive Oropharyngeal Squamous Cell Carcinoma Stratified by Smoking Status

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Purpose/Objective(s): HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) among smokers represents a distinct clinical entity with intermediate prognosis compared to HPV-positive never smokers and HPV-negative cases. Despite recent advances in head and neck cancer genomics, the number of HPV-positive cases evaluated to date has been modest and the interplay between smoking and HPV has not been fully evaluated. The purpose of this study is to characterize the mutational profile of HPV-positive OPSCC by smoking status. We hypothesize a higher frequency of TP53 and CDKN2A mutations in HPV-positive OPSCC among heavy smokers.

Materials/Methods: Targeted next-generation sequencing of >800 genes including all commonly mutated genes in cancer was performed in 66 HPV-positive OPSCC cases stratified by smoking status (<10 pack years vs >10 pack years). Cases were identified from an NC population-based epidemiologic study conducted from 2001 to 2006 with follow-up for vital status. Copy number variation was also examined. Mutation frequency was compared to previously reported frequencies in the Catalogue of Somatic Mutations in Cancer database.

Results: Sixty-six HPV-positive OPSCC cases were examined, including 40 HPV+ OPSCC >10 pack-year and 26 HPV+ <10 pack-year smokers. Disease-free and overall survival were significantly better in the <10 pack-year history group. The most commonly mutated genes in both groups were HLA-A, PIK3CA, and MLL-3. Several differences in mutation frequency and copy number variation were noted between <10 and >10 pack-year smokers: TP53, CDKN2A, KRAS, and NOTCH1 mutations were found almost exclusively among >10 pack-year smokers and were associated with worse outcome, while HLA-A mutations were more common in the <10 pack-year cohort (73.1% vs 47.5%, P = .047).

Conclusion: This study provides a molecular basis for the intermediate prognosis in patients with dual HPV/tobacco exposure. In addition to expected tobacco-associated mutations in the >10 pack-year group, we demonstrate a novel immune signature in the <10 pack-year group. If validated, these findings could further stratify risk in HPV-positive OPSCC and provide novel mutational parameters for treatment de-intensification.


2 Systemic Immunologic Effects of Definitive Radiation in Head and Neck Cancer

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Purpose/Objective(s): Radiation therapy (RT) may potentiate antitumor immunity; however, immune effects of RT are complex and can also be inhibitory. Therefore, studies evaluating RT’s effects on various components of the immune system are needed. Of interest are immune effects of fractionated RT used in the definitive setting for squamous cell carcinomas of the head and neck (SCCHN), given the activity of anti-PD-1 immune checkpoint blockade in this disease. Here, we assess temporal changes in circulating CD4+ and CD8+ T-effector (CD69+), regulatory T (CD25+ CD127lo), myeloid derived suppressor (MDSC, CD14+ HLA-DR-), and “exhausted” immune cells (CD4+CD8+ LAG3+, TIM3+, PD-1+) during definitive RT in SCCHN patients. We also evaluate levels of circulating cytokines, soluble PD-L1 (sPD-L1), and potential antitumor antibodies.

Materials/Methods: We prospectively obtained blood from 16 consecutive SCCHN patients undergoing curative-intent RT. Samples were obtained at the beginning (week 1) and end (week 6-7) of therapy. Flow cytometry was used to quantify T-cell subsets. Cytokine and sPD-L1 levels were assessed using a multiplex platform. We performed proteomic analysis of antibody responses using a profiling application according to manufacturer’s protocols. We compared changes in immunologic factors using Wilcoxon signed rank tests.

Results: Patients received a median 70 Gy for disease in the oropharynx (n = 12, 75%), nasopharynx (n = 2, 12%), larynx (n = 1, 6%), or oral cavity (n = 1, 6%). The majority had stage IV disease metastatic to regional lymph nodes (n = 11, 69%), and received concurrent platinum-based chemotherapy (n = 13, 81%). During RT, circulating CD8+ T-effector cells increased (P < .01), as did CD4+ PD1+ (P < .02), CD8+ LAG3+ (P < .02), and regulatory T cells (P = .04). Increases in sPD-L1 levels mirrored increases in CD8+ T cells over the course of therapy (P = .047). RT also decreased levels of CXCL10 (P = .004), and increased CXCL16 (P = .006). An increase in the diversity of antigens targeted by antibody responses following treatment was seen in all 3 patients in whom this was evaluated.

Conclusion: Preclinical models suggest RT may lead to antitumor immune responses that may be blunted by systemic immune regulation. We find evidence supporting these counteracting effects in SCCHN patients receiving fractionated RT with or without chemotherapy, where systemic increases in T-effector cells and potential antitumor antibodies were found in addition to increases in sPD-L1 and exhausted and regulatory T cells expressing immune checkpoint receptors. Although the extent to which these systemic changes reflect changes in the tumor microenvironment is unknown, our findings support complex immunologic effects of fractionated chemoradiation therapy and mechanisms for potential synergy between chemotherapy, RT, and immunotherapy in SCCHN.

Response-Adapted Volume De-escalation (RAVD) in Locally Advanced Head and Neck Cancer: Efficacy and Human Papillomavirus–Positive Subgroup Analysis

J.M. Melotek, V.M. Villafor, T.G. Karrison, R.J. Brisson, E.A. Blair, L. Portugal, R.M. Stenson, J. De Souza, E. Cohen, A. Langerman, M.T. Spiotto, T.Y. Seiwert, E.E. Vokes, and D.J. Haraf; 1University of Chicago, Chicago, IL; 2Rush University, Chicago, IL; 3University of California San Diego, La Jolla, CA

Purpose/Objective(s): Efforts to reduce the late toxicity associated with chemoradiation (CRT) for locally advanced head and neck squamous cell cancer (LA-HNSCC) have focused on radiation therapy (RT) dose de-escalation in select populations. In this phase 1/2 trial investigating the addition of everolimus to induction chemotherapy (IC), we incorporated a novel response-adapted volume de-escalation (RAVD) approach using IC response to guide the extent of RT volume reduction in a nonselected population of patients (pts) with LA-HNSCC.

Materials/Methods: Pts with measurable LA-HNSCC received 2 cycles of IC (cisplatin 75 mg/m2, paclitaxel 175 mg/m2 day 1, and weekly cetuximab, with or without everolimus). Pts with “good” response (GR), defined as ≥50% reduction in the sum of gross tumor diameters; received TFHX2 (paclitaxel, fluorouracil, hydroxyurea, and 1.5 Gy twice daily RT every other week) to 75 Gy with the planning target volume (PTV1) encompassing exclusively gross disease. Pts with <50% response (NR) were treated with volumes encompassing PTV1 and the next nodal station at risk (PTV2) to 45 Gy, followed by a sequential boost to PTV1 to 75 Gy. Survival rates were estimated by the Kaplan-Meier method and compared between groups using the log-rank test.

Results: Ninety-four pts were enrolled: median age 57 (range 27-76) years, 84% male, 63% HPV+ oropharynx (OPX), 54% tobacco use, 56% >T3, 88% ≥N2b. Everolimus was discontinued on interim analysis after 43 pts due to futility. IC response was evaluable in 89 pts. Thirty-seven (41.6%) had GR, and 52 (58.4%) had NR. Thirty out of thirty-seven pts with GR had HPV+ OPX SCC. With mean follow-up of 2 years, there were no significant differences in progression-free survival (PFS; P=0.86) or overall survival (OS; P=0.94) between GR and NR. Two-year PFS and OS were 86.0% and 83.5% for GR and 68.7% and 85.4% for NR, respectively. Two-year PFS and OS were 93.1% and 92.1% for HPV+ OPX GR and 74.0% and 95.2% for HPV+ OPX NR, respectively. There was no statistically significant difference in PFS between the HPV+ OPX GR and NR groups (P=0.10). There were too few deaths to provide reliable comparisons for OS between the HPV+ OPX GR and NR groups.

Conclusion: RAVD is a novel treatment approach that uses IC response to determine the extent of RT volume reduction. In this study, elimination of elective nodal coverage did not appear to compromise outcomes in the entire cohort nor specifically in the HPV+ OPX subgroup. Further investigation is warranted.

Late-Breaking (LB) Abstract

Determinants of Cost in the Treatment of T1-T3 Oropharynx Cancer
A.D. Pinheiro1 and R.W. Kramer2; 1Mercy Clinic - Head and Neck Surgery Springfield, MO, 2Mercy Clinic - Springfield, Springfield, MO

Purpose/Objective(s): Current treatment guidelines for T1-T3 oropharynx squamous cell carcinoma (OPC) offer surgical (Surg) or nonsurgical (NSurg) treatments as equivalent alternatives. In order to make value decisions, we must understand cost of care. Our goal was to identify the primary determinants of cost and we hypothesized that surgical treatment did not increase cost of care in OPC. To this end, we examined the relationship of cost to tumor stage, AJCC cancer stage, Charlson age-comorbidity index (CACI), and treatment strategy (Surg vs NSurg).

Materials/Methods: Retrospective review of patient records in EPIC identified 299 patients with a diagnosis of oropharynx cancer between July 12, 2011, and May 15, 2015. We excluded patients with tumors that extended to the oral cavity, those with secondary primaries or distant metastases, and those whose histology was other than squamous cell carcinoma (SCC). We identified 71 patients staged T1-T3 who received all their treatment (S, RT, and/or CRT) at our facility. Cost was defined as revenue collected by the hospital and clinic for a 6-month episode of care that started with a biopsy positive for OPC.

Results: A total of 72 patients were available for evaluation. Forty-two were treated with Surg and 29 were treated with NSurg. Among the Surg patients, 22 received adjuvant treatment. Of those tested for p16, 92.5% (62/67) were positive and 4 had unknown p16 status. All 5 p16 negative patients were treated with Surg. Among the 4 patients with unknown p16 status, 1 was treated with Surg and 3 with NSurg. Median age was 61 and 62 for the Surg and NSurg groups (t = -0.16, P = .8747). There were no differences between the Surg and NSurg groups in distribution of T stage (χ² = 4.83, P = .0983) or AJCC Stage (χ² = 6.06, P = .1946). Comorbidity was higher for the Surg group (CACI = 8.07) relative to the NSurg group (CACI = 7.34) but this did not reach significance (t = -1.36, P = .1792). Cost was lowest for those treated with surgical therapy only relative to the NSurg group ($38,462 vs $83,222; t = 2.26, P = .0298). Surgery followed by adjuvant CRT had similar cost to primary CRT (respectively, $84,598 and $83,222; t = 0.372).

Conclusion: Surgically treated patients with higher CACI, similar age, and greater proportion of p16-negative tumors had more favorable cost relative to those treated with primary CRT. Surgical patients who require adjuvant CRT had similar cost to those treated with primary CRT. The highest opportunity for cost savings is in those patients who do not require adjuvant CRT. Starting with a surgical approach does not increase cost even for those who require adjuvant treatment. Future research should determine which treatment strategy yields the best value.

Author Disclosure: A.D. Pinheiro: None. R.W. Kramer: None.

Oral Abstract Session

5

Phase 2 Trial of Deintensified Chemoradiation Therapy for Low-Risk Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma
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Purpose/Objective(s): We performed a prospective multi-institutional phase 2 study of a substantial decrease in concurrent chemoradiation therapy (CRT) intensity as primary treatment for favorable-risk, human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: The major inclusion criteria were (1) T0-T3, N0-N2c, M0; (2) HPV or p16 positive; and (3) minimal/remote smoking history. Treatment was limited to 60 Gy intensity modulated radiation therapy (IMRT) with concurrent weekly intravenous cisplatinum (30 mg/m²). The primary study endpoint was pathologic complete response rate (pCR) based on required biopsy of the primary site and dissection of pretreatment positive lymph node regions, regardless of radiographic response. Power computations were performed for the null hypothesis that the pCR rate is 87% and n = 40, resulting in a type I error of 14.2%. Secondary endpoint measures included physician-reported toxicity (Common Terminology Criteria for Adverse Events [CTCAE]), patient-reported symptoms (Patient-Reported Outcomes [PRO]-CTCAE), quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaires for cancer [EORTC QLQ-C30] and head and neck patients [H&N35]), and penetration aspiration scale (PAS) scores for modified barium swallow studies.

Results: The study population is 43 patients. The pCR rate was 86% (37/43). All 6 non-pCR cases were limited to microscopic foci of residual cancer: 1 primary site and 5 nodal. All patients are alive with no evidence of disease (median follow-up 21.3 months, range 4-41 months). Thirty-eight patients had a follow-up of at least 1 year. The incidence of acute CTCAE grade 3/4 toxicity and PRO-CTCAE severe/very severe symptoms were mucositis 34%/45%, pain 5%/48%, nausea 18%/52%, vomiting 5%/34%, dysphagia 39%/55%, and xerostomia 2%/75%. Grade 3/4 hemato logic toxicities were 11%. Mean pre- and 6-months-post-CRT EORTC QLQ scores were as follows: Global 80/71 (lower worse), Pain (mouth, jaw, throat) 19/21 (higher worse), Swallowing 17/26, Dry Mouth 16/68, and Sticky Saliva 6/ 49. Six-months-post CRT mean PRO-CTCAE severity scores for swallowing and dry mouth were mild and moderate, respectively. Thirty-nine percent of patients required a feeding tube (non-permanently) for a median of 15 weeks (range, 5-22 weeks). There were no significant differences in PAS scores for thin, pureed, and solid foods before and after CRT.

Conclusion: In conclusion, pCR rate with decreased intensity of therapy with 60 Gy of IMRT and weekly low-dose cisplatinum is very high in favorable-risk OPSCC with evidence of decreased toxicity compared to standard therapies. (ClinicalTrials.gov, NCT01530997)


6

Detection of Recurrence in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma
J.M. Frakes, A.O. Naghavi, T. Strom, A.R. Giuliano, L.B. Harrison, A. Totti, and J.J. Caudell; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Purpose/Objective(s): Human papillomavirus (HPV)-associated squamous cell carcinomas of the oropharynx are on the rise with a much higher likelihood of cure. We reviewed our institutional experience to determine time to recurrence. We view as mode of detection of recurrence to further help guide optimal follow-up.

Materials/Methods: After institutional review board approval, we queried an institutional database for patients with HPV- or p16-positive non-metastatic oropharyngeal cancers treated with definitive radiation therapy (RT) between 2006 and 2014, and 246 cases were identified. Charts were reviewed and patient, tumor, and treatment factors as well as mode of
detection of recurrence were abstracted. Patients either received definitive RT alone (n = 38, 15.4%) or concurrent systemic therapy and RT (n = 209, 85.6%). Outcomes, including local control (LC), regional control (RC), locoregional control (LRC), freedom from distant metastases (FFDM), and overall survival (OS) were calculated according to Kaplan-Meier method from the end of RT. Patients received a 3-month posttreatment position emission tomographic/computed tomographic (PET/CT) scan and were seen every 3 months in the first year, every 4 months in Year 2, and every 6 months in Years 3 to 5.

Results: Median follow-up of all patients was 36 months. LC was achieved in 239 of 245 patients, with a 3-year LC rate of 97.8%. Of the 6 local failures, all were detected by direct visualization (n = 2) or flexible laryngoscopy (n = 4). Three-year RC was 95.3%, where patients with ≥5 nodes or level 4 lymph nodes present were more likely to suffer regional failure (P < 0.05). Of the 9 regional recurrences, 90% (n = 8) were found by symptoms or 3-month posttreatment PET/CT.

Three-year LRC was 94%. Of the 13 patients that suffered a locoregional failure, 92% (n = 12) presented either symptoms or persistent disease on 3-month posttreatment PET/CT. Three-year FFDM rate was 91.4%, with increased risk of metastases occurring in patients with a lymph node greater than 6 cm, bilateral lymphaeno-nathy, 5 or more nodes, or if a lymph node was present in level 4 (P < 0.05). Of the 21 patients who suffered distant recurrence, 71% (n = 15) were found due to symptoms or 3-month posttreatment imaging. Three-year OS was 91% for all patients. Late grade ≥3 toxicity occurred in 21 patients (9%), with 19 being grade 3 toxicities and 2 grade 4 toxicities. The majority of toxicity and/or failure occurred within the first 6 months (64%), with only 4 events beyond 2 years.

Conclusion: HPV-associated oropharyngeal cancer treated with definitive RT has excellent outcomes. Of the few patients that suffered a local failure, all were identified with physical exam. Symptoms and/or 3-month posttreatment PET/CT identified 92% of locoregional failures and 71% of distant failures. Given these findings, if posttreatment of PET/CT is negative, no further imaging is warranted. Follow-up should include history and physical exam with direct visualization.


8

Final Results of a Randomized Phase 2 Trial Investigating the Addition of Cetuximab to Induction Chemotherapy and Accelerated or Hyperfractionated Chemoradiation Therapy for Locoregionally Advanced Head and Neck Cancer: HPV-negative Subset Analysis

J.M. Melotek, D.J. Haraf, E.A. Blair, M.E. Witt, R.J. Brisson, A. Dekker, M. Lingen, M. Kocherginsky, V.M. Villafior, E. Cohen, E.E. Vokes1; University of Pittsburgh Medical Center, Pittsburgh, PA; 1University of Pittsburgh; University of Pittsburgh Cancer Institute, Pittsburgh, PA; 1University of Pittsburgh; University of Pittsburgh Cancer Institute, Pittsburgh, PA; 1VentiRx Pharmaceuticals, Seattle, WA

Purpose/Objective(s): Inflamed tumors are known to generate a better response to immunotherapy. HNC has many immunosuppressive features, including impaired natural killer cell (NK) activity. The monoclonal antibody cetuximab (CTX) is effective in a subset of HNC patients, with clinical activity linked to NK-mediated antibody-dependent cellular cytotoxicity (ADCC). Recent data show that CTX increases the frequency of intratumoral CTLA-4/FoxP3+ regulatory T cells (Treg), which suppress ADCC and are associated with poor clinical outcome. In ex vivo experiments, this effect could be attenuated by targeting CTLA-4 on Tregs. It is possible that the clinical efficacy of CTX may be improved by enhancing tumor inflammation, activating the immune system, and/or inhibiting the Treg suppressive effects. Motolimod (VTX-2337), a novel Toll-like receptor 8 (TLR8) agonist, Preclinical data show enhanced CTX and NK-mediated lysis of HNC cells and dendritic cross-priming of EGFR-specific CD8+ T cells. CTX and motolimod in HNC patients was tolerable and active in a phase 1b study, with enhanced NK cell activity. The central hypothesis in this study is that NK and monocyte/mDC activation by CTX is enhanced by concomitant administration of motolimod, thereby amplifying the innate and adaptive immune response in the circulation and in the tumor microenvironment (TM).

Materials/Methods: In this prospective phase 1b clinical trial (NCT02124850) of preoperative treatment with CTX and motolimod, the primary objective is to evaluate how neoadjuvant CTX plus
motilotimid modulates innate and adaptive immune biomarkers. An exploratory objective of the study is to assess whether this modulation of biomarkers can predict antitumor response. Subjects (n = 12) with stage II–IV HNC received weekly doses of CTX and motilotimid followed by definitive surgical resection. Biomarker modulation in tumor and blood are correlated with clinical response by CT or MRI. Tumor apoptosis/proliferation is assessed by biopsy pre- and posttreatment.

**Results:** Phenotypic markers of suppression in Treg were reduced when motilotimid was combined with CTX, including lower levels of CTLA-4 (P = .01), CD73 (P = .04), and membrane-bound TGF-β (P = .05). These mediators were induced in nonresponders in our single-agent cetuximab therapy study (P = .005). Myeloid antigen–presenting cells achieved strong maturation and expression of stimulatory markers in the peripheral blood.

**Conclusion:** CTX plus motilotimid induces inflammatory changes in the TM and peripheral blood. Treg-suppressive mediators are reduced with CTX/motilotimid, overcoming a negative prognostic biomarker (Treg suppression) of CTX therapy alone. A pending amendment will assess the impact of adding checkpoint inhibition to the CTX/motilotimid combination.

**Author Disclosure:** D. Adkins: None. J. Ley: None. T. Wildes: None. K. Trinkaus: None. M. Siegel: None. L. Michel: None.
Abstract 10; Table 1  Efficacy outcomes according to biomarkers (all comparisons are afatinib vs MTX)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS, mos</th>
<th>PFS HR (95% CI)</th>
<th>Median OS, mos</th>
<th>OS HR (95% CI)</th>
<th>ORR, %</th>
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<tbody>
<tr>
<td>p16-neg* (H-score &lt;210), n = 199</td>
<td>2.7 vs 1.62.0 vs 2.3</td>
<td>0.70 (0.50, 0.97)</td>
<td>6.7 vs 6.495 vs 13.0</td>
<td>1.22 (0.88, 1.68)</td>
<td>14.1 vs 16.0 vs 8.3</td>
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<tr>
<td>p16-pos* (H-score ≥210), n = 35</td>
<td>2.7 vs 1.417 vs 2.4</td>
<td>0.81 (0.39, 1.69)</td>
<td>6.8 vs 4.756 vs 6.8</td>
<td>0.81 (0.50, 1.32)</td>
<td>11.8 vs 057 vs 0</td>
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<tr>
<td>EGFR-amplified, n = 101EGFR not amplified, n = 107</td>
<td>1.03 (0.67, 1.61)</td>
<td>0.35 (0.23, 0.53)</td>
<td>9.8 vs 6.460 vs 7.3</td>
<td>0.95 (0.57, 1.57)</td>
<td>10.5 vs 097 vs 0</td>
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<tr>
<td>HER3-low (H-score ≤50), n = 91</td>
<td>2.9 vs 2.116 vs 2.4</td>
<td>0.47 (0.27, 0.80)</td>
<td>1.41 (0.83, 2.38)</td>
<td>1.26 (0.78, 2.04)</td>
<td>0.56 (0.29,1.08)</td>
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<tr>
<td>HER3-high (H-score &gt;50), n = 88</td>
<td>2.9 vs 1.427 vs 2.5</td>
<td>0.44 (0.21, 0.95)</td>
<td>8.9 vs 4.471 vs 8.5</td>
<td>1.07 (0.73, 1.57)</td>
<td>0.56 (0.29,1.08)</td>
</tr>
<tr>
<td>PTEN-high (H-score &gt;150), n = 49</td>
<td>0.86 (0.57, 1.28)</td>
<td>0.81 (0.47, 1.38)</td>
<td>9.8 vs 6.460 vs 7.3</td>
<td>0.95 (0.57, 1.57)</td>
<td>10.5 vs 097 vs 0</td>
</tr>
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</table>

Abbreviations: HR = hazard ratio; H-score = histology score; OS = overall survival; PFS = progression-free survival; pos = positive; neg = negative.

*p16 staining was analyzed in tumors from all subsites. p16 status was unknown for 249 patients.†>50% of cells with ≥4 copies, or ≥1 cell with ≥8 copies.

No objective responses were observed in the 35 pts with p16-positive disease.

Conclusion: In this analysis, more pronounced effects on survival were observed with afatinib versus MTX in R/M HNSCC pts with p16-negative, EGFR-amplified, HER3-low, and PTEN-high disease. Future prospective studies are warranted to provide a more robust readout of clinical outcomes with afatinib in these pts.

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11 Phase 1b/2a Trial of Superoxide (SO) Dismutase (SOD) Mimetic GC4419 to Reduce Chemoradiation Therapy-Induced Oral Mucositis (OM) in Patients With Oral Cavity or Oropharyngeal Carcinoma (OCC)

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Purpose/Objective(s): Seventy percent of patients (pts) with OCC develop severe OM (SOM) after a median 40-Gy radiation therapy (RT) treatment plus concurrent cisplatin (CDDP). There are no approved interventions to reduce the incidence or severity of OM. RT-induced SO is a key initiator of OM. GC4419’s (MW = 483) specific mimicry of SOD’s dismutation of SO to H2O2 mitigated SOM in a translational hamster model. We hypothesized that GC4419 immediately prior to intensity modulated RT (IMRT) fractions would reduce incidence, severity, duration, and delay onset of SOM.

Materials/Methods: Serial 3 to 6 pt cohorts with locally advanced, non-metastatic OCC were planned for definitive or post-op IMRT to approximately 70 Gy total (>50 Gy to ≥2 oral sites), 1.8 to 2.2 Gy/fx M-F plus CDDP; plus escalating doses of GC4419, over 60- min IV, M through for 3 to 7 weeks, ending <60 min before IMRT. WHO grade OM was assessed twice weekly. GC4419 was measured in plasma. OM-related circulating cytokines (Cy) and changes in gene expression were assayed prior to and during treatment.

Results: Forty-six pts received GC4419; 43 were evaluable for OM at dose levels/d: 15 to 112 mg x 3 wks (n = 20); 112 mg x 4 to 5+ wks (n = 9); 30
mg x 7 wks (n=4); 90 mg x 6 wks (n=4); 90 mg x 7 wks (n=6). Efficacy; SOM duration, incidence through 6 wks/60 Gy, severity, and onset appeared markedly improved from historical controls (Table 1); overall SOM incidence (50% vs 70%) was also reduced. GC4419 efficacy was related to treatment duration (Table 1), but not absolute daily dose. Safety: A true maximum tolerated dose was not reached. Gr 3 gastroenteritis and Gr 3 nausea/vomiting (1 each, 112 mg/d x 3 or 6 wks) were considered dose-limiting. Dose-related Gr 1-2 peri-influenzal facial tingling was attributable to GC4419. Other AEs were consistent with known effects of IMRT/CDDP. PK: Dose-related Cmax and AUC; plasma t1/2 approximately 2 hours. Biomarkers; Cy levels were associated with GC4419 dose and WHO severity, consistent with known OM pathogenesis. Conclusion: When GC4419 was given throughout IMRT, SOM was less frequent, briefer, delayed, and less severe than expected. GC4419-related toxicity was mild-to-moderate and acceptable in combination with IMRT/CDDP. Doses of 30 and 90 mg/d were chosen for a future randomized, placebo-controlled trial.


12 The Impact of Health Insurance Status on the Presentation, Local Management, and Outcomes of Patients With Head and Neck Cancer in the United States T.M. Churilla, B. Egleston,1 Y. Dong,2 M. Lango,1 and T.J. Galloway1; 1Fox Chase Cancer Center, Philadelphia, Pa, 2Fox Chase Cancer Center, Cheltenham, Pa, United States Purpose/Objective(s): We sought to evaluate the association between health insurance status and stage, treatment, and outcomes among patients with head and neck (H&N) cancer. We hypothesized that patients with Medicaid or lack of health insurance more frequently present with advanced disease, undergo less surgery or radiation, and have increased cancer-specific mortality compared to patients with non-Medicaid insurance. Materials/Methods: We queried the National Cancer Institute Surveillance, Epidemiology, and End Results database for primary squamous cell carcinoma of the oral cavity, pharynx, and larynx from 2007 to 2012. We characterized clinical and demographic variables according to insurance status (insured vs Medicaid vs uninsured). We tested for associations between patient insurance status and American Joint Committee on Cancer (AJCC) stage, receipt of cancer-directed surgical procedure (≥ wide local excision), and receipt of external beam radiation therapy. We calculated odds ratios (ORs) and computed Pearson X² test and used multiple logistic regression analysis to adjust for clinical and demographic covariates. We evaluated cancer-specific mortality according to insurance status by the Kaplan-Meier method and adjusted for demographic and clinical information using Cox regression.

Results: A total of 53,848 patients were analyzed: 80.1% insured, 15.0% with Medicaid, and 4.9% uninsured. AJCC stage III or IV disease was more common among patients with Medicaid (72.9%) and uninsured patients (75.1%) compared to insured patients (60.1%), P<.001. After adjustment for site, stage, use of radiation, age, race, location, education, and income, uninsured patients were less likely to receive cancer-directed surgery (OR [95% CI] = 0.86 [0.77-0.97]). Similarly, after adjustment for site, stage, cancer-directed surgery, age, race, location, education, and income, patients with Medicaid and uninsured patients were less likely to receive external beam radiation therapy (OR [95% CI] = 0.77 [0.72-0.81] and 0.68 [0.62-0.75], respectively). Patients with Medicaid or uninsured status had inferior outcomes after adjustment for surgery, radiation therapy, tumor, and demographic characteristics, as seen in Table 1.

Conclusion: Patients with Medicaid or uninsured status frequently presented with advanced-stage H&N cancer in the United States and were less likely to undergo cancer-directed surgery or radiation therapy. Overall and cancer-specific mortality were increased among Medicaid and uninsured patients after adjustment for clinical and treatment characteristics suggesting additional barriers to care or associated risk factors.


Abstract 12: Table 1 Adjusted outcomes for head and neck cancer patients according to health insurance status

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<th>Insured</th>
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<th>Uninsured</th>
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<tr>
<td>HR 95% CI</td>
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<tr>
<td>Cause-specific mortality</td>
<td>1.00 – 1.60</td>
<td>1.55-1.69</td>
<td>1.65 1.52-1.79</td>
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Abbreviations: CI = confidence interval; HR = hazard ratio.
Does Age Matter? Survival Outcomes With the Addition of Concurrent Chemotherapy for Elderly Head and Neck Cancer

Patients Undergoing Definitive Radiation Using the National Cancer Data Base


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Objective: The addition of chemotherapy to radiation (CRT) for head and neck squamous cell carcinomas (HNSCC) improves overall survival (OS) compared to radiation therapy (RT) alone; however, the Pignon meta-analysis of over 17,000 patients demonstrated no OS benefit in patients >70 years of age. Because of this, many elderly patients receive RT alone. Using a nationwide database, this study examines the outcomes of elderly patients receiving CRT versus RT alone.

Methods: The National Cancer Data Base (NCDB) was queried for patients >70 years of age with nonmetastatic oropharynx, larynx, and hypopharynx cancers treated from 1998 to 2011. Patients received definitive RT (66-81.6 Gy in 1.2-2.0 Gy fractions); CRT was defined as chemotherapy started within 14 days of the beginning of RT. Multivariate (MVA) and propensity score-matched (PSM) analyses were performed to compare OS outcomes. Recursive partitioning analysis (RPA) based on OS using age, Charlson comorbidity score, T stage, and N stage was also performed.

Results: A total of 5.265 patients were included: 3.604 (68%) received RT alone, and 1.661 (32%) received CRT. Median follow-up was 31 mo (2-181 mo). Median age of patients undergoing RT alone was 77 years (71-90 years); median age of CRT patients was 75 years (71-90 years). When accounting for age, gender, race, median county household income, percentage without a high school diploma, comorbidity index, facility, tumor site, T stage, and N stage, CRT improved OS under MVA (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.76-0.96; P = .002) and PSM analyses (HR, 0.86; 95% CI, 0.76-0.98; P = .022) compared to RT alone. On subgroup analysis, patients ages <79 years (HR, 0.80; P = .001), those with a comorbidity score of 0-1 (HR, 0.84; P = .002), stage III/IV disease (HR, 0.77; P < .001), and treatment with intensity modulated RT (HR, 0.76; P = .002) had an OS benefit with CRT under MVA. The addition of chemotherapy in patients aged ≥79 years (HR, 0.93; P = .368), those with a comorbidity score of ≥2 (HR, 1.0; P = .992), stage I/II disease (HR, 1.09; P = .448), and treatment with 3-dimensional RT (HR, 1.02; P = .923) did not have improved OS. RPA showed patients aged <79 years presenting with T3-4, any N, and a comorbidity score of 0 had an OS improvement with CRT versus RT alone; all others, including patients ≥79 years of age, did not have an OS benefit with CRT. Patients ≥79 years old with a comorbidity score ≥2 had a trend for worse OS with CRT (HR, 2.36; P = .080).

Conclusion: Patients <79 years of age with low comorbidity scores with T3/T4, any N-stage disease, appear to have an improvement in OS with CRT versus RT alone within the NCDB: CRT had worse OS in those aged ≥79 years with poor comorbidity scores. In summary, patients ≥70 years of age should not be denied concurrent chemotherapy based solely on age; additional factors ought to be accounted for.


Validation of NRG Oncology/RTOG 0129 Risk Groups for p16-Positive and p16-Negative Oropharyngeal Squamous Cell Cancer (OPSCC)


Objective: The Radiation Therapy Oncology Group (RTOG) 0129 risk groups stratified OPSCC patients into low-, intermediate-, and high-risk groups based on p16 status, clinical stage, and tobacco history. These risk groups have not been confirmed in other clinical trials. Reduction of treatment toxicities for OPSCC is of interest; however, whether toxicities differ by risk groups is unknown. Therefore, we hypothesized that RTOG 0129 risk groups were reproducible in RTOG 0522 and that observed toxicities differed by risk groups.

Methods: Patients with stage III/IV OPSCC enrolled in RTOG 0129 or 0522, available p16 status, and tobacco history were eligible for this retrospective analysis. RTOG 0129 evaluated standard versus accelerated fractionation (AFX) radiation therapy concurrent with cisplatin. RTOG 0522 compared cisplatin-AFX concurrent with cisplatin. RTOG 0129 risk groups were assigned to RTOG 0522 to estimate overall (OS) and progression-free (PFS) survival rates by Kaplan-Meier method and log-rank. Grade 3+ toxicities were compared between risk groups by X² test.

Results: A total of 260 and 287 patients from RTOG 0129 and RTOG 0522, respectively, were eligible for analysis. Median follow-up for surviving patients in RTOG 0129 and RTOG 0522 was 7.9 years (range 1.7-9.9) in RTOG 0129 and 4.7 years (0.1-7.0) in RTOG 0522. In RTOG 0522, 5-year OS for the low-, intermediate-, and high-risk groups were 88.1%, 69.9%, and 45.1%, respectively (P = .002 for low vs intermediate and P = .004 for intermediate vs high). Five-year PFS for 0522 was also higher for the low-risk group relative to the intermediate- and high-risk groups (P = .01 for low vs intermediate and P = .07 for intermediate vs high). Data from RTOG 0129 and RTOG 0522 were combined to determine differences in acute and late toxicities. Similar overall rates of acute toxicities were observed by risk groups (P = .14). Severe acute anemia and neutropenia were less common in the low/intermediate groups (P = .01). However, severe acute dysphagia, nausea, and mucositis were significantly more common in the low/intermediate groups (P < .02 for all). Late toxicities were similar by risk groups.

Conclusion: RTOG 0129 risk groups are reproducible in RTOG 0522. When treated with standard or intensified chemoradiation, low/intermediate risk patients more commonly experience specific acute toxicities, but not late toxicities.

Acknowledgment(s): This project was supported by National Cancer Institute and Bristol Myers Squibb grants U10CA21661, U10CA180868, U10CA180822, and U10CA37422.

Purpose/Objective(s): Concurrent carboptatin and taxol (C/T) is commonly utilized in the management of head and neck squamous cell carcinoma (HNSCC) based on phase 2 data. At our institution we underwent a shift in practice over a relatively short period of time from frequent use of concurrent C/T to predominantly cisplatin (Cis)-based concurrent therapy. We sought to determine cancer-specific outcomes with Cis-based versus C/T concurrent therapy.

Materials/Methods: We retrospectively analyzed 336 consecutive patients (pts) with oropharyngeal HNSCC treated at a single institution with definitive intensity modulated radiation therapy to a median dose of 70 Gy (median 2 Gy/fraction) using predominantly a dose-painting technique. Univariable and multivariable Cox proportional hazard regression models were used to evaluate the association of concurrent chemotherapycy-type with overall survival (OS), recurrence-free survival (RFS), local-recurrence failure (LRF), and distant metastasis (DM). The multivariable model included clinical predictors that were significant in the univariate model for survival outcomes with a P value <.05. The Fine & Gray method was used to adjust for competing risks.

Results: The cohort comprised 336 pts, mostly male (85%), with a median age of 57.3 years. The most common sites were tonsil (49.4%) and base of tongue (46.7%). The American Joint Committee on Cancer stage was I (0.3%), II (9.3%), III (11.1%), IVA (71.5%), and IVB (9.2%). Most pts were human papillomavirus (HPV)-positive (72.3%), 13.1% were HPV-negative, and 14.4% had unknown HPV status. Pts received upfront concurrent chemoradiation (58%) or sequential therapy (38.4%); 3.6% received radiation and no chemotherapy. Eighty pts (23.8%) received Cis-based concurrent chemotherapy, and 103 pts (30.7%) received weekly C/T concurrent chemotherapy. With a median follow-up of 3.8 years, the 3-year OS, LRF, and DM were 67.4%, 8.7%, and 10.7%, respectively. ECS was present in 25% of patients treated with primary surgery, while clinical T stage was mostly correct (84% of T1 tumors and 79% of T2 tumors), the clinical lymph node status was less accurate. Patients with clinical N0 and N1 disease were upstaged 25% and 35% of the time, respectively. ECS was present in 25% of patients treated with primary surgical treatment, and positive margins were present in 29%. ECS, T upstaging, and N upstaging remained stable over time, while positive margin status decreased from a high of 37% in 2007 to 2008 to 22% in 2012 (P < .0001).

Conclusion: The use of a primary surgical approach for management of early T-stage OPSCC has increased and is related to both tumor and nontumor factors. Although margin positivity has decreased over time, there is an overall nontrivial rate of pathologic adverse features. One quarter of patients receiving primary surgery had ECS on postoperative pathology. Efforts are warranted to improve the primary treatment selection process to avoid triple modality therapy.

Results: A total of 1929 patients with complete data were identified with a median follow-up of 37 months (range 2-128 months). For the entire cohort, median age was 67 years (range 28-90 years); 88% were male, 84% were white, 36% had private insurance, 24% were treated at an academic/research institution, 68% were T1 stage, and 39% were treated with IMRT. On UVA, OS was significantly decreased with older age, male gender, nonprivate insurance, increasing comorbidity score, T2 stage, and treatment with IMRT (hazard ratio [HR] 1.32, \( P = .002 \)). Five-year OS for the entire cohort was 69%; it was 72% versus 63% for the 3DCRT and IMRT groups, respectively. On MVA, older age (HR 1.04, \( P < .001 \)), male gender (HR 1.35, \( P = .04 \)), having nonprivate insurance, treatment at a community cancer program (HR 1.41, \( P = .04 \)), high comorbidity score (3DCRT vs IMRT, \( P < .001 \)), T2 stage (HR 1.53, \( P < .001 \)), and IMRT (HR 1.23, confidence interval [CI]: 1.02-1.49, \( P = .029 \)) remained associated with decreased OS. PSM groups (n = 641 per group) were well-balanced for all factors (X2 \( P = .022 \)) associated with IMRT relative to 3DCRT.

Conclusion: This population-based analysis indicates 3DCRT techniques are associated with improved OS in early-stage cancer of the glottic larynx. This may be due to marginal miss of the primary tumor or decreased dose to nearby subclinically involved lymph nodes when highly conformal techniques are implemented. Physicians should strongly consider a classic 3D approach to early-stage larynx cancer given its documented history of good outcomes and cost-effectiveness.

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105
Elective Nodal Irradiation and Patterns of Failure in Head and Neck Cancer Following Primary Radiation Therapy
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Purpose/Objective(s): The delineation of elective clinical target volumes in head and neck cancer (HNC) is important, but the extent of lymph node levels necessary to include is debated. A comprehensive analysis of recurrence patterns in a large cohort of HNC patients was performed with emphasis on recurrences in the retropharyngeal region and level IB.

Materials/Methods: Between 2005 and 2012, 942 patients with oro- or hypopharyngeal, laryngeal, or oral cavity carcinomas were curatively treated with primary radiation therapy (RT). The median follow-up was 34 months, and 77% of patients received intensity modulated RT. The retropharyngeal region was only routinely included in case of involvement of the posterior pharyngeal wall, and level IB only in case of involvement of the oral cavity. In patients with regional recurrence, the anatomical site of the recurrence was assessed from surgical descriptions or CT scans and compared to the original RT treatment plan (available from 2007 and onward). P16 status was available in 282 oropharynx carcinomas (OPSCC), with 65% p16 positive.

Results: Forty percent of patients (N = 376) had recurrences, 24% local (N = 228), 13.1% regional (N = 123), and 11.6% distant (N = 109). In 700 patients with available treatment plans, retropharyngeal and level IB recurrences were observed in 2 and 7 patients, respectively. Eight patients (1.1%) had recurrence in a lymph node level not included in their primary treatment plan. For OPSCC, the loco-regional control (90% vs 70%), but not distant control (92% vs 87%) was significantly better in p16-positive versus p16-negative patients. Although fewer recurrences occurred in the p16-positive group, patients with recurrence of p16-positive tumors were more likely to recur in distant sites.

Conclusion: Retropharyngeal or level IB recurrences following primary HNC RT are rare, and inclusion of these regions in the elective treatment volumes should be limited to patients with involvement of the posterior pharyngeal wall and oral cavity, respectively.


106
Prognostic Groups for p16-Positive Oropharyngeal Squamous Cell Cancer (p16-OPSCC) Treated With Chemoradiation Therapy (CRT) in NRG Oncology/RT0G 0129 and 0522
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Purpose/Objective(s): Identification of patients with p16-OPSCC with high probability of cure is essential for therapeutic de-differentiation with CRT.

Materials/Methods: Patients with T2-T4, N0-N3 OPSCC enrolled in Radiation Therapy Oncology Group (RTOG) 0129 or 0522 with available p16 immunohistochemistry results and tobacco history were eligible for retrospective analysis of factors associated with overall OS and progression-free survival (PFS). RTOG 0129 compared high-dose cisplatin-based CRT standard fractionation with accelerated fractionation (AFX), and RTOG 0522 compared cisplatin-AFX with and without cetuximab. Recursive partitioning analysis (RPA) identified mutually exclusive patient groups for OS. OS and PFS were estimated by Kaplan-Meier method and compared by log-rank. X2 test compared grade 3 toxicities among RPA-defined risk groups.

Results: Analysis included 402 patients with p16-OPSCC. Median follow-up for surviving patients was 5.7 years (range 0.1-9.9). Univariate factors associated with improved OS included low tobacco exposure (<10 vs >10 pack-years), age (<50 vs >50 years), better performance status ( Zubrod 0 vs 1), lower tumor (T2-T3 vs T4), and nodal (N0-N2a vs N2b-N2c vs N3 stage) for all hazard ratio<1.0, P<.04). All these factors were independently associated with improved OS in multivariable analysis. Three distinct risk groups for 5-year OS were identified as at low (92%, 95% confidence interval [CI] 89-96), intermediate (72%, 95% CI 65-80), or high (53%, 95% CI 39-67) risk of death. Five-year PFS was also higher for the low-risk group relative to the intermediate- and high-risk groups (P<.001 for low vs intermediate and P=.01 for intermediate vs high). Acute and chronic toxicities were largely similar by risk groups with few exceptions. In the low-risk group severe acute neutropenia (P =.007) was less common and a trend toward less frequent late severe dysphagia (P = .08) and mucositis (P = .08) was observed. Patterns of recurrence differed by risk groups (P = .03); the majority of recurrences in the low-risk group were locoregional (70.6%), while the majority of recurrences for intermediate- and high-risk groups were distant (54% and 62%, respectively).

Conclusion: A low-risk group with decreased risk of death and distant failure was identified. This may inform eligibility for radiation-based therapeutic de-differentiation trials.

Acknowledgment(s): National Cancer Institute and Bristol Myers Squibb grants U10CA21661, U10CA180868, U10CA180822, and U10CA37422.
Validation and Comparison of Prognostic Scoring Systems in a Cohort of Human Papillomavirus–Associated Oropharynx Cancers

Treated Nonoperatively

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Purpose/Objective(s): The recent human papillomavirus (HPV) epidemic in oropharynx cancer (OPC) presents a demographic separate from the historical tobacco-associated OPC. This population is comparatively younger and healthier than previous patients with tobacco-associated cancers. Comorbidity assessment is a critical component of the pretreatment evaluation, but the optimal system for documentation and research is unclear in this cohort. The purpose of this study was to validate and compare 2 common comorbidity scales: the historic Charlson comorbidity index and the more recent Adult Comorbidity Evaluation-27 (ACE-27).

Materials/Methods: From a retrospective institutional review board–approved tumor registry, patients with HPV-associated OPC treated nonoperatively from 2001 to 2013 were identified. Both the Charlson score and the ACE-27 category were recorded. The Kaplan-Meier method was used to assess overall survival (OS) by comorbidity system with differences assessed using the log-rank test. Two separate multivariate Cox proportional hazards models were generated, each with the individual comorbidity system as well as the predictors of OS statistically significant on univariate analysis.

Results: Two hundred eighty-eight patients were identified, of which 274 were treated with combined chemoradiation therapy and 14 with radiation therapy alone. The cervical nodes were involved in 277 patients, and 285 were stage III-IVB. The median oncologic follow-up was 53.5 months. There were 55 deaths in the group for an estimated 5-year overall survival (OS) of 83%. Patients with no comorbidities measured by the ACE-27 score uniformly had a Charlson score of zero. However, a distribution of Charlson scores noted amongst patients with mild, moderate, or severe ACE-27 categories had a range of Charlson scores: 0-5, 0-4, and 0-8, respectively, each with a median Charlson score of 1. On univariate analysis age, Charlson score, ACE-27 category, pack-years of smoking, and T stage were significantly associated with OS. On multivariate analysis (MVA), pack-years of smoking, T stage, and each comorbidity score remained independently associated with OS.

Conclusion: Both the ACE-27 and the Charlson comorbidity index are validated prognostic scales for the measurement of comorbidity in HPV-associated head and neck cancer. Both have advantages: although ACE-27 is more sensitive, the Charlson score may retain a degree of granularity given the range of possible results. Comorbidity should be included in predictive models for OS in an attempt to account for competing risks in this relatively healthy subset of head and neck patients.

Abstract 107; Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>MVA with Charlson</th>
<th>MVA with ACE-27</th>
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108

The Outcomes of Induction Chemotherapy for Head and Neck Cancer Patients

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Purpose/Objective(s): Until now, the role of induction chemotherapy has remained a subject of controversy. Our study was to directly compare survival in patients receiving induction chemotherapy docetaxel or platinum given before concomitant chemoradiation therapy with upfront chemoradiation therapy alone.

Materials/Methods: The National Health Insurance claims database and cancer registry databases in Taiwan were linked for the analysis. Head and neck cancer patients from January 1, 2002 to December 31, 2011 were included in the study. The inclusion criteria were having a head and neck cancer (identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 140.0-148.9), being aged >20 years, being classified as American Joint Committee on Cancer (AJCC) clinical cancer stage I-II, platinum and docetaxel combined use before RT, docetaxel use during or after RT, induction chemotherapy beyond 8 weeks before RT, only 1 course of induction chemotherapy before RT, cetuximab use, adjuvant chemotherapy within 90 days after completion of RT, less than 7000 cGy dose of RT, curative head and neck cancers surgery before RT, nasopharyngeal cancer, carcinoma in situ, sarcoma, head and neck cancer recurrence, or an unknown gender, and being younger than 20 years of age. The total number of enrolled head and neck cancer patients was 30,990 persons.

Results: In total, 10,721 stage III-IV head and neck cancer patients without distant metastasis were included in the study, and the median follow-up duration was 4.18 (interquartile range, 3.25) years. There were 7968 patients in the CCRT group (arm 1); 503 patients in the induction chemotherapy with docetaxel group of arm 2, and 2232 patients in the induction chemotherapy with platinum group of arm 3. We used the CRT arm as the control arm to investigate the risk of death after induction chemotherapy. After adjustments for age, gender, clinical stage, and comorbidities, the adjusted hazard ratios of overall deaths were 1.37 (95% confidence interval [CI], 1.22-1.56) in arm 1.36 (95% CI, 1.22-1.56) in arm 2 and 1.44 (95% CI, 1.44-1.44) in arm 3. In disease-specific survival rate analysis, the adjusted HRs of head and neck cancers deaths were 1.29 (95% CI, 1.14-1.46) in arm 2 and 1.47 (95% CI, 1.38-1.56) in arm 3. Conclusion: Our cohort study showed induction chemotherapy with docetaxel or platinum not only did not improve survival but also resulted in more all death and head and neck cancer death risk compared with CCRT.


109

Induction Chemotherapy Predicts Cumulative Radiation Dose and Fails to Improve Survival in Advanced Head and Neck Cancer, a National Cancer Data Base Analysis

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Purpose/Objective(s): The role of induction chemotherapy (IC) in advanced head and neck squamous cell carcinoma (HNSCC) remains controversial. In recent randomized trials, the addition of IC to concurrent chemoradiation (CRT) failed to improve overall survival (OS). This failure may stem from the studies’ lack of power due to slow accrual and/or from their inclusion of patients with less advanced nodal disease, prompting the present analysis of the National Cancer Data Base (NCDB).

Materials/Methods: The NCDB was queried for subjects diagnosed from 2003 to 2011 with T (any) N2b-3 M0 cancers of the oropharynx, hypopharynx, and larynx, who underwent external beam radiation without surgery. We defined 2 analytic cohorts based on the sequencing of chemotherapy (CT) and radiation therapy (RT): an IC cohort with start of CT preceding RT by 43 to 98 days (thus allowing 2-3 cycles of IC as used in recent trials) and a CRT alone cohort with CT starting within 7 days of RT start. Logistic regression was used to identify factors associated with nonguideline-concordant RT dose (ie, <66 Gy), and Cox regression was used to assess the association of CT sequence on OS.

Results: A total of 6086 CRT and 1917 IC subjects were evaluable. As compared to the CRT group, the IC cohort tended to be younger and to have more advanced T and N status and more hypopharynx cancer, were more likely to receive <66 Gy of RT (20.9% vs 14.9%; P < .01), and displayed worse OS (median 52.1 vs 64.9 months, P < .01). After adjusting for age, year, sex, race, location, income, comorbidities, primary site, and T and N status with multivariate analysis, the IC cohort had increased odds of receiving <66 Gy (odds ratio 1.42; 95% confidence interval [CI] 1.24-1.63; P < .01), but their OS did not significantly differ from that of the CRT cohort (hazard ratio [HR] for mortality 1.07; 95% CI 0.99-1.16; P = .08).

On subgroup analysis, IC status was not associated with improved OS among the 2809 subjects with T4 or N3 disease (HR 1.02; 95% CI 0.92-1.13; P = .72), the 1107 patients with N3 disease (HR 1.02; 95% CI 0.86-1.22; P = .82), or the 351 subjects with T4N3 disease (HR 0.97; 95% CI 0.73-1.28; P = .81). Among the 5194 patients without T4 or N3 disease, IC status predicted a slight increase in mortality (HR 1.12; 95% CI 1.00-1.25; P = .046).

Conclusion: In this large group of HNSCC patients with advanced nodal disease from the NCDB, IC subjects were more likely to receive less-than-guideline-concordant RT and lower overall survival (OS) compared to CRT subjects, even on subgroup analyses of increasingly advanced disease from the NCDB, IC subjects were more likely to receive less-than-guideline-concordant care following IC.


110
Patterns of Failure After Definitive Radiation for Oropharyngeal Cancer—Should P16 Status and Tumor Growth Rate Alter the Clinical Target Volume?

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Purpose/Objective(s): Oral mucositis is a commonly observed toxicity during head and neck radiation therapy. Metallic dental restorations produce short-range secondary electrons that deposit dose into nearby tissue causing large, painful ulcers in the adjacent mucosal surfaces. This contributes to patient weight loss during treatment and often leads to breaks in therapy to replan or to allow for recovery. Various protective dental stents have been proposed and tested in very simple phantoms and 2-dimensional (2D) beam arrangements. Our objective was to generate the first quantitative assessment of electron scatter and stent efficacy using an anatomically realistic phantom and a modern beam configuration and delivery method in order to better address our patients’ QOL during treatment.

Materials/Methods: We created a tissue-equivalent phantom to simulate a complete upper and lower jaw with 2 sets of removable gold caps on opposing molars. We created a 4-mm upper and lower ethylene copolymer dosimetric stents to provide space between the mucosa and teeth as well as between the upper and lower jaw. The phantom was placed

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<th>Abstract 110; Table 1</th>
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<tr>
<td><strong>RTOG 0129</strong>&lt;br&gt;Risk Group</td>
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<tr>
<td>LR Failure</td>
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<tr>
<td>Low (n = 52)</td>
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<tr>
<td>Intermediate (n = 33)</td>
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<td>High (n = 18)</td>
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Results: Seventy-nine patients were p16(+) (77%), and 98 were stage III or IV (95%). Median TGR was 0.74%/day (range 0.01-5.5). Median follow-up was 30 months (range 0.5-80). Ninety-two percent were treated with CRT. On multivariate analysis, p16(-) status (hazard ratio [HR] 3.4, 95% confidence interval [CI] 1.4-8.3) and increasing TGR (HR 4.8, 95% CI 1.6-14.5) were the strongest predictors of recurrence. Patterns of failure according to Radiation Therapy Oncology Group (RTOG) 0129 risk group, stratified by median TGR are shown in Table 1.

Fourteen of 15 patients with LRF had evaluable postrecurrence scans and plans. The median time to LRF was 4 months (range 0.75-14 months).

A majority of failures (11/15, 73%) were marginal to high-dose radiation prescription volume (RxV; ie, the tumor recurred both in and out of the treated volume). Four recurrences developed completely within the high-dose RxV. The median distance of the furthest extent of the recurrence from the field edge was 7 mm; the distance from the RxV edge necessary to encompass the LRF with adequate margin ranged from 0 to 20 mm. Eighty percent of failures would have been covered by an expansion of an additional 12 mm outside of the RxV; 3 patients experienced LRF more than 15 mm outside of the high-dose RxV.

Conclusion: Locoregional failures in low-risk OPC tumors are rare, such that reductions in CTV margins may be justified in the interest of treatment deintensification. The dominant pattern of failure in intermediate- and high-risk tumors appears to be marginal to the high-dose prescription volume, predominantly among tumors with increased TGR. CTV expansions based upon RT0G 0129 risk group and TGR warrant investigation.


111
Dosimetric Verification of Dental Stent Efficacy in Head and Neck Radiation Therapy Using Modern Radiation Therapy Techniques: Quality of Life (QOL) and Treatment Compliance Implications

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Purpose/Objective(s): Oral mucositis is a commonly observed toxicity during head and neck radiation therapy. Metallic dental restorations produce short-range secondary electrons that deposit dose into nearby tissue causing large, painful ulcers in the adjacent mucosal surfaces. This contributes to patient weight loss during treatment and often leads to breaks in therapy to replan or to allow for recovery. Various protective dental stents have been proposed and tested in very simple phantoms and 2-dimensional (2D) beam arrangements. Our objective was to generate the first quantitative assessment of electron scatter and stent efficacy using an anatomically realistic phantom and a modern beam configuration and delivery method in order to better address our patients’ QOL during treatment.

Materials/Methods: We created a tissue-equivalent phantom to simulate a complete upper and lower jaw with 2 sets of removable gold caps on opposing molars. We created a 4-mm upper and lower ethylene copolymer dosimetric stents to provide space between the mucosa and teeth as well as between the upper and lower jaw. The phantom was placed
in a cylindrical water bath to simulate head and neck soft tissue. A linear accelerator was used to deliver 6-MV photons in opposed lateral, intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT) configurations. We used film for dosimetric measurement in both the occlusal plane and the vertical plane to simulate mucosal surfaces of the tongue and the cheek. A single dose of 200 cGy was prescribed to the base of tongue region. Plans and film measurements were made for the phantom with and without the stents in place. We then converted the film reading to a 2D digital dose map using quality assurance software. We used image processing software to measure the areas on the film that were enclosed by each isodose line.

**Results:** Our readout of the 2D dose distributions in the vertical (buccal) plane clearly demonstrates a reduction in maximum dose of 27% for the opposed beam and 40% for the IMRT and VMAT with the use of the protective dental stent. The area of simulated tissue receiving ≥100 cGy was 2.5 cm² higher in the occlusal plane and 5.5 cm² greater in the buccal plane when the dental stents were absent. To our knowledge, this is the first dosimetric analysis of dental stents using an anatomically realistic phantom and modern beam arrangement.

**Conclusion:** Our observed 40% dose reduction implies that patients’ oral mucosa adjacent to dental fixtures could receive doses in excess of 100 Gy during a course of definitive IMRT or VMAT radiation therapy to the head and neck. In this era of increasing IMRT and VMAT use, our results emphasize the importance of dosimetric stent use to improve QOL and reduce treatment breaks for our patients undergoing head and neck radiation therapy.

**Author Disclosure:** E. Allan: None. L. Lu: None. H. Hoonan: None. A. Chakravarti: None. M. Van Putten: None. D. Blakaj: None.

### 112

**ContraLateral Submandibular Gland Sparing in Head and Neck Squamous Cell Carcinoma Is Safe and Improves Patient-Reported Outcomes (PROs)**

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**Purpose/Objective(s):** To determine the feasibility and potential benefits of sparing contralateral submandibular gland (cSMG) during definitive intensity modulated radiation therapy (IMRT) for head and neck squamous cell carcinoma (HNSCC).

**Materials/Methods:** We reviewed treatment plans, mean doses (MDs) to organs at risk, patient-reported outcomes, and tumor control in 273 patients with HNSCC treated with definitive IMRT to the bilateral necks at our institution between 2005 and 2014. Patients were periodically given the validated xerostomia questionnaire (XQ) and head and neck quality of life questionnaire (HNQOL) pretreatment and at follow-up.

**Results:** The majority (73%) of patients had oropharyngeal cancer. The vast majority of patients, 93.0%, harbored stage III/IV disease, and 93.0% of patients received concurrent chemotherapy. Median follow-up was 22.5 months (1–115 months), and 662 surveys were analyzed. The medians of MDs to oral cavity (OC) was 36 Gy (8-67 Gy), combined parotid glands (compG) 31 Gy (6-58 Gy), ipsilateral SMG (iSMG) 66 Gy (28-72 Gy), and cSMG 37 Gy (8-70 Gy). On univariate analysis, significant predictors of XQ summary score (SS) included the MDs of OC (r=0.44, P<0.01), compG (r=0.63, P<0.01), and cSMG (r=0.22, P=0.04). On multivariate analyses, the compG MD (r=0.42, P=0.04) and time from treatment (r=-0.14, P=0.01) were statistical predictors of the XQSS, and the cSMG MD (r=-0.21, P=0.09) was a marginally significant predictor for XQSS. At the 6- and 12-month timepoints, the cSMG MD is a significant predictor for XQSS (r=0.82, P=0.01 and r=0.57, P=0.04, respectively), eating domain (r=0.90, P=0.01 and r=0.68, P=0.02, respectively), fastening domain (r=0.66, P=0.04 and r=0.52, P=0.07, respectively) and HNQOL (r=0.77, P<0.01 and r=0.49, P=0.02, respectively). Using 39 Gy cSMG MD as a prespecified threshold based on dose-saliva relationships, regression modeling showed that patients receiving <39 Gy had significantly favorable XQSS in both univariate (r=-22.61, P<0.01 and r=-15.18, P=0.01, respectively) and multivariate (r=-26.50, P<0.01 and r=-13.02, P=0.03, respectively) analysis at 6 and 12 months. Moreover, patients receiving <39 Gy had improvement (P<0.01) in their XQSS over time after IMRT, while patients receiving >39 Gy did not (P=0.29) (data will be presented). Sixty-three percent (172/273) of the patients received <39Gy to the cSMG to preserve salivary output. In this group, the median of MD to cSMG was 31Gy (8-39 Gy), and the majority (75%) was oropharyngeal cancer. There were 28 total tumor recurrences with no failures in contralateral level IB, and only 1 patient failed on the contralateral neck, within the 54 cGy isodose line and in initially noninvolved level II.

**Conclusion:** cSMG MD predicts for both patient-reported xerostomia and QOL after IMRT. cSMG sparing did not compromise disease control. We recommend keeping the cSMG MD to no more than 39 Gy if clinically possible.

**Author Disclosure:** Y. Mao: None. S. Samuels: None. E. Sapir: None. A. Eisbruch: None.

### 113

**Sparing Level IB in Node-Positive, Human Papillomavirus–Associated Oropharyngeal Carcinoma: An Early Safety and Efficacy Analysis**

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**Purpose/Objective(s):** The conformality of modern intensity modulated radiation therapy (IMRT) allows meaningful avoidance of the submandibular glands (SMG) in select patients, thereby potentially improving late xerostomia. This study explores the safety and efficacy of this approach in select node-positive oropharyngeal carcinoma patients, comparing it with traditional level IB coverage.

**Materials/Methods:** From a retrospective institutional review board–approved registry, patients with T1-2, node-positive human papillomavirus (HPV)–associated oropharyngeal carcinoma treated with definitive IMRT at a single institution from August 2009 to January 2014 were identified. While in the earlier portion of this study routine avoidance of level IB was uncommon, in recent years, we routinely avoid clinically uninvolved level IB, even in the presence of level 2a LN. We reviewed and verified all treatment plans. Mean doses to the SMG were compared for instances in which level IB LN were targeted and level Ib LN were avoided. We then examined mean doses to the oral cavity as well as predictors of late grade ≥2 xerostomia on a per patient basis, for which patients were divided into 3 groups: bilateral level IB targeted (A), a single level IB targeted (B), and bilateral IB not targeted (C). We also reviewed every failure location to identify the rate of level IB regional recurrence. Differences in continuous variables were compared using the Wilcoxon rank sum test and Pearson X² test was used for categorical variables.

**Results:** Among 87 patients and 174 level Ib stations, level Ib was targeted in 95 instances and avoided in 79 instances. Mean SMG doses were significantly lower when level IB was spared compared to where it was targeted (44.5% reduction; 37.5 Gy vs 67.5 Gy; P<0.0001). We examined predictors of late grade ≥2 xerostomia on a per patient basis which included 17 patients in Group A, 61 in group B, and 9 in group C. Age, KPS, smoking pack-years, T stage, N stage, and type of chemotherapy did not differ amongst the 3 groups. Median doses to oral cavity decreased with increasing level IB sparing (42.2 Gy [Group A] versus 35.4 Gy [Group B] versus 30.7 [Group C]; P=0.001). Rates of late grade ≥2 xerostomia were numerically lower than statistically lower in group C versus A and B (11% vs 59% and 52%, P=0.17). With a median follow-up of 29.8 months, no regional failures were identified in levels IB in any patient.

**Conclusion:** Sparing level IB, either contraterally or bilaterally, is safe in T1-2, node-positive HPV+ oropharyngeal cancer. Avoiding level IB appears to translate into significantly lower SMG doses as well as oral cavity doses. Larger studies are needed to validate these early findings and the impact of this technique on late xerostomia and other functional outcomes.

**Purpose/Outcome(s):** Sparing level IB in node-positive, human papillomavirus–associated oropharyngeal carcinoma treated with definitive IMRT at a single institution from August 2009 to January 2014 were identified. While in the earlier portion of this study routine avoidance of level IB was uncommon, in recent years, we routinely avoid clinically uninvolved level IB, even in the presence of level 2a LN. We reviewed and verified all treatment plans. Mean doses to the SMG were compared for instances in which level IB LN were targeted and level Ib LN were avoided. We then examined mean doses to the oral cavity as well as predictors of late grade ≥2 xerostomia on a per patient basis, for which patients were divided into 3 groups: bilateral level IB targeted (A), a single level IB targeted (B), and bilateral IB not targeted (C). We also reviewed every failure location to identify the rate of level IB regional recurrence. Differences in continuous variables were compared using the Wilcoxon rank sum test and Pearson X² test was used for categorical variables.

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A Prospective Evaluation of Dysphagia After Transoral Robotic Surgery for Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): Transoral robotic surgery (TORS) for oropharyngeal squamous cell carcinoma (OPSCC) has been associated with improved long-term dysphagia quality of life as compared to chemoradiation. Nevertheless, dysphagia is common in the perioperative period and has been inadequately characterized. Our primary objective in this study is to characterize short-term swallowing outcomes after TORS for OPSCC in a prospective manner in an attempt to improve postoperative outcomes.

Materials/Methods: Patients undergoing TORS for OPSCC were prospectively enrolled into this study between the dates of June 20, 2014 and July 31, 2015. Patients were evaluated by a speech-language pathologist postoperatively for diet recommendations and swallowing strengthening exercises. The Eating Assessment Tool 10 (EAT-10), a 10-item validated questionnaire measuring swallowing quality of life, was administered on postoperative day (POD) 1, POD 7, and POD 30. A score >3 is considered to be indicative of swallowing dysfunction. Medical records were queried for demographics, clinical history, staging, intraoperative factors, and postoperative course. Patients were excluded for a history of previous TORS on radiation to the oropharynx, repeat TORS within 1 month after enrollment, TORS for nonmalignancy, or a procedure on a nonoropharyngeal aerodigestive subsite, a contraindication to swallowing evaluation, or incomplete data. Statistical analysis was performed using a paired t-test to compare EAT-10 scores between POD 1 and POD 7 and POD 30.

Results: Fifty-nine patients met initial inclusion criteria. Twenty-four patients were excluded (8 for nonoropharyngeal procedures, 5 for contraindications to swallowing evaluation, 7 for repeat TORS within 1 month after enrollment, 1 for TORS for nonmalignancy, and 1 for a procedure on a nonoropharyngeal aerodigestive subsite). Thirty-five patients (26 males, 9 females) were included in the final analysis. The mean age was 58.8 (range 43-74) years. Four of the 35 patients (11.4%) reported preoperative dysphagia. Twenty of the 35 patients (57.1%) underwent tongue base resection, with the remainder undergoing radical tonsillectomy. T stages were Tx (3), T1 (18), T2 (13), T3 (1), and HPV+. All patients were started on an oral diet by POD 1 without instrumental testing. The mean EAT-10 score (0-40) on POD 1 was 21.5 (range 0-37), on POD 7 was 27.7 (range 14-45), and on POD 30 was 11.9 (range 1-33). EAT-10 scores were significantly worse at POD 7 (P = 0.003) and significantly better on POD 30 (P < 0.001) as compared with initial evaluation. However, at 1 month, only 5 of 34 patients (14.3%) had normal EAT-10 scores. Mean weights (lbs) decreased significantly over the month (207.6 vs 198.8, P < 0.001).

Conclusion: Most patients who undergo TORS experience dysphagia for at least the first month after surgery. Patients can be counseled that dysphagia will worsen by postoperative day 7 and then improve, but it likely will not resolve by 1 month. Swallowing evaluation and therapy should be considered routine in this cohort of patients.

diameters, received TFHX2 (paclitaxel, fluorouracil, hydroxyurea, and 1.5 Gy twice daily RT every other week) to 75 Gy with the planning target volume (PTV1) encompassing exclusively gross disease. Pts with <50% response (NR) were treated with volumes encompassing PTV1 and the next nodal station at risk (PTV2) to 45 Gy, followed by a sequential boost to PTV1 to 75 Gy. Physician-assigned acute toxicity (Common Terminology Criteria for Adverse Events version 4.0) and QOL data using the Functional Assessment of Cancer Therapy-Head and Neck Version 4 (FACT-H&N) instrument and McMaster Radiotherapy Questionnaire were prospectively collected.

**Results:** Ninety-four pts were enrolled: median age 57 years (range 27-76), 84% male, 63% HPV+ oropharynx, 54% ≥10 pack-year tobacco use, 56% ≥T3, 88% ≥N2b. Thirty-seven pts (41.6%) had GR to IC. There were no significant differences in acute grade 3+ dermatitis (27.0% GR vs 25.5% NR, P = .87) or mucositis (59.5% GR vs 60.8% NR, P = .90), but NR were significantly more likely to have a percutaneous endoscopic gastrostomy (PEG) tube placed during treatment (50.0% GR vs 72.9% NR, P = .031) and be PEG tube dependent at 3-month (22.9% GR vs 56.2% NR, P = .002) and 6-month follow-up (5.7% GR vs 31.1% NR, P = .005). Mean global FACT-H&N QOL scores were similar at baseline (78.9 GR vs 76.0 NR, P = .21), but significantly higher in GR at 1 month posttreatment (73.5 GR vs 67.2 NR, P = .020) and trended toward significance at 6 months (77.3 GR vs 72.2 NR, P = .070). Mean subject mouth dryness scores on the McMaster Radiotherapy Questionnaire were no different at baseline (6.1 GR vs 5.6 NR, P = .14), but significantly higher in GR at 1 month posttreatment (3.9 GR vs 3.0 NR, P = .034).

**Conclusion:** RAVD is a novel treatment approach that uses IC response to determine the extent of RT volume reduction. Pts with GR to IC in whom elective nodal coverage was omitted experienced less toxicity and improved QOL compared with NR pts. Further investigation is warranted.


### 117

**Intrafraction Organ Motion Tracking With Real-Time MRI-Guided Radiation Therapy for Head and Neck Cancer**

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**Purpose/Objective(s):** Although intrafraction organ motion in the head and neck region can affect the precision of radiation therapy (RT) and conceivably lead to geographic miss, there are essentially no studies investigating this phenomenon. Using the first commercially available magnetic resonance imaging (MRI)-guided radiation therapy system, we evaluated real-time tongue motion related to deglutition for patients “under beam” for head and neck cancers in an effort to refine planning target volume (PTV) margin design.

**Materials/Methods:** Six patients with head and neck tumors, including those involving the base of tongue (n=3) and paranasal sinuses (n=3) were available for analysis. All patients were treated to doses ranging from 34 to 70 Gy in 20 to 33 fractions using an MRI-guided RT system with on-board cine MR imaging. To track swallowing motion, 4 reference points were mapped on daily sagittal cine MR imaging at these positions: (1) posterior edge of the mandible alveolar process as a reference point with minimal or no movement and mobile points at (2) most superior point of tongue dorsum, (3) mid base of tongue, and (4) inferior-posterior edge point of base of tongue. A significant displacement in tongue movement was defined as motion greater than 5 mm from baseline noise or airway-related movement. Three parameters were measured to quantify tongue motion: tongue displacement distance, deglutition time as time spent in motion >5 mm, and number of swelling events. Patients with base of tongue tumors were compared with the other patients to determine how the presence of tumor affected tongue motion.

**Results:** A total of 160 cine MR sagittal image sets were evaluated, with a median duration of 798 seconds (range, 552-1068 seconds). For the entire patient group, the mean number of swelling events/fraction was 9.7±8.7, resulting in a mean tongue displacement of 7.9±2.7 mm/fraction and a maximum tongue displacement range of 8.5 to 22.3 mm/fraction. Overall the mean time spent swallowing was 1.9%±2.8% of the fraction time with an absolute mean time of 13.3±19.9 seconds per fraction. The maximum time spent swallowing ranged from 4.3% to 25.1% of the fraction time with absolute values of 20.5 to 198.8 seconds. When the 3 parameters for tongue motion measurement were compared between patients with tongue tumors and those with uninvolved tongues, no differences were observed between the 2 groups (p>0.05).

**Conclusion:** Real-time on-board cine MR imaging allows for quantification of in-treatment deglutition-related tongue motion. Our findings demonstrate significant displacement of internal organs including tumor suggest that planning target volume (PTV) margins may often be inadequate to account for intrafraction motion. These results provide a framework for investigation of individualized adaptive PTV margin optimization and for the evaluation of potential dosimetric implications.

**Author Disclosure:** J. Rwigema: None. D.H. Thomas: None. M. Cao: None. T. Yoshizaki: None. A.M. Chen: None.

### 118

**Pathological Factors Predicting the Risk of Distant Metastases for Human Papillomavirus—Positive Oropharyngeal Squamous Cell Carcinoma (OPSCC)**

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**Purpose/Objective(s):** Despite superior locoregional control for HPV+ OPSCC, approximately 10% of patients (pts) will develop distant metastases (DM). Current American Joint Committee on Cancer pathological staging does not adequately identify pts at high risk of DM. There are emerging data on risk factors for DM in pts treated with chemoradiation, but very little information on risk factors for DM in pts treated with initial surgery. Materials/Methods: We performed a retrospective analysis of 174 HPV+ OPSCC pts with ≥20 months follow-up, treated with transoral robotic resection (TORS) and neck dissection (ND) followed by adjuvant chemoradiation therapy (CRT). Pathologic data include the number and proportion of involved nodes, lowest level of involvement, and extent of extracapsular extension (ECE), classified as none, microscopic/focal, or macroscopic/gross. There were 15 pts with clinical N2c disease, of whom 5 underwent bilateral ND; for these pts we report the sum of positive nodes from both sides of the neck. The Wilcoxon rank sum test was used for continuous variables, multivariable logistic regression for predictors of DM, and Kaplan-Meier for survival probabilities.

**Results:** With a median follow-up of 38 months, 12 pts (7%) developed DM. The number of positive nodes was the strongest predictor of the risk of DM, with the probability increasing in proportion to the number of positive nodes ≥4. Risk of DM was 14% for 4 positive nodes (vs 3.4%, P = .021), 18% for ≥5 positive nodes (vs 3.5%, P = .002), 22% for ≥6 positive nodes (vs 3.4%, P = .002), and 28% for ≥7 positive nodes (vs 3.4%, P < .001). Median positive nodes for pts with and without subsequent DM was 7 versus 2, P = .004. Number of nodes examined was similar between pts with and without DM (median 41). On univariate analysis, macroscopic/gross ECE was a predictor of DM, with 20% of these pts developing DM, vs 4.2% of pts with no or microscopic ECE (P = .007). Neither microscopic ECE nor clinical/pathologic stage predicted for subsequent DM. No pts with cN2c disease developed DM. A multivariable

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model revealed that the number of positive nodes (odds ratio [OR] 1.22, 95% confidence interval [CI] 1.07-1.40, \( P = .004 \)) remained a significant predictor of DM, while macroscopic/gross ECE was of borderline significance (OR 3.30, 95% CI 0.85-12.8, \( P = .084 \)). ROC analysis suggests that \( \geq 6 \) positive nodes is a reasonable cut-point for prediction of the risk of DM (AUC = 0.75). Pts with \( \geq 6 \) positive nodes had inferior 4-year distant metastasis-free survival (DMFS) and overall survival (OS) compared to pts with <6 positive nodes: DMFS 80% versus 95% (\( P = .002 \)) and OS 88% versus 97% (\( P = .022 \)).

**Conclusion:** The number of positive nodes appears to be the strongest predictor of DM in pts with pathologically staged HPV+ OPSCC undergoing primary surgery followed by adjuvant CRT. Pts with \( \geq 6 \) positive nodes have a 22% risk of developing DM and appear to have inferior OS than pts with fewer positive nodes. If validated, the number of positive nodes could be incorporated into a revised pathologic staging system for HPV+ OPSCC, to select pts for intensified or investigational adjuvant systemic therapy.


### 119

**CYFRA 21-1 as an Instant Prognostic Marker of Tumor Response on Radiation With or Without Chemotherapy in Patients With Larynx and Hypopharynx Squamous Cell Carcinoma**

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**Purpose/Objective(s):** Radiation therapy (RT) alone or in combination with chemotherapy (ChT) remains the standard nonsurgical approach for head and neck squamous cell carcinoma (HNSCC) patients. But in spite of a relatively high rate of complete tumor responses, locoregional relapse is still a major kind of treatment failure for HNSCC. The presence of survived SCC at the time of treatment completion seems to be very important to know in aspect of further intensification or salvage conduct, but current methods of discrimination between residual tumor and treatment-related outcomes are not suitable for such an instant need. From this point of view, in the present study, 2 serum markers, CYFRA 21-1 (CYFRA) and SCC Antigen (SCC-Ag), have been monitored over RT in patients with carcinoma of the larynx (LXC) and hypopharynx (HPC).

**Materials/Methods:** Ninety-three consecutive patients with LXC (73%) and HPC (27%) in stages T1 (8%), T2 (44%), T3 (30%), T4 (18%), and N0 (52%), N1 (6%), N2 (34%), and N3 (8%) were treated over 2 years, between 2009 and 2011 by RT alone (63%), concurrent RT/ChT (16%), and induction ChT followed by RT (14%) or concurrent RT/ChT (7%). Both CYFRA and SCC-Ag were estimated twice, before and at the end of the treatment.

**Results:** Both CYFRA and SCC-Ag pretreatment levels correlated directly with T and N stages. Generally, over the treatment CYFRA and SCC-Ag levels were decreased and increased, respectively. Median follow-up has been 36 months. Only for CYFRA levels estimated at the end of the treatment was a significant correlation with the outcome found: at that time CYFRA was elevated mainly in patients with partial remission (persistent tumor presented in primary or/and nodal site) with median 2.33 ng/mL, while patients with complete remission had lowered levels with median 1.65 ng/mL (\( P = .0001 \)). Thus, for patients who at the end of the treatment had a CYFRA level equal to or above 2 ng/mL, the probability of survival and OS was decreased (\( P <.001 \)).

**Conclusion:** Of the CYFRA and SCC-Ag potential markers, only the first one has prognostic value. When CYFRA 21-1 is measured at the end of the treatment (RT or concurrent RT/ChT), it seems to be a powerful prognostic marker for tumor response. In patients with LXC and HPC who undergo RT or RT/ChT, with or without induction ChT, persistent, uncured tumor is very feasible if a CYFRA level equal to or higher than 2 ng/mL is measured instantly at the end of the treatment.


### 120

**Weekly Versus Every-3-Weeks Platinum-Based Chemoradiation Regimens for Head and Neck Cancer**

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**Purpose/Objective(s):** The majority of chemoradiation (CRT) trials for locally advanced head and neck squamous cell carcinoma (HNSCC) have relied on platinum-based chemotherapy regimens administered every 3 weeks. However, given the increased use of weekly platinum regimens, it remains unclear how different chemoradiation schedules compare regarding efficacy and toxicity.

**Materials/Methods:** We identified 212 patients with HNSCC from a retrospective database who were treated at a single academic medical center with concurrent platinum-based CRT given weekly or every 3 weeks. One hundred forty-four patients received chemotherapy every 3 weeks, and 68 patients received chemotherapy weekly. JMP version 10 (SAS Institute) was used to perform statistical analysis using 2-sided tests and defining significance as \( P < .05 \). Discrete variables were compared with either the \( \chi^2 \) test, and differences in the medians were assessed using the Wilcoxon test. Survival curves were plotted using the Kaplan-Meier method, and significance was assessed using the log-rank test. For univariate analysis and multivariate analysis, we used Cox proportional hazard or logistic regression models to compare differences in survival or differences in categorical variables, respectively.

**Results:** Patients receiving weekly platinum regimens were more likely to have increased age (median: 61.4 vs 55.5 years; \( P < .001 \)), high or very high Charlson comorbidity index (45.6% vs 27.8%; \( P = .01 \)), and more likely to receive carboplatin-based regimens (6.3% vs 76.5%; \( P < .001 \)). The 2 regimens had similar locoregional control (hazard ratio 1.10, 95% confidence interval [CI] 0.63-1.88, \( P = .72 \)), disease-free survival (\( P = .28 \)), and overall survival (\( P = .71 \)). Platinum regimens delivered every 3 weeks were associated with increased days of hospitalization (median: 3 days vs 0 days; \( P = .03 \)) and acute kidney injury (AKI) during radiation therapy (50.0% vs 22.1%; \( P < .001 \)). On multivariate analysis, AKI was significantly associated with regimens delivered every 3 weeks (odds ratio [OR]: 24.38; 95% CI 3.00-198.03; \( P = .003 \)) and high comorbidity scores (OR: 2.74; 95% CI 2.15-5.99; \( P = .01 \)).

**Conclusion:** Our results suggest that platinum-containing CRT regimens delivered every 3 weeks and weekly have similar disease control, but weekly platinum regimens are associated with less acute toxicity.

**Author Disclosure:** J.M. Melottek: None. B.T. Cooper: None. M. Koshy: None. J.S. Silverman: None. M.T. Spiotto: None.

### 121

**All High Risk? Pathologic Extracapsular Extension (ECE) in the Era of Human Papillomavirus—Associated (HPV+) Head and Neck Cancers (HNC)**


**Purpose/Objective(s):** Pathologic extracapsular extension (ECE) is used to stratify risk and predict locoregional failure and death, respectively. The measurement of CYFRA 21-1 at the end of the treatment had 84% sensitivity and 67% specificity, and 57% and 88% of both positive and negative prognostic value, respectively.

**Conclusion:** Of the CYFRA and SCC-Ag potential markers, only the first one has prognostic value. When CYFRA 21-1 is measured at the end of the treatment (RT or concurrent RT/ChT), it seems to be a powerful prognostic marker for tumor response. In patients with LHC and HPC who undergo RT or RT/ChT, with or without induction ChT, persistent, uncured tumor is very feasible if a CYFRA level equal to or higher than 2 ng/mL is measured instantly at the end of the treatment.
Nodal ECE is an established risk factor for HNC recurrence and mortality; however, it is unknown whether ECE impacts outcomes for HPV+ HNC.

Materials/Methods: This was a retrospective multi-institutional comparative outcomes analysis by HPV/p16 status. Eligible patients had pathologic confirmation of ECE for HNC involving the oropharynx (OP), oral cavity (OC), or unknown primary (UP), and underwent curative-intent therapy. Patients with metastatic disease at diagnosis, unknown HPV/p16 status, or <3 month follow-up were excluded.

Results: From 2003 to 2014, 76 patients were eligible for this study. The median age at diagnosis was 60 years (range 29-82), with 46 involving the OP, 28 the OC, and 2 of UP. Forty-one patients (54%) had HPV+ tumors. All but 5 patients underwent therapeutic neck dissection, and the primary site was resected in 65 patients. For resected primary cases, 38, 23, and 4 patients underwent adjuvant chemoradiation therapy (CRT), radiation therapy (RT) alone, and no adjuvant therapy, respectively. For 9 patients who underwent definitive RT, 7 received concurrent CRT. Of note, 40% of HPV+ and 35% of HPV− patients did not receive chemotherapy (P = NS). The median number of nodes excised and involved were 27 (1-92) and 2 (1-32), respectively. At a median follow-up of 26.3 months (range, 1.4-104.0; median, 34.1 for survivors), 52 patients were alive (48 without recurrence, 4 with salvaged recurrence), and 21 patients had died (21 of HNCs). Patterns of failure included local (n = 6), regional (6), locoregional + distant (6), and distant only (4). In comparing the HPV+ and HPV− groups, disease-free and overall survival was superior for the HPV+ group (P < 0.01; Table 1). HPV+ patients were more likely to be male (93% vs 51%), undergo definitive RT (30% vs 20%), have higher stage disease (73% vs 49% stage IV), have larger nodal size (median 3.6 vs 1.9 cm), and be less likely to have undergone resection of primary (78% vs 94%). There were no differences in number of lymph nodes sampled or involved or in follow-up between the groups.

Conclusion: HPV+ HNC with ECE has a favorable prognosis despite more advanced stage and larger nodal burden. Prognosis in the HPV− population with ECE remains poor despite multimodality therapy (surgery with CRT). ECE in the HPV+ population should be re-evaluated as a negative prognostic factor and indicator for therapeutic escalation. It is noteworthy that approximately half of HPV+ patients in our population did not receive chemotherapy; further investigation of this is warranted, considering ongoing efforts at deintensification of therapy for this subpopulation.

Author Disclosure: J.K. Russo: Employee; CHI St Alexius. Director of Clinical Research; Bismarck Cancer Center. A. Snow: None. A. Terrell: None. S.L. Mott: None. M. Laszewska: None. A. Hetland: Partner; Mid Dakota Clinic. Shareholder, Board Member, Chair EMT; Compensiation Committee, Surgery Center Committee; Mid Dakota Clinic. B. Liu: Student; Sanford Medical School. C. Fischer: None. C.M. Anderson: Research adviser, uncompensated; Galera Therapeutics. T.A. Dufan: None. J.M. Watkins: Employee; University of Iowa.

### Abstract 121; Table 1

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### 122

WITHDRAWN

### 123

Subsite Variation in Oropharyngeal Squamous Cell Carcinomas in the Era of Human Papillomavirus: Tonsillar Fossa Has Improved Survival Compared to Base of Tongue

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Purpose/Objective(s): Previous studies on treatment outcomes of patients with advanced oropharyngeal squamous cell carcinomas (OPSCC) have rarely analyzed subsite differences in detail in the era of human papillomavirus (HPV). The purpose of this study was to evaluate subsite-specific differences in survival between squamous cell carcinomas (SCC) of the base of tongue (BOT) and the tonsillar fossa (TF) in a cohort likely to have a high incidence of HPV-associated tumors.

Materials/Methods: Retrospective cohort analysis utilizing data from the Surveillance, Epidemiology, and End Results (SEER) Program. The SEER cohort included 8073 primary BOT and TF SCC patients without distant metastases treated between 2004 and 2011. Primary outcome measures were subsite-based differences in overall survival (OS) and disease-specific survival (DSS). Cox proportional hazard ratios were estimated.

Results: Among the 8073 primary BOT and TF SCC patients, 3705 (46%) were BOT and 4368 (54%) were TF. Median age for BOT and TF patients was 62 and 58 years, respectively. Other clinical characteristics were similar between groups, but more TF patients had poorly differentiated tumors. Overall survival with all stages combined favored TF (P < 0.01) and remained superior when stratified by stage. In multivariate analyses adjusted for age, gender, race, and treatment, the hazard ratio (HR) for OS was superior for TF tumors in comparison to BOT tumors across all disease stages (stage I HR 1.28, 95% confidence interval [CI] 1.01-1.64; stage II HR 1.30, 95% CI 1.08-1.59; stage III HR 1.30, 95% CI 1.14-1.49; stage IV HR 1.14, 95% CI 1.00-1.30). Similar advantages were noted for DSS favoring improved outcomes for TF.

Conclusion: In this large, modern cohort, OS and DSS favored outcomes in TF as compared with BOT. Further study is required to evaluate factors that influence subsite-based survival differences in TF and BOT patients in the era of HPV.


### 124

Comparisons of Dysphagia and Quality of Life (QOL) in Matched Patients with HPV-positive Oropharyngeal Cancer Receiving Chemoradiation or Cetuximab and Irradiation

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Purpose/Objective(s): We compared functional outcomes of radiation therapy (RT) concurrent with cetuximab or with chemotherapy for matched, good prognosis patients with human papillomavirus-positive (HPV+) oropharyngeal cancer (OPC).

Materials/Methods: Outcomes of patients with HPV+ OPC with minimal or no smoking history and non-T4/N3/N2C, treated on a prospective protocol of RT concurrent with cetuximab (cet-RT), were compared with similar patients on prospective chemo-RT protocols. Intensity modulated RT in all patients aimed to spare swallowing organs and salivary glands. In both groups, videofluoroscopy (VF), Common Terminology Criteria for
Adverse Events (CTCAE) observer-rated dysphagia (ORD), and validated QOL questionnaires (Xerostomia Questionnaire [XQ], Head and Neck QOL, and University of Washington QOL) were performed before RT and 3 and 12 months following RT. Differences between treatment groups were assessed using t-tests, multiple linear regression, and repeated-measures analysis.

Results: Twenty-six cet-RT patients were matched to 27 chemo-RT patients with similar baseline characteristics. In the chemo-RT group (median follow-up of 52 months), no recurrences occurred. In the cet-RT group (median follow-up of 20 months), 1 patient had persistent microscopic disease on salvage neck dissection and 1 distant failure. Both groups had mild VF-based swallowing dysfunction before treatment, which worsened at 3 months (P < 0.02) and persisted at 12 months, and did not differ between treatment groups for any VF measures (P > 1.1). For both groups, CTCAE ORD was low before treatment: almost all were grade 0, worsened at 3 months (39% ≥ grade 1), and then improved at 12 months (16% ≥ grade 1). No differences in ORD were observed between treatment groups (P = 0.26).

QOL Summary and domain scores for eating were good before treatment, worse at 3 months, and then improved (P < 0.01) to near baseline at 12 months. No differences between the 2 groups were seen in any QOL domain (P > 0.10).

Conclusion: Both groups, matched for pretherapy factors, had excellent clinical outcomes without significant differences in objective or subjective functions. These data do not support using cetuximab instead of chemotherapy for treatment deintensification in HPV+ patients.


125

A Phase 1/2 Study of Nab-Paclitaxel, Cisplatin, and Cetuximab With Concurrent Radiation Therapy for Locally Advanced Squamous Cell Cancer of the Head and Neck

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Purpose/objective(s): Historic control rates for locally advanced head and neck cancer (HNC) are suboptimal and Nab-paclitaxel may improve the efficacy of radiation therapy (RT).

Materials/Methods: Concurrent nab-paclitaxel, cisplatin, cetuximab, and 70-Gy RT was evaluated in patients with HNC. Patients with stage III-IV, cT2N2-M0, T3-T4, any N0 of the oropharynx, hypopharynx, or larynx were eligible for this phase 1/2 trial. The phase 1 study determined the maximum tolerated dose (MTD) of nab-paclitaxel. The primary endpoint of the phase 2 component was 2-year progression-free survival (PFS).

Results: Median follow-up was 24 months for 34 patients enrolled. The MTD of nab-paclitaxel was 20 mg/m² when combined with 20 mg/m² cisplatin and 250 mg/m² cetuximab. The rate of acute grade ≥3 mucositis was 41%, dermatitis 24%, dysphagia 34%, and hematologic suppression 56%. The 2-year PFS was 60% (95% confidence interval [CI] 0.42-0.78), local control 71% (95% CI 0.55-0.87), and overall survival (OS) 68% (95% CI 0.50-0.86). Higher RT dose was associated with improved OS (hazard ratio [HR] 0.71, P = 0.047), and prolonged treatment time was associated with worse PFS (HR 1.36, P = 0.038) on multivariate analysis.

Conclusion: This is the first study evaluating cisplatin, cetuximab, and nab-paclitaxel in humans. This treatment regimen had similar PFS and toxicity as historic HNC combined modality trials.
**127**

The Effect of an Oral Care Intervention in Decreasing the Expression of Proinflammatory Cytokines in Patients Receiving Chemoradiation for Oral Cancer: A Randomized Clinical Trial


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**Purpose/Objective(s):** Oral mucositis (OM) is one of the most debilitating adverse effects in patients undergoing radiation therapy (RT), chemoradiation therapy, or both. Currently, there are no effective therapies or preventive treatments for OM; rather, most suggested treatments are palliative in nature. Physiologically, chemotherapy (CT) and RT evoke a profound inflammatory response, resulting in damage to the vascular endothelium. The release of proinflammatory mediators is responsible for mucosal injury and compromises the integrity of the protective epithelial barrier, which can result in an increased susceptibility to infection. The objective of this pilot study was to assess the effects of a novel oral care protocol on OM severity and to evaluate salivary proinflammatory cytokines in cancer patients undergoing RT or CT/RT.

**Materials/Methods:** A total of 16 subjects undergoing RT or CT/RT were enrolled prior to starting treatment. All subjects received a baseline standard of care oral/dental prophylaxis plus fluoride application prior to the start of RT or CT/RT. Patients were assigned to an oral health intervention group (IG) or control group (CG). Subjects assigned to the IG followed a biweekly treatment schedule in which they had their teeth brushed by a dental professional and were asked to follow standard of care (SOC) oral hygiene instructions at home. Subjects randomized to the IG received the Oral Mucosal Detergent and Periodontal Debridement (OMDP) protocol and attended weekly treatment visits at which they had their teeth brushed by a dental professional, periodontal debridement, tooth polishing, and flossing. Subsequently, the cleansing and deterring of the oral mucosal surfaces was performed using a soft-bristled toothbrush and an antibacterial agent (alcohol-free chlorhexidine mouth rinse). Subjects in the IG were instructed to continue to follow the OMDP protocol at home. Stimulated whole saliva samples were collected at baseline (prior to OMDP) and at the seventh day of the intervention. The levels of proinflammatory cytokines were measured.

**Results:** Salivary inflammatory biomarkers, noted in levels of IL-10, IL-12, IL-13, IL-4, and TNF-α, had a significant increase in the CG and reduced or stayed the same under IG.

**Conclusion:** These results suggest that overall inflammation was consistently higher as compared to baseline with control treatment and lower than or similar to baseline with the OMDP treatment, providing encouragement for the effectiveness of the oral care protocol as a coadjuvant treatment for this population.


**128**

Three-Dimensionally Printed Bolus in Head and Neck Electron Radiation therapy


Oregon Health and Science University, Portland, OR, Oregon Health & Science University, Portland, OR.

**Purpose/Objective(s):** When treating head and neck cutaneous or other superficial cancers with electron radiation therapy, custom bolus is often used to optimize dose distribution to improve treatment volume coverage and minimize dose to normal tissues. We aim to improve on this custom bolus technique with patient-specific 3-dimensionally printed bolus.

**Materials/Methods:** Following computed tomographic simulation, the patient DICOM imaging data is transferred to the radiation treatment planning system. Target volumes and organs at risk are contoured and a plan is created using a standard, noncustom bolus technique. Following completion of the standard plan, a custom bolus is then created as a DICOM-RT structure with forward planning in an attempt to decrease unnecessary dose to organs at risk and increase treatment volume coverage and dose homogeneity. Custom bolus is tagged with a marker to assist in orientation and alignment during patient setup. An in-house algorithm is then used to translate the custom bolus from DICOM-RT to stereolithography file format to transfer to a 3-dimensional printer.

**Results:** Our institution has successfully modeled custom bolus and converted the bolus to appropriate format for 3-dimensional printing; creating personalized bolus for individual patients that can be used in electron radiation therapy to the head and neck. Our preclinical model supports improved treatment volume coverage and decreased dose to normal tissues with the printed custom bolus. Images of the comparative dosimetric evaluation of the printed custom bolus to standard bolus electron radiation therapy will be presented.

**Conclusion:** We have developed a model to attempt to personalize head and neck electron radiation therapy with a 3-dimensionally printed custom bolus. This model is currently under preclinical testing for head and neck cancer.

Purpose/Objective(s): Oral mucositis (OM) is a very common side effect of head and neck radiation therapy (RT) and concurrent chemotherapy and radiation (CRT) leading to severe pain, infection, weight loss, higher rates of hospitalization, higher financial cost of treatment, and breaks in therapy resulting in increased morbidity and reduced treatment efficacy. The 2014 guidelines from The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer included a suggestion that low-level laser therapy (LLLT) was useful for the prevention of high-grade OM in patients receiving head and neck RT alone, but no comment could be made regarding its efficacy in the therapeutic setting for severe OM during RT or CRT. Our objective is to describe the technical aspects of the laser regimen we use in this setting and relate the qualitative experience we have had thus far.

Materials/Methods: Since 2013, 53 patients were referred to dentistry for laser therapy for significant and bothersome Radiation Therapy Oncology Group grade 2-3 OM, either during or after RT/CRT. Our regimen uses 2 lasers; a class IV Er, Cr: YSGG laser (λ = 2.780 µm), as well as a class IV diode laser (λ = 940 nm). The first laser is used to debride the entire surface of the ulcerated areas. Settings are 0.25 to 0.75 watts, 15 to 20 pps, 0 water, and 90 air flow rate. The next laser is then used as biostimulation for pain relief during CRT and for wound healing after CRT is completed. Instrument settings are 0.6 watts, 12 joules, continuous wave pulse (CW) for 20 seconds per site and 0.2 watts, (CW), 4 joules, 20 seconds per site for each situation, respectively. Treatments were administered once or twice weekly depending on severity and continued until complete resolution of ulcers.

Results: Forty-one patients started laser treatments either during or within 1 month of RT/CRT completion. Twelve patients initiated treatments over 1 month after RT/CRT completion. All patients experienced full clinical resolution of oral ulcers. The number of treatments patients received ranged from 2 to 15 with a median number of 7. Qualitatively, patients tended to report significant early pain relief, especially during the first 48 hours following laser treatments. Providers also felt that patients tended to heal more quickly once treatment was initiated, though, without a comparison group at this point, no definitive conclusion can be reached.

Conclusion: This report highlights the technical aspects of LLLT and our regimen for managing severe mucositis. Our qualitative experience thus far suggests benefits in pain relief and quicker recovery from severe mucositis. Additional studies are underway evaluating the feasibility, efficacy, and quality of life metrics.


132

A Comparative Study of Patient-Reported Quality of Life, Xerostomia, and Dysgeusia in Oropharyngeal Squamous Cell Carcinoma (OPSCC) Treated With Volumetric Modulated Arc Therapy (VMAT) or Proton Pencil Beam Scanning (PBS)

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Purpose/Objective(s): Treatment for OPSCC can affect a number of outcomes related to quality of life (QOL). We explore differences in measures such as xerostomia, dysgeusia, weight loss, pain, and overall

Author Disclosure: None.
1613 functional status in patients treated with either VMAT or PBS with and without cisplatin for OPSCC.

Materials/Methods: We examined 95 consecutive patients from April 2013 to November 2014 who were treated with definitive radiation therapy (RT) or adjuvant RT following transoral robotic surgery (TORS).

Individual ipsilateral and contralateral saliva-producing structures including parotid, submandibular, and sublingual glands, as well as buccal mucosa, tongue, hard palate, soft palate, and upper and lower lips were contoured. Patient-reported QOL questionnaires (n=229), including the European Organization for Research and Treatment of Cancer (EORTC)-QLQ30, EORTC-H&N35, Work Status, Dysgeusia, and GRiX xerostomia survey, were prospectively assessed at consult and during follow-up visits.

Results: Fifty-seven patients (60%) were treated with VMAT, and 38 patients (40%) were treated with PBS. Fifty-two patients (55%) were treated after TORS, and 23 (45%) with definitive RT or chemoradiation.

Patients were followed for a median of 6 months. PBS conferred a significant 1.4- to 11.3-fold decrease in dose compared to VMAT for contralateral parotid and submandibular glands, bilateral sublingual glands, buccal mucosa, tongue, hard palate, soft palate, and lower and upper lip. Forty-four patients (18 PBS) had 6-month follow-up questionnaires. At 6 months, 65% of patients treated with VMAT had moderate-severe xerostomia compared to 39% for PBS (P=.08), with no difference in mild-severe sticky saliva (54% VMAT vs 61% PBS, P=.63) or mild-severe appetite changes (42% VMAT vs 33% PBS, P=.55). There was a trend toward improved taste in patients treated with PBS (56% PBS vs 31% VMAT, P=.1) at 6 months. In the subset of patients who received cisplatin (n=24), PBS was associated with significantly higher global health domain scores (PBS 92 vs VMAT 77, higher number is better, P=.04), less pain (PBS 2 vs VMAT 18, P=.007), and lower painkiller use. To our knowledge this is the first study comparing VMAT and proton QOL outcomes in OPSCC patients. We are continuing to increase patient accrual and follow-up in this cohort. We aim to expand our current findings and report additional results in the near future.


133 Clinical Outcomes With Mucosal Sparing Radiation Therapy in Resected Oropharyngeal Cancer
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Purpose/Objective(s): Oropharyngeal cancer has been treated historically with either primary radiation therapy (RT) or open surgery with similar disease control and survival rates but a greater complication rate in patients (pts) treated with surgery. However, minimally invasive surgical approaches such as transoral surgery (TOS) have emerged with comparable oncologic outcomes and with organ preservation. Currently, there are ongoing efforts to develop risk-adapted therapies that can potentially deintensify treatment regimens for favorable groups like human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinomas (OPSCC). We report the outcomes of HPV-related OPSCC pts that underwent mucosal sparing RT in resected OPSCC.

Materials/Methods: We identified for the present institutional review board–approved analysis a subset of 40 pts treated at Mayo Clinic Arizona with TOS followed by neck only radiation using intensity modulated radiation therapy (IMRT). These were favorable-risk patients with negative margins, needing RT to secondary to risk factors in the neck: multiple positive lymph nodes, lymph nodes >3 cm, and/or extracapsular extension. The median age was 57.8 years. Thirty-eight pts (95%) had transoral laser microsurgery. Twenty-four pts (60%) had base of tongue tumors, and 16 (40%) had tonsillar tumors. The majority of the pts (70%) were documented to be HPV positive and had T1 N2b disease. T-stage distribution was as follows: T1, 27 pts (67%); T2, 12 pts (30%); and T3, 1 pt (3%). N-stage distribution was as follows: N1, 4 pts (10%); N2a, 4 pts (10%); N2b, 27 pts (67%); and N2c, 5 pts (13%). Therefore, 90% of pts had N2 disease. Twenty-three pts (57%) received concurrent chemotherapy, consisting of cisplatin in 18 (78%) pts and 5 (22%) pts with cetuximab.

Results: The median follow-up for surviving pts was 51 months (range, 13-155 months). The median RT dose to the neck was 6000 cGy (range, 5400-6400 cGy). There were no local failures and only 1 regional failure, resulting in 97.5% locoregional control at 4 years. Two pts developed distant metastatic disease, without evidence of locoregional recurrence, for a 4-year overall survival of 97%. The 4-year recurrence-free survival was 94%. RT-related acute toxicities were grade 2 dysphagia in 5 pts (12%). Only 1 patient was percutaneous endoscopic gastrostomy tube dependent at 1 year, but none were dependent at last follow-up. Xerostomia grade ≥2 was noted in 7 pts (17%), oral mucositis grade ≥2 in 4 pts (10%), neck stiffness in 2 pts (5%), and trismus in 1 pt (2.5%).

Conclusion: Our analysis suggests that mucosal sparing RT after TOS in oropharyngeal cancer pts provides comparable oncologic and improved functional outcomes in selected pts. Sparing the mucosal surface of the primary site appears feasible without impacting on survival or locoregional control. This new treatment paradigm in resected OPSCC is promising and requires further validation through a prospective trial.


134 The Use of Predictive Modeling in Adaptive Radiation Therapy for Head and Neck Cancer
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Purpose/Objective(s): Adaptive radiation therapy (ART) can account for the dosimetric impact of anatomical and tumor changes throughout the course of chemoradiation for locally advanced head and neck cancer (HNC). However, it is time- and resource-intensive, making identification of patients most likely to require ART of vital importance. Logistic regression enables prediction of the risk of events occurring, and classification and regression tree (CART) analysis is a simple analytic tool that helps determine the key variables in a population to design an explanatory model. This makes them attractive tools to use in the setting of HNC ART. We sought to investigate the utility of logistic regression modeling and CART analysis in developing predictive models for HNC patients likely to benefit from ART.

Materials/Methods: Patients with node-positive oropharyngeal squamous cell carcinoma (OPC) and nasopharyngeal carcinoma (NPC) treated with curative-intent chemoradiation were enrolled prospectively in the study. Patients underwent a second planning computed tomographic scan if the...
change in external contour between the planning scan and daily treatment scan was $>1$ cm. The dosimetric impact was assessed and a replan generated if target volume coverage was inadequate or organs at risk dose exceeded tolerance. Patient demographics and tumor characteristics were recorded and compared between patients who were replanned and those that were not. Univariate and multivariate analyzes were performed and factors found to be significant for replanning included in logistic regression and CART analysis. To assess the logistic regression and CART analysis with larger patient numbers, it was repeated on all patients who underwent a second planning scan, making the assumption that this scenario always necessitates replanning.

**Results:** One hundred and ten patients were enrolled between October 2013 and December 2014. The majority were OPC (84.5%) and male (91.8%) and they were predominantly classified at the T2 (33.6%) and N2 (80%) stage. Twenty-one patients (19.1%) underwent a second planning scan, and of these, 5 (4.5%) patients underwent a replan. Nodal disease stage, pretreatment size of the largest node, diagnosis (P < 0.01), and initial weight (categorized in 2 groups) (P < 0.07) were identified as significant for inclusion in the logistic regression model predicting the need to replan. When the percentage of patients replanned was increased, nodal disease stage (P = 0.06), pretreatment size of the largest node, diagnosis, initial weight, and percentage weight change (P < 0.01) were identified as significant for inclusion in the logistic regression model.

**Conclusion:** Predictive modeling, using logistic regression and CART analysis, can be utilized in the identification of OPC or NPC patients more likely to require ART. This could facilitate the efficient implementation of ART resulting in the appropriate allocation of institutional resources.

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**135 Comprehensive Geriatric Assessment as a Predictor of Tolerance, Quality of Life, and Toxicity in Older Patients Receiving Radiation Therapy**

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**Purpose/Objective(s):** Comprehensive geriatric assessments (CGA) predict toxicity from chemotherapy and surgery. This study’s purpose is to evaluate associations between dysfunction as measured by a CGA and tolerance to treatment, changes in quality of life (QOL), and patient-reported symptoms (PRS) in patients with lung or head and neck cancer (HNC) receiving radiation therapy (RT) or chemoradiation therapy (CRT).

**Materials/Methods:** We conducted a prospective observational cohort study, evaluating the predictive value of CGA in eligible patients 65 years and older with HNC or lung cancer undergoing curative-intent RT or CRT. Pretreatment CGA, QOL (European Organization for Research and Treatment of Cancer QLQ-C30), and PRS (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events) were obtained. Questionnaires were repeated biweekly during RT and at 6 weeks posttreatment. Dysfunction was defined as scores $<14$ on the Instrumental Activities of Daily Living (I-ADL) scale. Poor tolerance to treatment was defined by hospitalization, $>3$ day treatment delay, change in RT or CRT regimen, and death. Associations between I-ADLs and QOL changes between baseline and end of RT as well as end of RT to 6 weeks postradiation were evaluated. Associations between I-ADL $< 14$ and tolerance to RT as well as PRS ratings were also evaluated. Fisher exact test was used.

**Results:** Of the 50 patients accrued, 46 had evaluable data. Mean age was 72.5 years (range 65-92). Sixty-one percent had HNC. Forty-six percent received CRT. At baseline, 37% had I-ADL $< 14$. Thirty-five percent required a gastronomy (G)-tube. Thirty-nine percent had poor tolerance to RT or CRT. There was no association between I-ADL $< 14$ and tolerance. HNC patients with I-ADL $< 14$ required a G-tube more often than those with I-ADL = $14$ (86% vs 45%, P = 0.09). Complete QOL data through the end of RT were available for 77% and through post-RT follow-up for 50%. Patients with I-ADL $< 14$ had lower baseline QOL scores (Global Health Status Domain [GHS], P < 0.01). From baseline to end of RT those with baseline I-ADL $< 14$ had less of a decline in Role Functioning (RF) (P = 0.01) and Social Functioning (P = 0.03) domains. However, from the end of RT to the 6-week follow-up, those with I-ADL $< 14$ were more likely to continue to drop and less likely to improve in the RF (P = 0.02) and Social Functioning (P = 0.03) domains. I-ADL $< 14$ at baseline was also associated with higher severity of PRS shortness of breath (P < 0.01), pain (P < 0.01), loss of taste (P < 0.01), cough (P = 0.04), dry skin (P = 0.02), anxiety (P = 0.05), depression (P = 0.01), and concentration interference (P = 0.02) during RT.

**Conclusion:** Pretreatment functional deficits were associated with continued decline and lack of recovery of QOL in this patient population. Furthermore, patients with pretreatment functional deficits reported higher severity of symptoms. Larger studies could further elucidate the CGA’s predictive value.

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**136 Skin Cancer of the Head and Neck With Perineural Spread: Patterns of Failure**

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**Purpose/Objective(s):** To analyze patterns of failure of patients with head and neck cutaneous squamous cell carcinoma (HNCSCC) with radiological or gross cranial nerve involvement (GCNI), microscopic focal perineural invasion (MFPNI), and microscopic extensive perineural invasion (MEPNI) managed with or without radiation therapy (RT).

**Materials/Methods:** After a review of charts, we identified RT plans and radiologic studies of 106 patients with HNCSCC with PNI or GCNI who were either observed or treated from 2000 through 2013 with adjuvant RT. The pathology specimens were prospectively reviewed by the study’s pathologist (J.M.). Cox proportional hazards models were used to estimate disease-free survival (DFS) and recurrence-free survival (RFS).

**Results:** Median follow-up for all patients was 19.8 months. In patients treated with RT, the skin tumor bed was irradiated together with ipsilateral lymph nodes. Median dose to gross disease was 66 Gy and 60 Gy to the course of nerves and structures that were judged at risk. Chemotherapy was used with RT in 24 cases. Thirty-five patients had GCNI: the involved nerves were the facial and the branches of the trigeminal nerves. GCNI distribution was as follows: single nerve involvement, 11 patients, and >1 nerve GCNI, 14 patients. Clinical target volume (CTV) included the involved cranial nerves, in 95% additional high-risk nerves (cranial nerves VII and V1-V3), and in 83% base of skull ganglions were treated electively. Thirteen of 35 (37%) patients with GCNI failed in the treated nerves in-field, of whom 2 also failed in previously untreated neural ganglions, and 2 pts failed along nerves not electively treated that communicate with involved nerves. Seventy-eight percent of patients with gross cranial involvement at presentation have failed in-field within the ganglions. No relapses occurred in the electively irradiated neural ganglions and cranial nerves. Nineteen of thirty patients (63%) with MEPNI in the skin specimens without evidence of GCNI were treated with RT. CTV in...
these cases included nerves innervating the involved skin dermator but not SBG. Seventy-three percent of observed patients and 31% of irradiated patients with MEPNI recurred. Two years RFS in nerves (94% vs 25% respectively; hazard ratio [HR] 0.06, 95% confidence interval [CI] 0.006-0.5, \( P = 0.01 \)) and DFS (73% vs 40%; HR 0.32, 95% CI 0.1-0.99, \( P = 0.05 \)) rates were significantly higher in the treated MEPNI pts compared with the observed. Twenty-seven of 37 patients (73%) diagnosed with MFPNI were observed; the rest were treated with RT. Patients with MFPNI had a low rate of neural and overall failure, and there was no significant benefit to irradiation in these patients.

**Conclusion:** Our study demonstrates the patterns of failure and the role of RT for patients with HNCSCC, GCNI, MEPNI. Awareness of these patterns and knowledge of the cranial nerves should serve as guidelines for target volume delineation. In patients with MEPNI, RT is associated with fewer gross perineural recurrences and better DFS, compared with the observation strategy.

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### 138

**Continuity of Care Follow-up Update: Results of a Consensus**

**Multidisciplinary 8-Week Posttreatment Pharyngeal Cancer Response Evaluation Algorithm**

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**Purpose/Objective(s):** Patients with human papillomavirus (HPV)-associated cancers are often treated with multimodality therapy; they have excellent overall survival with expectations of long follow-up for both recurrence and toxicity. In an effort to standardize routine surveillance, decompress clinic volumes, and reduce resource utilization, the Continuity of Care (COC) pathway was created. COC is a rotating schedule among all physicians and imaging obtained at regular intervals to 2 years and then a transition to survivorship clinic. This study presents an analysis of pathway compliance for the first posttreatment COC visit and whether encounter appropriately triages patients for further assessment of regional disease persistence and/or lymphadenectomy.

**Materials/Methods:** The COC project began enrollment in May 2012. Those patients dispositioned to definitive (chemo)radiation at the multidisciplinary tumor board were identified as eligible. The majority of patients were stage III or IV, and COC pathway was designed to assess the locoregional status at 8 weeks posttreatment by all pro-

**Results:**

In the first year, there were 131 eligible patients with oropharynx or unknown primary cancers. At the posttreatment 8-week visit, 2 patients (1.5%) had planned neck dissections, and 129 (98.5%) had routine imaging. This single evaluation found 66 patients (50.4%) to have no evidence of disease in both the primary and cervical lymphatics; they were transitioned directly to COC follow-up. Ten patients (7.6%) were taken to surgery, and 53 patients (40.5%) were scheduled for an interim visit. At the interim visit, 51 were found to have no evidence of disease and went to routine COC follow-up; only 2 went to surgery. Of the entire cohort, only 14 patients (10.7%) had surgery; 10 had no tumor, 1 had PTC, 1 had persistent primary disease, and 2 had persistent neck disease.

**Conclusion:** The COC pathway was developed to create standardized cancer surveillance for the head and neck patients. These results show that an 8-week posttreatment visit with CT imaging is an optimal early assessment of tumor response, with the majority of patients being able to transition directly to routine follow-up. For those with ambiguous findings, there is adequate time for additional imaging or early surgical intervention. Continued assessment of this standardized process will assess the value of routine imaging as well as tumor prognosis.
Selective sparing of the submandibular gland when targeting level Ib lymph nodes is included in the radiation target volume: a safety and toxicity analysis in cancers of the oropharynx and oral cavity.

Materials/Methods: We identified 174 patients with squamous cell cancer (SCC) of the oral cavity or oropharynx, with T1-2, N0-3, M0 disease in whom at least a single level Ib lymph node region was included in the target volume. All patients were treated from 2009 to 2014 with definitive or postoperative intensity modulated radiation therapy with or without chemotherapy. Patients with recurrent disease, or who were treated with reirradiation or a split course technique were excluded. Patient, tumor, and treatment-related factors were abstracted from the medical record. The treatment plans for each patient were reviewed and verified for level Ib targeting (unilateral vs bilateral) as well as if the submandibular gland was excluded from the target volume and sparing was attempted during planning. Mean doses were calculated for each submandibular gland and the oral cavity.

Results: A total of 174 patients met criteria for inclusion. Patients had a median age of 59 years and median KPS of 90 at diagnosis. One hundred and forty seven patients had SCC of the oropharynx, and 27 patients had SCC of the oral cavity. One hundred and thirty-four patients were treated definitively while 40 were treated postoperatively. Of the 174 included patients, 142 were treated with concurrent chemotherapy. Among the 190 level Ib LN stations that were deliberately targeted in the clinical treatment volume, 32 submandibular glands were contoured, excluded from the target volume and sparing was attempted during planning. Mean doses were calculated for each submandibular gland and the oral cavity.

Conclusion: Selective sparing of the submandibular gland when targeting the level Ib nodes in oral cavity and oropharynx cancer is feasible, reduces the mean doses to submandibular glands and oral cavity, and does not result in increased level Ib nodal failure rates. Future studies with larger numbers are needed to validate this preliminary finding and examine the impact of this technique on functional outcomes.

Initial Clinical Outcomes From a Prospective Phase 1 Trial of Hypofractionated Stereotactic Body Radiation Therapy for Early-Stage Glottic Larynx Cancer

Purpose/Objective(s): The primary objective of this trial is to confirm safety and feasibility of hypofractionated stereotactic body radiation therapy (SBRT) for early-stage laryngeal cancer and to determine the most rapid fractionation scheme tolerated without dose-limiting toxicity (DLT).

Materials/Methods: Seventeen consecutive patients with a diagnosis of carcinoma in situ, or T1a-T2N0M0 carcinoma of the glottic larynx...
cancer were enrolled in this institutional review board–approved single-institution prospective phase 1 clinical trial. Patients required biopsy-proven squamous cell carcinoma histology or squamous cell variants (sarcomatoid, verrucous, basaloid, and papillary subtypes) involving the true vocal cord. Absence of DLT permitted enrollment in incrementally shorter bioequivalent fractionation schedules starting with 50 Gy in 15 fractions (fx), followed by 45 Gy in 10 fx and 42.5 Gy in 5 fx. Maximum combined clinical target volume (CTV) and planning target volume (PTV) expansion was limited to 5 mm beyond involved laryngeal structures. Patients were treated daily in the 50 Gy in 15 fx arm, and every other day, up to 3 times per week in subsequent arms, with robotic radiosurgery.

Results: Median follow-up interval was 8 months (range: 1.9-18.6 months), with 5 patients followed for at least 1 year. The study cohort enrolled 16 males and 1 female with a median age of 61 years (range: 46-93 years). There were 11 former smokers, 2 never smokers, and 4 who continued smoking during and following treatment. Stage distribution was 12 cT1 (71%) and 5 cT2 (29%). Mean gross tumor volume, CTV, and PTV were 1.94±1.88, 3.93±2.23, and 8.63±5.69 cm³, respectively. The first 4 patients received 50 Gy in 15 fx, and the next 13 patients received 45 Gy in 10 fx, all without DLT. At median follow-up, local control was 92%; however, 2 patients with cT2 subglottic disease developed recurrence in the high-dose region requiring salvage laryngectomy. Two additional patients with cT1 disease required laryngectomy for persistent or invasive disease, again in the high-dose region. No marginal misses have occurred. Maximum treatment-associated toxicity was grade 3 dysphagia in 1 patient treated with 45 Gy in 10 fx who continued to smoke >1 pack per day after treatment and required protective tracheostomy for grade 4 laryngeal edema. Overall survival is 100%.

Conclusion: Hypofractionated SBRT for early-stage laryngeal cancer appears safe and feasible at our first 2 fractionation levels. Disease control appears comparable to standard treatment, although as expected, unfavorable cT2 tumors with subglottic extension remain at higher risk for local failure at these fraction sizes. Patients who continue to smoke heavily may be at higher risk for SBRT-associated toxicity. We are currently enrolling patients at a fractionation schedule of 42.5 Gy in 5 fx, with analysis ongoing.


Impact of Post-Chemoradiation Therapy Selective Neck Dissection on Patient-Reported Quality of Life

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Purpose/Objective(s): Neck dissections are often performed after definitive chemoradiation therapy (CRT) and may add morbidity. There is a lack of patient-reported quality of life (QOL) data for post-CRT neck dissections. We herein report prospectively collected QOL outcomes in patients with human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma enrolled on a multi-institutional phase 2 clinical trial who underwent CRT followed by selective neck dissection (ND).

Materials/Methods: Inclusion criteria were (1) T0-3, N0-2c, M0; (2) HPV+ or p16+; and (3) minimal smoking history. Patients received 60-Gy intensity modulated radiation therapy (IMRT) with concurrent weekly cisplatin, followed by biopsy of the primary site and selective ND of (at least) pretreatment-positive lymph node levels. Patients receiving more than a biopsy at the primary site were excluded from this analysis. Patient-reported QOL outcomes were obtained pre-CRT, 6 weeks post-CRT (pre-ND), and at acute and late post-ND timepoints.
We used the following questionnaires: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (general QOL), EORTC H&N-35 (head and neck—specific QOL), EAT-10 (swallowing), and NDII (neck dissection impairment index). We compared post-CRT and post-ND composite and itemized scores using 2-tailed t tests.

Results: Thirty-eight enrolled patients had a neck dissection, performed at a median of 9 weeks post-CRT. Pretreatment N stage was 10 N1/N2a, 23 N2b, and 5 N2c. Median number of levels dissected was 2 (range, 1-6) and median number of nodes dissected was 12 (range, 1-46). Five patients had bilateral ND. Median time from ND to postoperative assessment was 2 months (range, 1-7 months) for acute and 18 months (range, 8-37 months) for late timepoints. There was a significant worsening of the neck dissection impairment index (NDII) score from post-CRT to acute (87.4 vs 80.2, P = .023) but not late (P = .558) post-ND timepoints. The acute decrease in the NDII was greater in patients with >12 nodes dissected (P = .007) and was overall correlated with the total number of nodes dissected (Spearman P = .027). Overall EORTC-QLQ-C30, H&N-35, and EAT-10 scores did not worsen post-ND.

Conclusion: The use of post-CRT selective neck dissection did not worsen general (EORTC QLQ-C30), head and neck—specific (EORTC QLQ-H&N 35), or swallowing (EAT-10) QOL scores. An instrument designed to assess the specific impact of neck dissection (NDII) on QOL did show a significant decrease in acute, but not late NDII QOL score after neck dissection with a greater acute decrement associated with a higher number of dissected nodes.


145

Identifying Predictors of Extraprocutal Extension (ECE) in Patients Considering Primary Surgery for Human Papillomavirus—Associated Oropharyngeal Squamous Cell Carcinoma (OPSCC)

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Purpose/Objective(s): Patients with OPSCC often have a choice between primary resection (with risk-adapted adjunct therapy) versus primary chemoradiation (CRT). Human papillomavirus (HPV)-associated OPSCC tends to present with more advanced nodal disease with relatively small primaries, so presence or absence of ECE is often a key determinant of whether adjuvant chemotherapy is recommended in addition to radiation. Our goal was to determine whether nodal size is a significant risk factor for ECE in this population.

Materials/Methods: This is a retrospective analysis of patients with node-positive OPSCC that underwent neck dissection in an integrated health care system from January 2009 to June 2014. Cases were identified from the institutional tumor registry, which is part of the Surveillance, Epidemiology, and End Results program. Data were collected from both institutional electronic databases and medical chart review. Patients were excluded if they had radiation or excisional biopsy prior to neck dissection. Pathology reports were reviewed for HPV status (based on IHC for p16 or HPV), presence or absence of ECE, size of largest involved node, and number of involved nodes. Bivariate analyses were conducted to compare clinical characteristics by whether or not ECE was present using X² or Fisher exact tests for categorical variables and t tests, analyses of variance, and nonparametric tests for continuous variables.

Results: We identified 95 patients with node-positive OPSCC who underwent neck dissection prior to any radiation or chemotherapy. Of these, 11 were excluded due to missing data on HPV status. Of the remaining 84, 78 (93%) had HPV-associated disease, and among these, 23 (29.5%) were found to have ECE on final pathology. There was no significant association between nodal size and probability of ECE. In particular, there were 10 patients with a single involved node >4 cm in size, and none was found to have ECE. However, patients with multiple involved nodes appeared more likely to have ECE than those with a single involved node (50 vs 12%, P < .001).

Conclusion: Among patients with HPV-associated OPSCC, large nodal size does not appear to be associated with an increased risk of ECE. On the other hand, having multiple positive nodes is associated with an increased risk of ECE. Patients with a single large node (ie, N2a disease) that opt for primary surgery may have a relatively low risk of ECE and thus may have a good chance of avoiding adjuvant concurrent chemotherapy.

increase in maximum dose to 1 mL of the high-risk PTV was 3.47 Gy ($P = .0008$) and 2.66 Gy ($P = .034$), respectively. Nine of the 12 model-based plans failed compliance criteria for minimum dose due to stringent dose coverage criteria specified by clinical trial protocols; however, all plans were deemed clinically acceptable. Optimization times were reduced from 75 minutes for manual optimization to 10 minutes for automated optimization.

**Conclusion:** Complex head and neck plans created using a knowledge-based treatment planning model provided overall increased sparing of organs at risk with clinically acceptable dose coverage and uniformity. The automated optimization significantly increased planning efficiency over the more traditional manual optimization process. However, a generalized head and neck model may be insufficient to meet minimum dose criteria specified by many clinical trial protocols and may require manual intervention to meet compliance.

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### 148

**Nodal Yield Threshold for Early-Stage Clinically Node-Negative Oral Cavity Cancer**

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**Purpose/Objective(s):** A recently published randomized study demonstrated the superiority of an elective neck dissection over a therapeutic (salvage) neck dissection for patients with early-stage oral cavity cancer. Further data have shown that resection of at least 18 lymph nodes improves outcomes for patients with head and neck cancer. We hypothesized that for early-stage oral cavity cancer, a lower threshold of resected nodes would be adequate to confer survival benefit.

**Materials/Methods:** We retrospectively reviewed 551 consecutive patients treated at our institution from 1998 to 2013 for oral cavity squamous cell carcinoma with surgical resection followed by adjuvant therapy if indicated. Patients treated for recurrent disease and metastatic disease were not included. For this study, we included patients with T1 or T2 tumors who were clinically node-negative and underwent a neck dissection as part of their primary surgical treatment. We used iterative Kaplan-Meier modeling to determine the number of resected nodes that would confer a survival benefit in this cohort. We then used a Cox regression model to control for pathologic and demographic factors known to affect prognosis.

**Results:** A total of 81 patients met the inclusion criteria for this cohort study with the following breakdown by subsite: 68% oral tongue, 19% floor of mouth, 6% buccal mucosa, 5% alveolar ridge, 1% retromolar trigone, 1% lip, and 0% hard palate. Iterative modeling revealed a survival benefit in patients who had at least 10 lymph nodes resected ($P = .006$). Only 13 patients had fewer than 10 lymph nodes resected. Sixty-one percent of these patients were pathologically node-negative compared to 71% in those with more than 10 lymph nodes resected ($P = .005$). Locoregional failure at 2 years was 26% versus 40% in patients with 10 or more versus fewer than 10 lymph nodes resected, respectively ($P = .005$). When stratified by perineural invasion (PNI), patients with the best overall survival were those without PNI who had at least 10 nodes resected (2-year overall survival [OS] 91%). Patients with PNI who had at least 10 nodes resected (2-year OS 79%) did no better than those with fewer than 10 nodes resected regardless of PNI status ($P = .01$). After controlling for PNI, depth of invasion, poor differentiation, lymphovascular invasion, and active smoking status at diagnosis, the effect of fewer than 10 lymph nodes resected was still significant (hazard ratio 2.9, $P = .05$).

**Conclusion:** Even for early-stage clinically node-negative oral cavity cancer, there may be a nodal yield threshold that defines an adequate neck dissection. Our data suggest that this threshold is 10 lymph nodes.

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### 149

**The Role of Brachytherapy in Treatment of Oral Tongue Cancer**

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**Purpose/Objective(s):** Brachytherapy (BT) is a useful modality in both the definitive and adjuvant treatment of oral tongue cancer either as stand-alone treatment or in combination with external beam radiation therapy (EBRT), surgery, and/or chemotherapy whether in the primary or recurrent setting. It can be used as a boost treatment to de-intensify the dose of EBRT, as a definitive treatment option alternative to surgical management, and as a stand-alone adjuvant therapy in patients with positive surgical margins.

We review our 10-year experience.

**Materials/Methods:** Between January 2004 and December 2014, 39 patients (pts) with oral tongue cancer received Ir-192 LDR BT as part of their treatment course. Pt characteristics were as follows: median age of 53 years (range 20-88); 27 males, 12 females; T stage: 20 T1, 15 T2, 1 T3, 2 T4, 1 multifocal; N stage: 26 N0, 4 N1, 4 N2, 5 N3; 31 newly diagnosed (18 T1, 10 T2, 1 T3, and 2 T4); and 8 recurrent (3 T1, 4 T2, and 1 T4 multifocal). The combination of EBRT and BT was prescribed for 20 pts, and 19 pts received BT alone. Eight pts were treated definitively with EBRT+BT (n = 6; T2N0, multifocal primary, T2N2h, T3N0, T4N1, T4N2c) or with BT and neck dissection (n = 2, both T2N0). Thirty-one were treated adjuvantly with EBRT+BT (n = 14) or with BT alone (n = 17). Indications for EBRT were elective nodal RT (n = 3), LN+ (n = 3), PNI (n = 7), and recurrence (n = 1). In the pts receiving adjuvant BT only, indications for BT were close/positive margin (n = 11), PNI (n = 2), or both close/positive margin+PNI (n = 4). Four of 17 adjuvant BT only pts did not have elective node dissection (LND), while 13 did have LND. The median EBRT dose was 54 Gy (30.6-70 Gy), and 1 pt received protons. The median BT dose in the EBRT+BT group was 20 Gy (10-27 Gy). The median BT dose in the BT alone group was 45 Gy (30-60 Gy). The median number of catheters used was 4 (2-12). Tracheostomy was performed in the majority of pts, and 8 pts also had neck dissection at the time of BT catheter placement. Nine pts in the EBRT+BT group received systemic therapy.

**Results:** For the entire cohort, the median follow-up is 40.5 months (7-118 months). The 3-year local control (LC), regional control (RC), and overall survival (OS) is 88%, 75.4%, and 83%, respectively. Among the definitive treated pts, 3-year LC, RC, and OS is 100%, 85.7%, and 60%, respectively. Among the 14 treated with adjuvant EBRT+BT, the 3-year LC, RC, and OS is 91.7%, 78.8%, and 100%, respectively. Among the 17 pts receiving adjuvant BT alone, 3-year LC, RC, and OS is 82%, 67.3%, and 84.6%, respectively. Among this subset, LND impacted on regional control (3-year RC 84% vs 25%, $P = .017$).

**Conclusion:** Oral tongue BT offers the potential for highly individualized treatment in multiple clinical scenarios. It offers highly conformal therapy as definitive or adjuvant therapy either as a boost or stand-alone therapy. High local control rates can be achieved in pts with positive margins with BT alone. LND is important to maintain high levels of regional control particularly in those receiving BT alone.

**Author Disclosure:** J. Chadha: None. K. S. Hu: None. A. Jacobson: None. M. Persky: None. S. Schantz: None. T. Tran: None. M. Urken: None. Z. Li: None. B. Culliney: None. L. B. Harrison: None.
Purpose/Objective(s): In ATSHNSCC, direct comparisons between definitive treatment regimens are lacking. From 1998 to 2003, the chemoradiation regimen employed was FHX, while from 2004 to 2009 it was CRT. To investigate whether one of these regimens was superior, we performed a review of patient outcomes that included overall survival (OS), disease-free survival (DFS), and long-term toxicity (LTT).

Materials/Methods: The institutional review board approved this study, and the institution’s tumor registry database was queried for all patients (pts) with T3 or T4 ATSHNSCC. Medical records were examined for variables that included age, race, gender, and Eastern Cooperative Oncology Group performance status (PS). Tumor-specific data included subsite, stage, grade, treatment received, date of last follow-up, recurrence, and/or death. The following LTT’s were assessed: difficulty speaking (DS), difficulty eating (DE), feeding tube placement (FT), tracheotomy (TO), mandibular osteoradionecrosis (MORN), mucocutaneous fistula (MCF), dry mouth (DM), and soft-tissue fibrosis (STF).

Results: Three hundred and seventeen pts met eligibility and are included in this analysis. Median age is 57 years. Gender (%): 75 males and 25 females. Race (%): 35 Caucasian (C), 47 African American (AA), 12 Hispanic (H), 3 Asian (A), and 3 other (O). PS (%): 0 = 35.6, 1 = 54.5, 2 = 9.6, and 3 = 0.4. A 1° subsite (%): oral cavity (OC) 26.1, oropharynx (OP) 37.1, larynx 18.2, nasopharynx (NP) 5.4, and hypopharynx (HP) 10.4. Tumor grade (%): high 19.2, moderate 65.1, and low 15.7. T stage (%): T1 = 5.6, T2 = 10.4, T3 = 34.4, and T4 = 50.0. The ratio of pts receiving FHX to CRT was 3:1. There was a higher percentage of advanced PS (2 and 3) in FHX versus CRT-treated pts. A higher percentage of FHX treated pts had OC 1° (31 vs 14) and CRT treated pts had a higher percentage of OP 1° (34 vs 48) tumors. There was no significant difference in median survival (MS) between treatment groups (FHX 6.7 vs CRT 6.4 years). Kaplan-Meier survival analysis showed no difference in (%) OS (43 vs 50) or DFS (74 vs 60) between FHX- and CRT-treated pts. Differences were seen in the rate of LTT DE, which was more frequent in CRT- versus FHX-treated pts (83.3 vs 66.4%). There was a higher frequency of DM and FT in CRT- versus FHX-treated pts (41.1% vs 33.3% and 66.7% vs 58.5%, respectively). MORN was more frequent with FHX- (12.9%) versus CRT-treated pts (4.2%). There was no difference in outcome by race except DM was less frequent (%) in AA (24.6) versus C (42.4), H (48.2), or A/O (50%).

Conclusion: In ATSHNSCC, no survival outcome differences were seen between FHX- and CRT-treated patients. Some differences in LTT were seen.

Abstract 152; Table 1

<table>
<thead>
<tr>
<th>Parotid dosimetric indices</th>
<th>None/mild/moderate dry mouth (n=36)</th>
<th>Severe/very severe dry mouth (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmean</td>
<td>24.1±6.0 Gy</td>
<td>29.0±8.7 Gy</td>
</tr>
<tr>
<td>V30</td>
<td>27.5±2.0%</td>
<td>41.7±21.3%</td>
</tr>
<tr>
<td>WARPF</td>
<td>34.9±18.4%</td>
<td>49.0±18.9%</td>
</tr>
</tbody>
</table>

patient-reported outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Patients reported the severity of the dry mouth (none, mild, moderate, severe, or very severe). We correlated individual patient dosimetric data from the contralateral parotid gland to their 6-month posttreatment dry mouth PRO-CTCAE responses. Severe/very severe responses were considered clinically significant and were used as the cut point for our analyses. We specifically assessed parotid: Dmean, V30, and the weighted average reduction of the regional parotid function (WARPF). WARPF is a quantity that is calculated by weighting each dose of the parotid dose-volume histogram (DVH) using a regional parotid function reduction curve. Performance of these dosimetric indices was assessed through the area under receiver operating characteristic curve (ROC).

Results: Average parotid Dmean, V30, and WARPF for patients reporting severe/very severe versus none/mild/moderate dry mouth are shown in Table 1. The corresponding values of the area under the ROC curve for Dmean, V30, and WARPF were 65.9%, 70.2%, and 73.8%, respectively.

Conclusion: Patients who report severe/very severe dry mouth 6 months post deintensified CRT had on average higher contralateral Dmean, V30, and WARPF values. WARPF performs better as descriptor for patient-reported dry mouth, and further investigation could verify its suitability as a dosimetric constraint in treatment planning.

Purpose/Objective(s): To compare outcomes of sinonasal adenocarcinoma (SAC) patients treated with radiotherapy (RT) to sinonasal adenoid cystic carcinoma (ACC) patients treated with RT.

Materials/Methods: A retrospective review of 70 patients (42 ACC, 28 SAC) who received RT for SAC or ACC from 2002 to 2016 was performed. SAC was defined as ACC without a sinonasal location. RT was delivered with a median fraction size of 2 Gy (range: 1.4-4.1 GY) once daily, 5 days/week, for a median of 7 weeks (range: 3-8 weeks). The median time from surgery to RT for ACC was 7.1 weeks (range: 1-67 weeks). The median time from surgery to RT for SAC was 16.4 weeks (range: 2-84 weeks).

Results: The overall 5-year survival rate was 82% (95% CI: 75-89). Among ACC patients, the overall 5-year survival rate was 66% (95% CI: 52-78), and among SAC patients, it was 96% (95% CI: 83-99). The median follow-up was 57 months (range: 6-217 months). Cox proportional hazards regression was used to determine factors associated with worse survival. Factors associated with worse survival included increased number of involved neck nodes (HR 1.9, 95% CI: 1.1-3.3, P = 0.01) and preoperative ECE (HR 2.8, 95% CI: 1.4-5.1, P = 0.007).

Conclusion: The outcomes of sinonasal adenoid cystic carcinoma patients treated with RT are similar to sinonasal adenocarcinoma patients treated with RT. The median overall survival was 57 months (range: 6-217 months). A future prospective study to determine the role of surgical resection in ACC is warranted.

but not the low likelihood cohort (80.1%; CI 71.9-88.6 vs 75.8% CI 73.0-78.6, P = .782).

**Conclusion:** While HPV-OPC patients who were selected to receive eHNS in the NCDB generally had more favorable clinical tumor stage, nearly two-thirds also received adjuvant CRT/RT. While recognizing the potential influence of patient selection that is not captured by covariates available in the NCDB, we did not find a significant OS difference among patients who received initial CRT/RT or eHNS. Prospective studies are needed to clarify whether a subset of HPV-OPC patients derive benefit from eHNS and whether the quality of life is impacted in eHNS patients by the high incidence of adjuvant therapy.

**Author Disclosure:** J.K. Molitoris: None. S.M. Bentzen: None. S.E. Strone: None. D.P. Zandberg: None. K.J. Cullen: None. N. Hanna: None. M.D. Chuong: None.

**155**

**Predictors of Unplanned Hospital Admissions and/or Feeding Tube Placement in Patients With Oropharyngeal Cancer Treated With Cisplatin-Based Chemoradiation**


**Purpose/Objective(s):** We sought to identify factors that were associated with increased risks of unplanned emergency room and hospital admissions and/or feeding tube placement (a complicated treatment course) in patients with oropharyngeal cancer treated with cisplatin-based chemoradiation (CRT).

**Materials/Methods:** We identified patients with oropharynx cancer who were treated with CRT and intensity modulated radiation therapy (IMRT) between 2009 and 2014 from our institutional review board-approved database. We examined patient-, tumor-, and treatment-related variables and their association with an adverse event (AE), defined as an unplanned emergency room or hospital admission and/or feeding tube placement during or within 90 days of completing CRT. Univariate and Multivariate analysis (MVA) was performed using logistic regression analysis to identify factors associated with AE.

**Results:** Of the 96 patients included in this study, 90% were men, 69% were married, 92% were HPV/p16 positive, 53% had >10 pack-years smoking history, and 63% were working at diagnosis with a mean Charlson comorbidity index of 0.7. High-risk disease features were uncommon, as 12% had T4 disease and 22% had N2c disease. Ninety percent were treated with bilateral IMRT, and the remainder (10%) were treated unilaterally. In addition, 62.5% were treated with 2 doses of bolus (100 mg/m²) cisplatin, with the remaining treated with either 3 bolus doses (32.5%) or weekly (40 mg/m², 52%) cisplatin. Median follow-up was 22.6 months, and the 2-year recurrence-free survival was 83%. A total of 53 patients (55%) had an AE, of which 25 had an admission only, 5 had a feeding tube only, and 23 had both. On MVA, higher N stage (N2c/3) was associated with significantly increased risk of AE (odds ratio [OR] 5.6; P = .01), while being unmarried carried a similar trend (OR 2.5; P = .06). Patient age, performance status, gender, T stage, HPV status, and comorbidities were not associated with higher risks of AE.

**Conclusion:** Unplanned hospital or ER admissions and feeding tube placement is common among oropharyngeal cancer patients treated with cisplatin-based CRT. Patients with higher N stage disease (and larger high-dose treatment volumes) are at significantly higher risk of AE, and unmarried patients demonstrate a similar trend. Using these results, we can better identify at-risk patients, and efforts can be made to reduce AE.


**156**

**Transoral Robotic-Assisted Resection Approach for Identifying Unknown Primaries of the Head and Neck**

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**Purpose/Objective(s):** In traditional squamous cell carcinoma (SCCA), unknown primaries are rare (2%-3%), and a site can be identified in 67% of cases. Recent case reports have suggested that transoral robotic-assisted resection (TORS) of the base of tongue (BOT) can improve upon traditional methods with identification of a primary tumor in up to 90% of patients. We reviewed our use of TORS in identifying unknown primaries as well as the usefulness of preoperative positron emission tomographic (PET) scans. In addition, we reviewed the postoperative management and oncologic outcomes.

**Materials/Methods:** This is an institutional review board–approved retrospective chart review of 280 consecutive cases between 2011 and 2015. Unknown primary was defined as follows: regional squamous cell carcinoma in the neck, confirmed by biopsy, with a negative clinical exam (including flexible fiberoptic nasolaryngoscopy) and negative preoperative computed tomographic (CT) scan. In nearly all cases (n = 20 of 21), a preoperative PET scan was also performed.

**Results:** Twenty-one cases were identified. Mean age at presentation was 56 years (range 42-72 years). All but 1 patient was male, and all were human papillomavirus (HPV) positive. Neck disease was most commonly unilateral and multimodal: N1 (n = 3), N2a (n = 5), N2b (n = 11), N2c (n = 1), N3 (n = 1). The largest node at presentation averaged 3.18 cm (range 1.7-6 cm). A primary tumor was found in 76% of cases (n = 16 of 21). The average size of the primary tumor was 0.78 cm (range 0.1-1.8 cm). Preoperative PET scans were unable to identify a primary tumor in 80% of cases (n = 14 of 20). In the 6 cases in which a primary site was anticipated, it was 67% accurate (n = 4 of 6). A primary tumor could not be found in the remaining 2. Operative plans were either unilateral (n = 14) or bilateral (n = 7) resection of the tonsil and/or BOT. Mean hospital stay was 1.7 days (range 1-3 days). Postoperative treatments varied widely: 4 were observed (including 2 cases in which the primary was not identified). The remaining were radiated with either 60 or 66 Gy to the primary site and ipsilateral or bilateral necks. Decisions on postoperative radiation and fields were based on a multidisciplinary review of the pathologic report including nodal disease burden, extracapsular spread, and/or perineural infiltration in the primary tumor. Postoperative CRT with cisplatin was used in 2 cases. All patients are currently disease free with a mean follow-up of 12 months (range 0.4-32 months).

**Conclusion:** TORS-assisted approaches to the unknown primary improve upon the traditional approach; however, there exists opportunity for improvement. PET-CT is helpful when definitively positive, but the scans often added little information. Oncologic outcomes are favorable in HPV-associated disease despite wide variation on postoperative management. In particular, a prospective clinical trial addressing observation versus XRT would be helpful in determining treatment algorithms in the subset of patients in which the primary site remains unknown.

**Author Disclosure:** J. Kass: None. N. Khan: None. M. Miles: None. E. Genden: None.

**157**

**Retrospective Analysis of Prophylactic Gabapentin on Pain and Weight Loss in Patients Undergoing Radiation Therapy for Oropharyngeal Cancer**

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**Purpose/Objective(s):** Pain and weight loss are common side effects of radiation therapy (RT) for head and neck cancer. Narcotic pain medication...
(NPM) is commonly used but often results in incomplete pain control and is associated with its own side effects. Single-institution retrospective reports have provided evidence that prophylactic gabapentin (GP) may reduce the need for NPM in patients undergoing RT, however the ideal dosing schedule is unknown. The purpose of this study was to evaluate whether the use of 300 mg 3 times daily (TID) of GP in a community oncology center will result in reduced need for NPM or reduced weight loss (WL) in patients undergoing RT with or without chemotherapy for oropharyngeal cancer. 

Materials/Methods: We performed a retrospective chart review of all patients treated with RT for oropharyngeal cancer in our clinic over the last 33 months. From these data, we stratified patients by the use of GP and compared the amount of NPM, the time to initiation of NPM, and the amount of WL between patients who did and did not receive GP. Two-tailed t-tests were used to determine significance with α for significance set at P < 0.05.

Results: From November 2012 through July 2015, 64 patients with oropharyngeal cancer completed their prescribed RT course and at least 1 month of post-RT follow-up at our institution. Thirty-one patients received GP (at least 300 mg TID) within the first 2 weeks of RT. Patients who received GP had less unintentional WL (9.03 vs 15.82 lbs, P = .004) and initiated NPM later in their RT course (34.6 vs 22.3 days, P < .001). On subset analysis, patients who underwent upfront surgery and patients with p16-positive disease had less unintentional WL with the use of GP. Oropharyngeal subsite did not influence the effect of GP. No adverse effects were attributed to GP.

Conclusion: Patients who initiated at least 300 mg TID of GP within the first 2 weeks of RT for oropharyngeal cancer experienced less WL, and a longer time to commencement of NPM compared to those that did not initiate GP. These differences were independent of oropharyngeal subsite. No adverse effects were attributed to GP. Patients who underwent upfront surgery and patients with p16-positive disease derived the greatest benefit from the use of GP. These data support continued exploration of GP use in this patient population. Our institution intends to continue to explore the effect of higher GP dosing in future patients to elucidate potential dose-response relationships.


158

Squamous Cell Cancer of an Unknown Primary Head and Neck Site: Is Upfront Neck Dissection Still Relevant in the Era of Chemoradiation?

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Purpose/Objective(s): We sought to identify prognostic factors for survival and the role of upfront neck dissection in the era of definitive chemoradiation for patients with squamous cell carcinoma (SCC) of an unknown primary head and neck site.

Materials/Methods: All patients with SCC of an unknown primary site of the head or neck were reviewed from a prospective database. Patient demographic, treatment, and toxicity data were collected. Toxicity was coded according to Common Terminology Criteria for Adverse Events version 4.03. The Kaplan-Meier method was used to estimate survival. The log-rank test and proportional hazards regression were used to analyze factors influencing outcomes using a least absolute shrinkage and selection operator (LASSO) to select relevant variables.

Results: Of 2258 patients seen in our multidisciplinary clinic with a new diagnosis of head and neck cancer between 2003 and 2013, no primary site was identified in 66 patients. Fifteen patients were treated with definitive chemoradiation (CRT), 14 patients were treated with radiation alone, and 37 patients received an upfront neck dissection followed by adjuvant radiation or CRT. With a median follow-up of 22.4 months for surviving patients, actuarial emergency of a primary, neck failure, progression-free survival (PFS), and overall survival (OS) at 5 years were 11.2%, 21.4%, 42.3%, and 65.9%, respectively. On multivariate analysis, OS was significantly correlated with level II and level IV neck involvement. Patients with level IV involvement at presentation had better OS (hazard ratio [HR] 0.236, 95% confidence interval [CI] 0.084-0.662), and patients with level IV had worse OS (HR 3.53, 95% CI 1.27-9.83). Patients who were current smokers (P = .054) or who had N2b or greater stage disease (P = .088) trended toward worse survival. Patients who underwent an upfront neck dissection followed by appropriate adjuvant therapy had a lower rate of local failure (P = .003), locoregional failure (P = .068), and emergence of the primary (P = .001) with no difference in PFS (P = .189) or OS (P = .641) compared to patients who underwent definitive chemoradiation. Patients who received definitive chemoradiation had more advanced neck disease at presentation (P < .001). Grade 3 or higher toxicity occurred in 25 of 66 patients (37.9%) following radiation therapy. Upfront neck dissection did not predict for increased toxicity.

Conclusion: Survival for patients with SCC of an unknown primary site of the head and neck is likely determined by occult primary site and subsequent presenting cervical lymph node metastases. Upfront neck dissection was well tolerated and reduces failures in the head and neck compared to definitive chemoradiation but does not improve overall survival.


159

A Comparison of Split-Field and Whole-Field Intensity Modulated Radiation Therapy and Volumetric Modulated Arc Therapy for Laryngeal Sparing in Oropharyngeal Cancer

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Purpose/Objective(s): We assessed the optimal intensity modulated radiation therapy (IMRT) technique for treatment of nonlaryngeal head and neck cancers with regard to clinical target volume (CTV) coverage and sparing of organs at risk (OARs), particularly the larynx. The split-field approach (SF-IMRT) has been advocated to avoid unnecessary dose to the nondiseased larynx, whereas concerns for match-line failures have led to the use of a whole-field approach (WF-IMRT). Volumetric arc-based IMRT (VMAT) is the “next generation” IMRT offering faster treatment time and potentially less radiation exposure. Here we compare SF-IMRT, WF-IMRT, and VMAT in a large cohort of oropharyngeal carcinoma patients.

Materials/Methods: Seventy oropharynx carcinoma patients definitively treated with SF-IMRT (40 treated unilaterally and 30 treated to the bilateral neck; T4 or N3 excluded) were replanned with WF-IMRT (7-11 noncoplanar beams) and VMAT (2-arcs) per institutional planning goals. OARs were delineated per Radiation Therapy Oncology Group 1016. All plans achieved institutional planning objectives and were analyzed by paired t-tests.

Results: All plans achieved institutional planning objectives and were clinically acceptable. VMAT resulted in 4 to 5 times faster treatment delivery, required 15% to 40% fewer monitor units, improved target clinical acceptable. VMAT resulted in 4 to 5 times faster treatment delivery, required 15% to 40% fewer monitor units, improved target
SF-IMRT isocenter location with each 0.25-cm distance superiorly from organ (up to 2 cm) corresponding to a 1.3-Gy drop in mean arytenoid dose (P < 0.01). For unilateral plans, the larynx dose was lower for VMAT (14.4 Gy) than WF-IMRT (15.1 Gy) and SF-IMRT (16.1 Gy) (P < 0.05). The larynx dose was lower by 10.1 Gy for unilateral compared to bilateral plans. The larynx dose was higher by 4.1 Gy for plans with level 3 adenopathy compared to plans with adenopathy above the hyoid or that were node-negative (P < 0.05).

Conclusion: In the treatment of oropharyngeal cancer, <30 Gy mean laryngeal dose is achievable with SF-IMRT, WF-IMRT, or VMAT techniques. VMAT should be considered in appropriate candidates when shorter delivery times, fewer monitoring units, and increased dose homogeneity are warranted.


160
Nurse-Led Multidisciplinary Team to Improve Adherence to Treatment for Patients With Head and Neck Cancer Receiving Radiation Therapy in a Community Hospital

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Purpose/Objective(s): The incidence of head and neck cancer associated with human papillomavirus (HPV) has increased in the United States. This community hospital has also seen an increase in this population. Our baseline data for the first half of 2014 revealed 31% of 13 patients treated with concurrent chemoradiation experienced treatment interruption, and 38% had weight loss >5 kg. The purpose of this project was to identify a patient-specific protocol using a nurse-led multidisciplinary team that would be used for all patients with head and neck cancer to reduce the toxicity, reduce treatment interruptions, improve nutrition, and thereby improve patients’ quality of life, adherence to treatment, and outcomes.

Materials/Methods: A checklist was created for the patient and the health care team along with an education packet for the patient. Checklist and packet items included the following: team member identification, dental care recommendations for the dentist with a return document for care received (new process); feeding tube placement education/care of tube; weekly dietician consultation; prehabilitation speech therapy to teach swallow exercises (new process); tobacco cessation specialist consultation; oral protectant prescription to start with treatment; social work screening; nurse twice weekly assessments and evaluation of oral cavity; and radiation, medical and surgical oncologists’ oversight/management of the combined modality treatment. Adherence was assessed by no interruptions in treatment, defined as unplanned treatment-related interruptions greater than 5 days, and the patient’s weight maintained. Interruptions greater than 5 days are statistically significant in changing the outcome of treatment.

Results: The head and neck protocol checklist was implemented July 2014. Initial data are promising and suggest effectiveness. Thirty-two patients were treated with head and neck cancers from July 2014 through June 2015. Of 32 patients, 17 had feeding tubes. Twenty-two percent or 7 patients received (new process); feeding tube placement education/care of tube; swallow exercises (new process); tobacco cessation specialist consultation; medical and surgical oncologists’ oversight/management of the combined modality treatment. Adherence was assessed by no interruptions in treatment, defined as unplanned treatment-related interruptions greater than 5 days, and the patient’s weight maintained. Interruptions greater than 5 days are statistically significant in changing the outcome of treatment.

Conclusion: This study confirms the importance of a nurse-led multidisciplinary team to improve the quality of care for patients undergoing head and neck cancer treatment to impact adherence to treatment.


161
High-Dose Versus Weekly Cisplatin Definitive Chemoradiation Therapy for Human Papillomavirus-Related Oropharyngeal Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): To compare the outcomes and toxicity of high-dose cisplatin (HDC) versus weekly (WC) definitive concurrent chemoradiation (CRT) for patients with human papillomavirus (HPV)-related squamous cell carcinoma of the oropharynx.

Materials/Methods: Patients with p16-positive SCC of the oropharynx treated using CRT with cisplatin at a single institution between 2010 and 2014 were reviewed from a prospective database. Patient demographic, treatment, toxicity, and outcome data were collected. Toxicity was coded according to Common Terminology Criteria for Adverse Events version 4.03. The Kaplan-Meier method was used to estimate overall survival (OS) and event-free survival (EFS).

Results: We identified 56 patients during the study period. One patient was excluded because of the presence of 2 synchronic primaries at presentation. Of the 55 patients included, 85% were male and 57% had a history of smoking >10 pack-years. Median age at time of diagnosis was 55.4 years (range 40.3 to 80.0 years). A total of 22 patients were treated with HDC at doses of 100 mg/m2 on days 1 and 22 of the CRT, and 33 were treated with WC at doses of 40 mg/m2 every week. Groups were well balanced in respect to sex (P = 0.454) and smoking history (P = 0.799). The median total dose of cisplatin for both cohorts was 200 mg/m2, with a mean of 195 mg/m2 for the HDC group and 189 mg/m2 for the WC group. After a median follow-up of 21 months, there was 1 local failure and no distant failures in the HDC cohort. In the WC cohort, there were 6 total failures (2 local and 4 distant). One patient in the WC died without a failure 2 months after therapy due to infection. At last follow-up, EFS was improved for patients treated with HDC compared to WC (95% vs 79%; P = 0.043), despite a longer follow-up in patients with HDC (26 months vs 16 months). There was no significant difference in OS (95% vs 91%; P = 0.421). In terms of toxicity, there was a nonsignificant trend toward higher rates of weight loss in the HDC arm compared with the WC arm, both in all weight loss grades (87% vs 100%, P = 128) and weight loss more than grade 1 (60% vs 77%; P = 0.190). However, gastric tube dependence at 6 months following therapy was similar between groups (13% vs 12%, P = 1.000). Also, acute renal injury of any grade (55% vs 36%, P = 0.183) and grade 3 or 4 hematological toxicity (20% vs 23%, P = 0.761) were similar between groups.

Conclusion: In patients with HPV-positive oropharyngeal SCC, definitive CRT with HDC and WC have a similar toxicity profile in terms of weight loss, gastric tube dependence 6 months after therapy, hematological and renal injury rate. HDC has better EFS when compared with WC, and this seems to be driven by increased distant failure rates, although the OS is similar. A longer follow-up will be needed to better assess whether the OS remains similar.


162
Successful Development, Implementation, and Assessment of a Clinical Care Path (CP) Guide for the Treatment of Human Papillomavirus (HPV)-Initiated Oropharynx Cancer

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Purpose/Objective(s): To describe the successful development, implementation, and assessment of a Clinical Care Path (CP) guide for the Treatment of Human Papillomavirus (HPV)-Initiated Oropharynx Cancer (OPC). The CP was developed as a result of the recognition of the need for a standardized care pathway to improve the quality of care for OPC patients.

Materials/Methods: The CP was developed in collaboration with key stakeholders, including physicians, nurses, social workers, dietitians, speech therapists, and pharmacist. The CP was designed to provide a comprehensive approach to the care of OPC patients, including diagnostic evaluation, treatment planning, and follow-up care.

Results: The CP was implemented in 2016 and included a series of interventions to ensure successful adoption and utilization. These interventions included education and training sessions, regular feedback and monitoring, and ongoing evaluation to assess the impact of the CP.

Conclusion: The CP has been successfully implemented and has demonstrated positive outcomes, including improved patient satisfaction and reduced treatment-related side effects. Further studies are needed to evaluate the long-term impact of the CP on patient outcomes.

Purpose/Objective(s): Sufficient evidence now exists to allow development of CP guides for most cancers. The goals of these CP guides are to standardize treatment, optimize outcomes, minimize toxicities, and control costs. We propose that meaningful metrics can be identified and used to assess both compliance with these CP guidelines and the quality of clinical care.

Materials/Methods: In a multidisciplinary effort initiated in 2013, a clinical CP guide was developed for the use of definitive chemoradiation therapy (CRT) in patients with newly diagnosed stage III-IVB HPV-initiated squamous cell carcinoma of the oropharynx, the most common head and neck cancer diagnosis at our institution. The guide was widely vetted among the head and neck oncology team and approved by consensus at both our main institution and regional satellites. It included diagnostic and staging criteria for CP eligibility, pretreatment evaluation, treatment specifics, and supportive care guidelines. Concurrent radiation therapy with either cisplatin or cetuximab was considered an acceptable treatment choice. CP-related metrics were defined and retrospectively analyzed.

Results: All head and neck cancer patients treated at our institution between January 2014 and June 2015 were reviewed. There were 82 CP-eligible patients identified, 60 of whom were treated according to the CRT CP. The 22 patients not treated on the CP included 15 who underwent primary surgery and 7 treated with radiation alone (4 with early-stage III tumors and 3 deemed inappropriate for chemotherapy). All 60 of the CRT CP-treated patients had their diagnosis of HPV-initiated squamous cell oropharynx cancer confirmed; all had multidisciplinary involvement including otolaryngology, radiation, and medical oncology; and all were given a formal clinical stage. All 60 received a radiation dose of at least 70 Gy using intensity modulated radiation therapy, concurrently with either high-dose cisplatin every 3 weeks (41 patients), weekly cisplatin (14 patients), or a standard cetuximab regimen (5 patients). Among the cisplatin-treated patients, a total cisplatin dose >200 mg/m² was targeted and was achieved in 96% of them. A total radiation treatment duration of <7 weeks was targeted and was achieved in 88% of patients. A requirement for disease restaging after treatment within 3 to 4 months was defined and was accomplished in all patients at a median of 94 (max 123) days.

Conclusion: CP development for locoregionally advanced HPV-initiated oropharynx cancer can successfully standardize patient management. Meaningful metrics can be defined and used to assess CP compliance.


164 Human Papillomavirus Status and Long-Term Outcomes for Stage III-IV Squamous Cell Carcinoma of the Oral Cavity, Oropharynx, and Hypopharynx Treated With a Multimodal Intensification Regimen

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Purpose/Objective(s): From February 1993 until December 2000, a series of 3 consecutive prospective phase 2 trials were carried out at a single institution to evaluate an intensified treatment regimen. Previously reported outcomes showed excellent rates of protocol compliance, disease control, and overall survival. Our objectives are to (1) analyze tumor human papillomavirus (HPV)p16 status for these patients, (2) provide long-term updates on disease control and overall survival, and (3) determine whether favorable outcomes were achieved for our HPV-negative cohort. We hypothesize that our intensification protocols provide favorable disease control for HPV-negative patients.

Materials/Methods: One hundred twenty-seven adult patients with clinical stage III-IV squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx were previously treated according to 1 of 3 "intensification protocols" consisting of preoperative chemoradiation (910 cGy in 7 bid fractions with concurrent cisplatin), surgical resection with intraoperative radiation therapy (750 cGy), and adjuvant chemoradiation (4500 cGy in 20 fractions with concurrent cisplatin or cisplatin/paclitaxel). We retrospectively reviewed patient charts to update long-term disease control and overall survival outcomes. For those who were lost to follow-up, the social security death index was used to gather survival data. The date and location of locoregional and distant disease failures were recorded. Long-term locoregional and systemic disease control rates were calculated at 5 years.
165
Chondroradiation Necrosis and Late Radiation-Related Tissue Changes in the Larynx: Twenty-Four-Year University of Wisconsin Experience
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Purpose/Objective(s): To review our series of patients with chondroradiation necrosis (CRN) of the larynx and review the current literature to help define the challenges with both the diagnosis and treatment of this uncommon complication of therapy.

Materials/Methods: Medical records were reviewed for 612 patients who underwent primary or salvage radiation for laryngeal cancer from 1991 to 2015. Two hundred ninety-three patients were treated initially at the University of Wisconsin Hospitals and Clinics. Patients receiving treatment at an outside institution were excluded. Records were reviewed to identify patients with a diagnosis of CRN and the characteristics, treatments, and outcomes related to those patients. Patients were not included if they were known to have persistence or recurrence of disease.

Results: Of the 293 patients, 7 cases (2.4%) of probable CRN were identified. Of these, 4 had supraglottic tumors and 3 had glottic tumors. All patients experienced at least grade 2 AE with 35.4% experiencing at least grade 3 AE. At the end of treatment, every patient had either a grade 2 or grade 3 AE. At baseline, patients experiencing a maximum grade 2 AE reported worse physical WB (48.6 for grade 2, 70.5 for grade 1, P = 0.0190). At week 1, the following QOL domains were statistically different according to maximum grade AE: overall QOL (77.4 for grade 1, 64.5 for grade 2, and 10.0 for grade 3, P = 0.0222), mental WB (81.3 for grade 1, 66.0 for grade 2, and 30.0 for grade 3, P = 0.0073), physical WB (73.9 for grade 1, 56.0 for grade 2, and 10.0 for grade 3, P = 0.0065), and fatigue (60.9 for grade 1, 42.5 for grade 2, and 20.0 for grade 3, P = 0.0336).

Conclusion: H&N RT is associated with diminished QOL and significant AEs. Diminished QOL at early time points appears to correlate with maximum grade AE for multiple ePRO QOL domains. Patients adapting to their circumstances or providers addressing AEs may account for the lack of correlation between ePRO QOL domains and maximum grade AE beyond week 1 of RT.


166
Correlating Patient-Reported Outcomes and Provider-Documented Adverse Events During Radiation Therapy for Head and Neck Cancer

Purpose/Objective(s): To correlate changes in real-time electronic patient-reported outcomes (ePROs) with provider-documented adverse events (AEs) at multiple time points during the course of radiation therapy (RT) for head and neck (H&N) cancer.

Materials/Methods: Sixty-five H&N RT patients completed an electronic real-time 12-item Linear Analog Self-Assessment (LASA) at baseline, before biweekly appointments, and at last week of RT. Changes in LASA item scores between time points were calculated. Clinical data were collected from the institutional medical record. AEs were recorded at baseline, before biweekly appointments, and at the last week of RT. We graded AEs using the Common Terminology Criteria for Adverse Events version 4.0. LASA item scores were categorized according to maximum grade AE experienced by each patient at any given time point and analyzed using Wilcoxon methodology.

Results: Over the course of H&N RT, a majority of patients reported a clinically significant decrease in most ePRO quality of life (QOL) domains. QOL domains for which patients most commonly reported a clinically significant decrease were fatigue (77.8% of patients), social activity (75.4%), and overall QOL (74.2%). At the last week of RT, patients reported average LASA scores worse than baseline for all QOL domains except level of support and financial concerns. During treatment, all patients experienced at least grade 2 AE with 35.4% experiencing at least grade 3 AE. At the end of treatment, every patient had either a grade 2 or grade 3 AE. At baseline, patients experiencing a maximum grade 2 AE reported worse physical WB (48.6 for grade 2, 70.5 for grade 1, P = 0.0190). At week 1, the following QOL domains were statistically different according to maximum grade AE: overall QOL (77.4 for grade 1, 64.5 for grade 2, and 10.0 for grade 3, P = 0.0222), mental WB (81.3 for grade 1, 66.0 for grade 2, and 30.0 for grade 3, P = 0.0073), physical WB (73.9 for grade 1, 56.0 for grade 2, and 10.0 for grade 3, P = 0.0065), and fatigue (60.9 for grade 1, 42.5 for grade 2, and 20.0 for grade 3, P = 0.0336).

Conclusion: H&N RT is associated with diminished QOL and significant AEs. Diminished QOL at early time points appears to correlate with maximum grade AE for multiple ePRO QOL domains. Patients adapting to their circumstances or providers addressing AEs may account for the lack of correlation between ePRO QOL domains and maximum grade AE beyond week 1 of RT.


167
Predictors of Dysphagia After Treatment With Submandibular Gland-Sparing Radiation Therapy for Advanced-Stage Oropharyngeal Squamous Cancer
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Purpose/Objective(s): Dysphagia is common after head and neck radiation therapy and has a detrimental effect on quality of life. Sparing the submandibular gland contralateral to the primary tumor (cSMG) from high radiation dose has recently been shown to reduce xerostomia. Xerostomia is known to worsen posttreatment dysphagia. SMG saliva is rich in mucins, which act as an essential lubricant during the swallowing process. The goal of this study was to determine whether cSMG sparing treatment is associated with reduced late posttreatment dysphagia in advanced-stage oropharyngeal squamous cancer patients.

Materials/Methods: Patients treated with definitive bilateral neck intensity modulated radiation therapy for stage III/IV oropharyngeal squamous cancer were eligible for this retrospective study. Those with disease recurrence were excluded. Salivary glands and swallowing-related organs at risk, including pharyngeal constrictor muscles, were contoured in a uniform manner. Primary (objective) endpoint was time from end of radiation treatment to freedom from gastrostomy tube dependence.


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Secondary (subjective) endpoint was presence or absence of grade 2+ observer-rated late dysphagia. Cox proportional hazards regression and logistic regression were used to assess influence of normal tissues doses on dysphagia endpoints.

**Results:** Sixty-nine patients were included. Ninety-seven percent received concurrent systemic therapy. Fifty-seven percent had cSMG mean dose \(<50\) Gy, a level shown to predict for xerostomia. Eighty-four percent of patients had a gastroscope tube placed. On univariate analysis, the strongest predictor of time to freedom from gastroscope tube dependence was cSMG dose (hazard ratio 0.97 per Gy [95% confidence interval 0.95-0.98], \(P<0.001\)). This relationship persisted on multivariate analysis (\(P=0.04\)). Patients with cSMG dose less than median (42 Gy, \(n=34\)) had significantly shorter time to freedom from gastroscope tube dependence: median 1.9 versus 3.5 months, \(P<0.001\). No patient with cSMG dose less than median was feeding tube dependent 1 year posttreatment. Higher cSMG dose was associated with worse observer-rated dysphagia on univariate but not multivariate analysis.

**Conclusion:** cSMG sparing radiation therapy with the goal of improving posttreatment xerostomia may improve dysphagia as well.


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**168**

**A Phase 1 Trial of Ketogenic Diet With Concurrent Chemoradiation (CRT) in Head and Neck Squamous Cell Carcinoma (HNSCC)**


**Purpose/Objective(s):** Ketogenic diet (KD) combined with CRT reduced tumor growth and improved survival in preclinical models. We hypothesized that KD could be able to remain compliant with KD because of percutaneous endoscopic gastroscope (PEG) tube requirement during CRT.

**Materials/Methods:** This institutional review board–approved phase 1 clinical trial enrolled stage III-IVB HNSCC patients receiving concurrent platinum-based CRT. PEG placement was required up front, but subjects were encouraged to continue KD by mouth due to benefits in continued swallowing activity on ultimate function. KD recipe ideas and shakes were provided to subjects for daily consumption for 5 weeks concurrent with CRT. Shakes could also be delivered by way of PEG tube for caloric requirements. Fingerstick ketones (FK) were checked Monday through Friday, and serum beta-hydroxybutyrate (BHB), glucose, and uric acid were checked weekly. Lipid panel was checked at week 3. In addition, serum oxidative stress parameters were assessed prior to, during, and after completing KD.

**Results:** Median follow-up for all enrolled subjects (\(n=9\)) from completion of RT was 7.1 months (range: 0.12-10.9 months). Three of 9 subjects successfully completed 5 weeks of KD as prescribed. Successful subjects used scheduled antiemetics, consumed shakes by way of PEG tube as opposed to orally, and had strong social support. Median days on KD for those who discontinued was 6 (range: 0-8). Reasons for discontinuation included additional stress of diet compliance (1 of 6 patients), Common Terminology Criteria for Adverse Events version 4.0 grade 2 nausea (2 of 6 patients), grade 3 nausea (1 of 6 patients), grade 3 fatigue (1 of 6 patients), and grade 3 hyperuricemia (1 of 6 patients). SAEs (\(n=6\)) included parotitis, nausea, vomiting, neutropenic fever, hyperuricemia, and pancreatitis, of which hyperuricemia and pancreatitis were possibly attributed to KD and considered DLTs. The trial was temporarily suspended after the grade 4 hyperuricemia (12.7 nd/dL; nl ref 2.4-7.0); the protocol was amended to initiate allopurinol and address treatment of diet-related hyperuricemia. In those who completed KD, the median days FK were elevated and weeks the BHB levels were above baseline were 24 days (range: 19-25) and 5 weeks (range: 4-5), respectively. FK levels were impacted by dexamethasone given for chemotherapy and by carbohydrate intake in liquid medications. Median uric acid levels were 5.3 nd/dL (range: 4.4-5.4). Lipids remained normal. Serum oxidative stress markers, as assessed by protein carbonyls, increased linearly with increasing days on KD.

**Conclusion:** While challenging despite PEG availability, KD compliance is possible when combined with concurrent CRT for HNSCC. Enrollment continues and updated results will be presented.

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**169**

**Prognostic Significance of Extracapsular Spread and Perineural and Lymphovascular Invasion in Patients with HPV- and Non-HPV–Related Oropharyngeal Squamous Cell Carcinoma.**

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**Purpose/Objective(s):** Approximately 15,000 cases of oropharyngeal squamous cell carcinoma (OPSCC) are diagnosed each year in the United States. Previously these cancers had a strong association with chronic alcohol and tobacco use. Over the past decade the increasing incidence of the human papillomavirus (HPV) has been identified as a major etiologic agent of oropharyngeal cancer and currently is associated in over 70% of cases in the United States. Although the prognostic significance of HPV is clear, the impact of traditional pathologic parameters remains unclear. Therefore, the goal of this study is to compare surgical pathologic variables in non-HPV– and HPV-associated OPSCC. We hypothesize the presence of lymphovascular invasion will portend a poor prognosis in HPV-related OPSCC, whereas perineural invasion and extracapsular spread will be associated with decreased survival in non-HPV–related disease.

**Materials/Methods:** We conducted a retrospective chart review of 240 patients treated for oropharyngeal SCC at a tertiary care cancer center. The primary outcome measures were overall and disease-free survival. The endpoints assessed were clinical and pathologic T and N stage and presence of extracapsular spread, perineural invasion, or lymphovascular invasion.

**Results:** Of the 240 patients with OPSCC reviewed, 116 patients underwent surgery as part of their primary treatment and had pathologic variables and pT6 status available for review. Of this cohort, 70 patients had HPV-related disease, while 46 patients had non-HPV–related disease. The presence of perineural invasion was associated with decreased disease-free survival in both HPV and non-HPV–related OPSCC (\(P=0.03\) and \(P=0.003\), respectively). Lymphovascular invasion portended a worse overall and disease-free survival in HPV-related disease (\(P=0.850\) and \(P=0.850\), respectively) but not non-HPV–related (\(P=0.717\) and \(P=0.942\), respectively). In contrast, extracapsular spread did not correlate with decreased overall or disease-free survival in either HPV-related OPSCC (\(P=0.399\) and \(P=0.575\), respectively) or non-HPV–related OPSCC (\(P=0.772\) and \(P=0.843\), respectively).

**Conclusion:** In the current series, the presence of perineural invasion portended a worse prognosis in patients with OPSCC independent of HPV, whereas there was not an associated prognostic significance of extracapsular spread regardless of HPV status. In contrast, lymphovascular invasion appears to correlate with decreased survival in patients with...
170

Initial Experience Using Transoral Robotic Surgery for Advanced-Stage (T3) Tumors of the Head and Neck

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Purpose/Objective(s): Currently transoral robotic surgery (TORS) using the DaVinci system is FDA approved for use in benign and malignant early-stage T1 and T2 tumors. At institutions with a robust TORS program, there is an increased comfort level with both the technology and transoral anatomy as such larger tumors are being excised. We sought to identify how many stage T3 oropharyngeal squamous cell carcinomas (OPSCC) have been attempted using robotic surgery at a high-volume institution (>50 cases per year). In particular, we evaluated the following outcomes: initial clinical T stage, margin status, hospital stay, tracheostomy, and percutaneous endoscopic gastrostomy (PEG) tube dependence and use of adjuvant therapy.

Materials/Methods: We conducted an institutional review board–approved retrospective chart review of 280 consecutive cases between 2011 and 2015. All pathology reports were reviewed, and those with final pathology demonstrating stage T3 and T4 (pT3–4) OPSCC were included. One patient with incomplete records was excluded. Results: Fourteen patients were identified as pT3, and 1 patient was excluded for incomplete preoperative staging. Mean age was 65 years (range 50–85 years) and 64% (n = 9 of 14) were human papillomavirus positive. All but 1 of the patients was male, and 57% (n = 8 of 14) had a history of tobacco use. Preoperative clinical staging for the cohort was cT1 (n = 2), cT2 (n = 9), cT3 (n = 2), and cT4 (n = 1). Tumors were pathologically staged as either pT3 (n = 13) or pT4a (n = 1). Overall length of stay was 5 days (range 2-8 days). Negative margins were achieved in 86% of patients (n = 12 of 14). One patient required a tracheostomy, and 1 patient remained PEG tube dependent. All patients had postoperative XRT, and the 2 patients with positive margins had chemotherapy (either docetaxel and cetuximab or cisplatin).

Conclusion: TORS may be used to resect advanced T-stage malignancies; however, there are risks of positive margins, tracheostomy, and PEG tube dependence, as well as hospital stays that exceed the typical 1 to 2 days. The potential benefit of avoiding 3-modality treatment (surgery, radiation, and chemotherapy) should only be considered in tumors in which negative margins can be achieved.


171

Predictive Factors Associated With Late Pulmonary Toxicity After Definitive Intensity Modulated Radiation Therapy With Induction Chemotherapy for Head and Neck Cancer

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Purpose/Objective(s): Pulmonary toxicity after radiation therapy in patients with head and neck cancer (HNC) represents an underreported complication, which is suggested from the long-term update of Intergroup Radiation Therapy Oncology Group 91-11. Recently, intensity modulated radiation therapy (IMRT) has been introduced in the treatment of HNC that may reduce the incidence of late toxicity. We evaluate the incidence and predictors of pulmonary toxicity in our clinical cohort of patients with HNC who received IMRT.

Materials/Methods: We reviewed a database of 181 consecutive patients with squamous cell carcinoma of the head and neck who received IMRT for whole neck irradiation field during 2002 to 2013 at our hospital. Of these patients, the data of 80 patients (diagnosed with oropharyngeal, hypopharyngeal, or laryngeal cancer) who underwent at least 1 cycle of induction chemotherapy and were scheduled for definitive chemoradiation therapy (CRT) were queried in this retrospective review. Patients were ineligible if they received less than 60 Gy or had a follow-up of less than 12 months with critical event. Time to pneumonia was calculated based on treatment start date to the date of last follow-up note or the first date that pneumonia was noted by clinical follow-up imaging. Several clinical and dosimetric parameters correlated with the swallowing structures and salivary glands were assessed.

Results: The average follow-up after treatment was 26 months (range, 12–72 months). Of 80 patients with HNC, 22 patients (27.5%) were recognized as the episodes of pneumonia at a median of 20 months after initiating treatment. The 1-year and 3-year cumulative incidence of aspiration pneumonia was 6.0% and 25.4%, respectively. Many of the patients (15%) had silent aspiration, not associated with clinical symptoms. Four patients (5%) developed fatal aspiration pneumonia at a median of 12 months (range, 0.9 to 62 months) from the start of IMRT. Among the patients with survivors, log-rank test identified risk factors (P < 0.05) for aspiration pneumonia, including the planning target volume receiving greater than 63 Gy, severe body weight loss during CRT, a serum albumin change from baseline, the volume of the supraglottis receiving greater than 60 Gy, and the mean dose of the major salivary glands. On multivariate analysis using logistic regression, a serum albumin lower than 2.5 g/dL (P = 0.02) and the mean major salivary glands dose greater than 48 Gy (P = 0.03) were significantly associated with the progression of asymptomatic pneumonia.

Conclusion: Various factors contributed to the risk for aspiration pneumonia, which is an important late toxicity of noncancer-related mortality among our advanced HNC cohorts who received IMRT with induction chemotherapy. Further studies with a longer follow-up are warranted to identify patients at risk for severe aspiration pneumonia after CRT.

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172

Contralateral Neck-Sparing Radiation Therapy in Select Patients With Locally Advanced Oropharyngeal Cancer After Primary Surgery With Neck Dissection

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Purpose/Objective(s): Current guidelines recommend postoperative radiation therapy (RT) in locally advanced oropharyngeal cancers to include bilateral neck lymph nodes (LNs). In select cases ipsilateral neck RT alone may be sufficient. We evaluated the efficacy of sparing the contralateral LNs in select postoperative patients with base of tongue (BOT) or locally advanced tonsillar cancers.

Materials/Methods: We queried our institutional review board–approved database in the Department of Radiation Oncology for patients with BOT or locally advanced (T3-4, N2a-b, or T1-4N1-2b with extracapsular extension [ECE]) tonsillar squamous cell carcinoma who underwent resection with LN dissection and received adjacent contralateral neck-sparing RT at our institution. On preoperative work up, none of the patients had suspicious LNs in the contralateral neck by physical exam or by positron emission tomographic/computed tomographic (PET/CT) scans. Most patients with BOT cancers had bilateral LN dissections with pathologically negative contralateral LNs (mean number of contralateral LNs dissected 20.3; range, 10-39), whereas those with tonsillar cancers only had ipsilateral LN dissections. Patients were followed posttherapy with physical exam every 2 to 3 months and with PET/CT imaging every 3 to 6 months. We determined the number of locoregional failures (LRF), contralateral LN failures, distant metastases, and deaths.
Results: Twenty-three patients met eligibility criteria. Staging is listed in Table 1. Of those tested, most had human papillomavirus-positive (HPV+) (19 of 21 = 90%) and p16-positive (21 of 22 = 95%) tumors by PCR and IHC staining, respectively. Indications for RT were LVI (n = 6; 26%), PNI (n = 2; 9%), close (n = 6; 26%) or positive (n = 3; 13%) margins, N2 (n = 16; 70%), and/or ECE (n = 6; 26%). The radiation fields included the primary site only (n = 4; 17%), ipsilateral neck only (n = 6; 26%), or primary and ipsilateral neck (n = 13; 57%) to a mean radiation dose of 62.2 Gy (range, 60-66 Gy). Three patients (13%) received concurrent cisplatin. Only 1 patient (4%) required percutaneous endoscopic gastrostomy tube for nutrition. After a mean follow-up time of 22 months (range, 6-47 months), there were no LRFs, contralateral LN failures, distant metastases, or deaths.

Conclusion: The absence of locoregional and contralateral LN failures or metastases provides promising evidence as to the safety of contralateral neck-sparing RT in select, mostly HPV+, postoperative SCC patients with BOT or locally advanced tonsillar cancers. Longer follow-up and more patients are needed to validate these findings.


174 Use of Supportive Care in Patients With Metastatic Squamous Cell Carcinoma of the Head and Neck—Own Experience
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Purpose/Objective(s): The high recurrence rate and short disease-free survival after curative treatment of squamous cell carcinoma of the head and neck (HNSCC) are still actual problems of modern radiation oncology. Irradiation with higher total doses extends the treatment course and leads to the tumor repopulation phenomenon, which decreases effectiveness of treatment. It is possible to overcome the phenomenon of repopulation by reducing the duration of treatment by increasing single doses delivered to the tumor.

Materials/Methods: One hundred two patients with histologically confirmed HNSCC of II-III clinical stages received platinum-based chemoradiation between 2013 and 2015 in a radiation therapy department at our clinic. The treatment volumes were formed as follows: the primary lesion (gross tumor volume [GTV] + 0.5-1.0 cm clinical target volume [CTV] + planning target volume [PTV] 0.3 cm) was treated to the total dose equivalent to 70 Gy of conventional fractionation, the upper neck (levels I-II + PTV 0.5 cm) to 60 Gy, the lower neck (levels IV-V + PTV 0.5 cm)—equivalent to 50 Gy. Single doses to these volumes were 2.21 Gy, 2.0 Gy, and 1.8 Gy, respectively. GTV delineation was performed using computed tomography (CT) and magnetic resonance imaging, and some patients had positron emission tomographic/CT scans with 18F-FDG. The irradiation regimen was once a day, 5 days a week, and the course duration was 6 weeks (30 fractions). A treatment planning system and medical linear accelerator were used. The volume, treated to the equivalent of 70 Gy in conventional fractionation, ranged from 164 to 370 mL. Intensity modulated radiation therapy with simultaneously integrated boost was used. Tolerances of the eye, lens, optic nerves and chiasm, brain stem, spinal cord, parotid gland, intact mucosa of the mouth, and pharynx were not exceeded. Patient positioning accuracy was controlled by kV-imaging daily and cone beam CT weekly.

Results: Eighty-six of 102 patients (84.3%) received full chemoradiation course without a break. Radiation toxicity manifested with grade 2 oral and pharyngeal mucositis and grade 2 radiation epidermitis. Sixteen patients (15.7%) took a break of 5 to 7 days after the 23 to 25 fractions due to the development of grade 3 mucositis (PTV30 Gy, in these cases exceeded 330 mL). After 1 month, we saw almost complete relief of radiation mucositis and dermatitis. During further observation, patients noted the satisfactory salivation and there was no incidence of xerostomy. Progressive disease in the first 6 months after irradiation registered in 4 patients with highly differentiated HNSCC.

Conclusion: Using the technique of simultaneously integrated boost with intensity modulated radiation therapy during chemoradiation therapy of HNSCC can increase effectiveness of treatment by reducing the duration of radiation therapy course while maintaining satisfactory tolerability.

**175**

**Prognostic Value of Midtreatment Nodal Response to Chemoradiation in Oropharyngeal Squamous Cell Carcinomas:**

**Implications for Treatment Modification**

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**Purpose/Objective(s):**

P16 status and smoking history have emerged as prognostic factors in oropharyngeal squamous cell carcinoma (OPX). Daily cone beam computed tomography (CBCT) used for image guidance can provide real-time volumetric assessment of disease response. It is not known if early tumor response to radiation therapy (RT) can have an impact on disease outcomes. This study examines the prognostic implications of midcourse nodal response to RT.

**Materials/Methods:** Forty-four patients (pts) with node-positive OPX underwent definitive concurrent chemoradiation therapy (CCRT) with daily CBCT between April 2012 and July 2014. Pts had a mean age of 60 years (47-74), 95.5% were male, and 4.5% were female. All received 70 Gy to gross disease, and 98% received concurrent chemotherapy. In all, 70.5% were p16-positive, 20.5% were p16-negative, and 9.1% had unknown p16 status. A total of 56.8% had 10 pack-year history (PYH) correlated with improved 2-year RC (100% vs 78.4% (CI: 71-85) of the high-, intermediate-, and low-risk group.

**Results:** At a median follow-up of 17 months (2-31), the 2-year actuarial survival (DFS)/LRC ratio, which was lowest for the high-risk group (Table 1). Two years after treatment, 10% (confidence interval [CI]: 4.8-21), 43% (CI: 34-54), and 78% (CI: 71-85) of the high-, intermediate-, and low-risk patients, respectively, were alive with no sign of tumor. The modes of failure from the competing risk model are shown in Table 1 (confidence interval data not shown); note that percentages add up to 100% in contrast to Kaplan-Meier analysis. The estimated effect of treatment intensification differed depending on risk group, both in magnitude and in the disease-free survival (DFS)/LRC ratio, which was lowest for the high-risk group (Table 1).

Independently prognostic for LRC (P = .039) and tended toward significance for DFS (P = .075).

**Conclusion:** ND of >40% by treatment day 20 is associated with improved LRC, with a trend to improved DFS. Smoking history was strongly associated with poorer RC and OS. Pts who were p16-negative and smokers had higher rates of DM. The prognostic value for LRC of midtreatment ND can potentially be used to select pts for locoregional treatment intensification strategies (eg, pts >10 PYH with D20ND <40%) and those for treatment de-escalation (<10 PYH pts with D20ND >40%).

**Author Disclosure:** K.S. Hu: leadership; ASTRO. R. Stewart: None. A. Jacobson: None. M. Persky: None. S. Schantz: None. T. Tran: None. M. Urken: None. B. Culliney: None. Z. Li: None. L.B. Harrison: None.

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**176**

**The Fate of Head and Neck Cancer Patients After (Chemo)radiation Therapy—Risk Group Stratified Outcome Analysis and Treatment Effect Modeling in the Presence of Competing Risks**

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**Purpose/Objective(s):** Tumor control after (chemo)radiation therapy for head and neck squamous cell carcinoma (HNSCC) is known to be affected by a number of risk factors. However, the literature on the risk of competing endpoints, potentially impacting optimal management, is scarce. In this study, the treatment outcome has been analyzed while taking competing events into account. The purpose was to assess the potential benefit from intensified local treatment.

**Materials/Methods:** A cohort of 286 patients treated for HNSCC was stratified by low, intermediate, and high risk, using a previously published model. Persistent disease, locoregional relapse, distant metastasis (DM), and death from other causes at 24 months after treatment were analyzed using a competing risk model. The effect of an intensified radiation therapy strategy (FDG-PET-based dose painting) was estimated while accounting for competing risks, expanding a previously published TCP model. It was assumed that the intensified treatment did not impact the competing events of DM and death and that patients achieving locoregional control (LRC) as a result of intensified treatment suffered the same risks of DM and death as other patients of their risk group.

**Results:** Two years after treatment, 10% (confidence interval [CI]: 4.8-21), 43% (CI: 34-54), and 78% (CI: 71-85) of the high-, intermediate-, and low-risk patients, respectively, were alive with no sign of tumor. The modes of failure from the competing risk model are shown in Table 1 (confidence interval data not shown); note that percentages add up to 100% in contrast to Kaplan-Meier analysis. The estimated effect of treatment intensification differed depending on risk group, both in magnitude and in the disease-free survival (DFS)/LRC ratio, which was lowest for the high-risk group (Table 1).
Abstract 176: Table 1  Two-year outcome, analyzed using a competing risk model, and expected benefit from local treatment intensification.

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent disease</td>
<td>4.6%</td>
<td>10%</td>
</tr>
<tr>
<td>Locoregional relapse</td>
<td>7.6%</td>
<td>18%</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>3.4%</td>
<td>13%</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>6.1%</td>
<td>16%</td>
</tr>
<tr>
<td>Alive (disease-free survival)</td>
<td>78%</td>
<td>43%</td>
</tr>
<tr>
<td>Expected benefit from local LRC (%-points)</td>
<td>7.5</td>
<td>15</td>
</tr>
<tr>
<td>treatment intensification DFS (%-points)</td>
<td>6.8</td>
<td>10</td>
</tr>
</tbody>
</table>

Conclusion: The outcome of high-risk patients is discouraging; in the <40% of patients achieving LRC, >70% develop DM or die from other causes within 24 months. The link between improvement in LRC and DFS depends heavily on risk group, as the benefit is negatively impacted by the risk of DM and death from other causes. Estimates of LRC without competing risks can be misleading in assessing benefits of novel treatments and when counseling patients.

Author Disclosure: K. Häkansson: None. J.H. Rasmussen: None. L. Specht: Research Grant; Varian Medical Systems. Honoraria for teaching courses held (to department); Varian Medical Systems. S.M. Bentzen: None. I. Vogelius: Research Grant; Varian Medical Systems. Honoraria for teaching courses held (to department); Varian Medical Systems.

177

Clinical Predictors of Locoregional Failure in Advanced Laryngeal Cancer Treated With Definitive Chemotherapy and Radiation

A.M. Khan,1 M.C. Ward,2 D.J. Adelstein,1 S. Koyfman,1 C.A. Reddy,1 P.H. Bhatia,1 P. Funchain,1 E. Lamarre,2 B.B. Burkey,1 M. Khan,1 J. Scharpf,1 B. Prendes,1 J.F. Greskovich, Jr,3 R. Lorenz,1 N.P. Joshi,2 A.M. Khan,3 M. Rahe,1 D. Ives,1 B. Harr,1 J. Bodmann,1 and T. Nwizu1

Purpose/Objective(s): Definitive chemoradiation (CRT) has become an established organ preservation treatment for patients with locoregionally advanced laryngeal cancer. Although most patients will experience long-term disease control after CRT, locoregional failure remains a concern for a subset of patients. This study is aimed to identify predictors of locoregional failure after larynx-preservation therapy in patients with stage III–IVB laryngeal cancer.

Materials/Methods: From an institutional review board–approved tumor registry, all patients with American Joint Committee on Cancer stage III–IVB squamous cell carcinoma of the larynx treated with definitive concurrent chemoradiation therapy between 1993 and 2014 were identified. Patient, tumor, and treatment characteristics were collected. The Cox proportional hazards method was used to identify predictors of locoregional failure. Statistical significance was inferred at the 0.05 level for all hypothesis testing.

Results: A total of 117 patients were included in the study with a median follow-up of 31 months (range: 1.8–185). The median age at diagnosis was 59 years (range: 43–77), 74% were male, 57% were current smokers, and 21% had a history of alcohol abuse. Fourteen percent of patients presented with T2 tumors, 70% with T3 tumors, and 16% with T4 disease. Sixty-two percent were node-positive; 23% with N1 disease, 4% with N2a, 14% with N2b, 21% with N2c, and 1% with N3 disease. Twenty-two percent were glottis, and 67% were supraglottic. Radiation therapy (RT) was administered once (68%) or twice daily (31%) to a total dose of 70 to 74.4 Gy, with either a 3-field approach (3D-RT) in 61% or, more recently, using intensity modulated radiation therapy (IMRT) in 37%. Chemotherapy consisted of either cisplatin and 5-fluorouracil (60%) or single-agent cisplatin (33%) at standard dosing. Twenty (17%) locoregional failures were observed. Univariate analysis found a significantly higher locoregional failure rate in those patients with both significant alcohol and ≥ 10 pack-year smoking history who were currently smoking at the time of diagnosis (hazard ratio = 3.66, 95% confidence interval 1.39 – 9.71, P < 0.009). T stage, N stage, chemotherapy regimen, or radiation therapy dose or fractionation were not associated with locoregional failure. Furthermore, 85% of the locoregional failures occurred within 2 years, with a median time to locoregional failure of 16 months.

Conclusion: Overall, these data suggest that patients treated with definitive CRT for stage III–IVB laryngeal cancer who fail locoregionally do so within 16 months. Heavy alcohol history combined with significant smoking history and continued smoking at time of treatment was a significant predictor of failure. Emphasis on smoking cessation and alcohol reform is warranted.


178

Tumor Board Checklists Affect Pretreatment Clinic Referral Patterns

W. Swegal and S. Chang: Henry Ford Health System, Detroit, MI

Purpose/Objective(s): Checklists have been utilized within the surgical community in recent years as a way to ensure that certain crucial steps or processes are completed. They are a process-related effort to ensure quality patient care. Patients with newly diagnosed head and neck cancer require multidisciplinary preoperative evaluation and counselling prior to their treatment, and postsurgical patients require proper review for referrals for adjuvant treatments. A checklist system was implemented at our tumor board during 2013 in order to improve quality of care and adherence to National Comprehensive Cancer Network guidelines.

Materials/Methods: We conducted a retrospective analysis of newly diagnosed head and neck cancer patients presented at our institution’s multidisciplinary tumor board between the years of 2010 and 2015. The year 2013 was considered the point when we started to use checklists during the tumor board discussion. We compared 100 newly diagnosed patients before the checklist was implemented to 100 patients afterward. Compliance with tumor board recommendations and pretreatment evaluation within 1 month were compared between groups. Pretreatment evaluation included appointments with a clinical psychologist, speech language pathologist, and nutritionist. Analysis was also performed on referral for audiogram and dental evaluation, as well as whether patients were reviewed for clinical trials.

Results: Preliminary analysis suggests that appropriate and completed referrals to medical oncology were similar between the 2 groups (P > 0.99). This was similar to radiation oncology, where 93% patients in the pre-checklist era and 100% patients from the postchecklist group were correctly referred or not referred (P = 0.3). Difference in referral patterns to pretreatment evaluation and counseling trended toward significant. Referral patterns for speech language pathology (P = 0.19), clinical psychology (P = 0.25), and nutrition (P = 0.6) all trended toward a significant difference with overall more appropriate referrals occurring after the checklist was implemented. This was a similar trend with optimization clinic (P = 0.23) and audiology (P = 0.6). Appropriate referrals to dental (P = 0.06) were significantly increased with the implementation of the checklist, and a great proportion of patients were reviewed for clinical trials (P = 0.002).

Conclusion: The use of the checklist during the tumor board presentation helped to increase follow through and adherence to recommendations for pretreatment evaluation. We hope to further highlight the benefits of the
Purpose/Objective(s): The effect of smoking and human papillomavirus (HPV) status on the survival of oropharyngeal squamous cell carcinoma

180

Proliferation Saturation Index Predicts Oropharyngeal Squamous Cell Cancer Gross Tumor Volume Reduction to Prospectively Identify Patients for Adaptive Radiation Therapy


Purpose/Objective(s): Radiation therapy (RT) for human papillomavirus (HPV)-positive oropharyngeal squamous cell cancer (OPX) provides 3-year locoregional control (LRC) rates of 75% to 95%. Given the excellent cancer control outcomes for OPX following RT, there is significant interest in reducing therapy intensity, such as adaptive radiation therapy (ART), for rapidly shrinking tumor volumes to improve organ at risk sparing. However, we have limited understanding of which patients will be suitable for ART. Proliferation saturation index (PSI) is defined as a ratio of tumor volume to host tissue carrying capacity. Tissue carrying capacity (K) is an integral measure of the maximum tumor volume that can be supported by the current tumor environment including oxygen and nutrient availability, immune surveillance, and acidity. The PSI can be measured from 2 pretreatment computed tomographic (CT) scans separated in time. We hypothesized that PSI may be able to define a subgroup of patients with rapidly shrinking tumors during RT who may gain the most benefit from ART.

Materials/Methods: From an MDACC institutional database, 9 patients with OPX treated with RT and concurrent chemotherapy were identified. Patient demographics, treatment, and outcomes were extracted. PSI was estimated from routine pre-RT and RT planning simulation computer tomography scans and the Gompertz tumor growth model. Gross tumor volume (GTV) was contoured on weekly CT scans obtained during treatment to estimate tumor shrinkage. GTV reductions during fractionated RT were calculated as a function of PSI.

Results: Gompertz tumor growth with patient-specific PSI values fit retrospective data with high confidence (R² > 0.93). Median PSI was 0.17 (range 0.01-0.3). Median GTV was 23.6 cm³ (range 3.5-62). Of the 9 patients, 3 had GTV reductions of >20% within the first 3 weeks. This was correlated with PSI values less than 0.07.

Conclusion: PSI derived from standard of care CT images may be able to prospectively identify candidates for ART prior to treatment.


181

The Effect of Smoking and Human Papillomavirus Status on Survival in Oropharyngeal Squamous Cell Carcinoma Patients Undergoing Concurrent Chemoradiation


Purpose/Objective(s): The effect of smoking and human papillomavirus (HPV) status on the survival of oropharyngeal squamous cell carcinoma

182

Abstract 179; Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>HPV+ oropharynx feeding tube</th>
<th>All other feeding tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>80%</td>
<td>34.37%</td>
</tr>
<tr>
<td>2008</td>
<td>59.25%</td>
<td>24.24%</td>
</tr>
<tr>
<td>2009</td>
<td>53.33%</td>
<td>32.43%</td>
</tr>
<tr>
<td>2010</td>
<td>54%</td>
<td>52.94%</td>
</tr>
<tr>
<td>2011</td>
<td>29.26%</td>
<td>61.53%</td>
</tr>
<tr>
<td>2012</td>
<td>41.86%</td>
<td>46.66%</td>
</tr>
<tr>
<td>2013</td>
<td>25%</td>
<td>38.46%</td>
</tr>
<tr>
<td>2014</td>
<td>23.91%</td>
<td>21.87%</td>
</tr>
</tbody>
</table>


Shrinkage Estimation Using Proliferation Saturation Index


Purpose/Objective(s): Radiation therapy (RT) for human papillomavirus (HPV)-positive oropharyngeal squamous cell cancer (OPX) provides 3-year locoregional control (LRC) rates of 75% to 95%. Given the excellent cancer control outcomes for OPX following RT, there is significant interest in reducing therapy intensity, such as adaptive radiation therapy (ART), for rapidly shrinking tumor volumes to improve organ at risk sparing. However, we have limited understanding of which patients will be suitable for ART. Proliferation saturation index (PSI) is defined as a ratio of tumor volume to host tissue carrying capacity. Tissue carrying capacity (K) is an integral measure of the maximum tumor volume that can be supported by the current tumor environment including oxygen and nutrient availability, immune surveillance, and acidity. The PSI can be measured from 2 pretreatment computed tomographic (CT) scans separated in time. We hypothesized that PSI may be able to define a subgroup of patients with rapidly shrinking tumors during RT who may gain the most benefit from ART.

Materials/Methods: From an MDACC institutional database, 9 patients with OPX treated with RT and concurrent chemotherapy were identified. Patient demographics, treatment, and outcomes were extracted. PSI was estimated from routine pre-RT and RT planning simulation computer tomography scans and the Gompertz tumor growth model. Gross tumor volume (GTV) was contoured on weekly CT scans obtained during treatment to estimate tumor shrinkage. GTV reductions during fractionated RT were calculated as a function of PSI.

Results: Gompertz tumor growth with patient-specific PSI values fit retrospective data with high confidence (R² > 0.93). Median PSI was 0.17 (range 0.01-0.3). Median GTV was 23.6 cm³ (range 3.5-62). Of the 9 patients, 3 had GTV reductions of >20% within the first 3 weeks. This was correlated with PSI values less than 0.07.

Conclusion: PSI derived from standard of care CT images may be able to prospectively identify candidates for ART prior to treatment.

OPSCC undergoing definitive concurrent chemoradiation (CCRT) remains unclear. The purpose of this review was to examine these effects on survival outcomes among a single institute population. **Materials/Methods:** This retrospective review of OPSCC patients treated with CCRT between 2008 and 2015 was conducted. All tumors were examined for HPV 16/18 status (+). Smoking status and other clinical characteristics were abstracted from the electronic medical record. Former smokers are patients who quit within a month of diagnosis or treatment. Descriptive summaries, overall survival (OS), and multivariate cox proportional hazard ratios (HR) were completed. **Results:** Out of 134 patients, 94 patients (71%) had HPV-positive (HPV+) tumors. Age, gender, and overall stage were not statistically different between patients with HPV+ or HPV-negative (HPV-) tumors. HPV+ patients had higher tumor grade (P<.01). Patients with HPV+ tumors had a higher percentage of never smokers than patients with HPV- tumors (10.5% vs 26.6%). Median pack-years were 18 for the HPV+ group versus 30 for the HPV- group. OS did not differ for HPV+ versus HPV- patients. Within HPV+ patients, current and former smokers had significantly worse OS than never smokers (P<.01). The same was true for HPV- patients, but the log-rank test for this group did not reach statistical significance (P = .06). The 3-year survival rate for former smokers in each group was similar (HPV+: 0.77 (0.60, 0.88) and HPV-: 0.75 (0.52, 0.88). Hazard ratios for OS among current smokers compared to never/former smokers in each patient group were statistically significantly higher. **Conclusion:** Current smoking is associated with poor prognosis, independent of HPV status in OPSCC patients treated with CCRT. Former smokers have similar outcomes irrespective of HPV tumor status. The amount of tobacco a patient is exposed to before diagnosis cannot be altered, but every effort should be made to get patients to quit smoking as soon as possible before CCRT regardless of HPV status.


## 182

### Positive Effect of Surgery Regardless of Stage on Oropharynx Subsites Base of Tongue and Tonsillar-Fossa: A SEER Analysis

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**Purpose/Objective(s):** There is increasing interest in the use of robotic surgery in carcinoma of the oropharynx. The purpose of this study was to examine survival outcomes among 2 oropharyngeal subsites (tonsillar-fossa [TF] and base of tongue [BOT]).

**Materials/Methods:** We conducted a retrospective cohort analysis utilizing data from the Surveillance, Epidemiology, and End Results (SEER) Program. The SEER cohort included 8073 primary BOT and TF SCC patients without distant metastases treated between 2004 and 2011. Primary outcome measures were subsite-based differences in overall survival (OS) and disease-specific survival (DSS) for TF and BOT patients stratified by overall stage and comparing treatment method for each subsite. Cox proportional hazard ratios were estimated for each group.

**Results:** For all stages combined, both BOT and TF patients who received surgery with radiation had superior OS (P<.01). The same was true when analyses were stratified by stage within each subsite. Multivariate hazard ratios adjusted for age, gender, race, and tumor grade for OS were statistically significantly higher for both BOT and TF patients who did not receive surgery compared to those who did receive surgery for each stage.

**Conclusion:** In this SEER cohort, OS was superior in both BOT and TF patients who received surgery with adjuvant radiation. OPSCC survival may be improved by treating more BOT and TF patients with surgery and adjuvant radiation. As modern, less invasive surgical techniques such as transoral robotic surgery gain wider acceptance, approaches that combine surgery and radiation (with or without chemotherapy) while minimizing morbidity and lack of function should be attempted.

Magnitude and Timing of Gross Tumor Volume Response to Neoadjuvant Chemotherapy and Concurrent Chemoradiation in the Treatment of Locally Advanced Nasopharyngeal Carcinoma

Purpose/Objective(s): Curative radiation therapy (RT) for locally advanced nasopharyngeal carcinoma (NPC) is based on the gross tumor volume (GTV), but the magnitude and timing of GTV changes during combined modality therapy remain unclear. This study analyzes GTV changes at phases of induction chemotherapy and sequential concurrent chemoradiation therapy (CRT) in patients with locally advanced NPC.

Materials/Methods: Subjects included 13 patients with newly diagnosed stage III-IV NPC who underwent treatment between 2011 and 2014. Criteria for eligibility included 2 cycles of neoadjuvant chemotherapy, at least 5 cycles of concurrent chemotherapy and 3 magnetic resonance imaging (MRI) scans at specific phases of treatment (T0: before treatment, T1: postinduction, and T3: 3 months after CRT). The induction phase consisted of 2 cycles of gemcitabine and cisplatin. The CRT phase consisted of weekly cisplatin and RT delivered using volumetric modulated arc therapy (VMAT). The total dose was 70 Gy over 35 daily fractions administered 5 days/week. A subset of 3 patients received an additional MRI 4 to 5 weeks into CRT (T2). Primary gross tumor volume (GTVp) was defined as the GTV and adjacent involved retropharyngeal lymph nodes. Tumor volumes were delineated on gadolinium-enhanced fat-saturation T1 weighted MRIs by 2 observers. Mean values are reported +/- one standard deviation.

Results: Preliminary analysis included 6 (out of 13) subjects. The mean initial GTVp was 62.7 +/- 32.8 mL. The mean GTVp response after induction phase was 21.4% +/- 12.3% with a mean rate of volume change of 0.31 +/- 0.19 mL/day which corresponded to a 0.56% +/- 0.35% daily reduction in tumor volume. The mean total GTVp response after completion of treatment (T3) was 77.6% +/- 21.6%. Subgroup analysis of 20 patients who underwent an additional MRI showed a mean GTVp reduction of 42.5% +/- 22.6% and a mean rate of volume change of 0.87 +/- 0.08 mL/day which corresponded to a 1.7% +/- 0.93% daily reduction in tumor volume (from T1 to T2).

Conclusion: Preliminary results suggest that the GTVp progressively diminishes following both induction chemotherapy and CRT. The mean GTVp response after 4 to 5 weeks of CRT exceeded the response observed after induction chemotherapy by a factor of 2. The mean rate of volume change at 4 to 5 weeks of CRT was threefold the rate seen during induction chemotherapy. These observations may support the optimal timing of imaging for replanning in the context of adaptive field RT. Analysis of the full NPC patient dataset is ongoing and will be reported.


C-Reactive Protein as a Biomarker of Radiation Therapy and Chemotherapy Toxicity Monitoring in Patients With Head and Neck Cancer

Purpose/Objective(s): C-reactive protein (CRP) is a serum protein elevated in a variety of illnesses, including cancer. Also some data exist that CRP level is correlated with acute mucositis in patients (pts) with head and neck cancer (HNC) treated with radiation therapy (RT) and significantly elevated when dose/fraction number is increased. The purpose of this study is to show how CRP behaves before and after HNC RT with or without chemotherapy.

Materials/Methods: From 2010 to 2015, 401 pts (318 men and 83 women) with a mean age of 58 years (range 20-81) with oral cavity (5), nasopharynx (30), oropharynx (133), hypopharynx (47), larynx (180), or unknown primary (6) cancer were under treatment. Tumor stage was evaluated in all pts: T0-6, T1-60, T2-147, T3-119, T4-69, and N0-174, N1-52, N2-143, and N3-32. Four schedules of treatment have been used: RT alone (RTA, 178 pts), concurrent chemoradiation therapy (CRT, 93 pts), and induction chemotherapy (IC) followed by RTA (46 pts) or CRC (84 pts). CRP (normal level, <2.87 mg/L) was measured as follows: before IC (if applied) or before RTA/CRC, every week during RTA/CRC, and, finally, 1 month after treatment. Total number of CRP measurements was 262.

Results: Initial CRP level was normal in 56% of pts; in 44% it was elevated (median 6.05 mg/L) but not correlated with tumor advancement. After IC, normalization of CRP was observed in 73% of pts (median CRP decreased from 3.12 to 1.24 mg/L). During RT progressive, week by week up to week 6, elevation of CRP was observed for RTA and CRC with no difference between both treatments. However, evident impacts of initial CRP level and IC were noted; in patients who had abnormal initial CRP and/or IC, significantly higher CRP levels were observed over RTA and CRC. There was no correlation observed between CRP and total dose or overall volume of radiated tissue.

Conclusion: CRP may be a useful laboratory parameter in monitoring of toxicity in HNC patients undergoing RTA and CRC. IC leads to significant reduction/normalization of CRP in the majority of patients, which may reflect an anti-inflammatory effect in tumor burden. Similar CRP levels in patients treated with RTA and CRC may suggest that tumor and normal tissue radiation sensitivity is an essential proinflammatory factor.

Results: For the entire series, ART plans had significantly better planning target volume (PTV) coverage. The mean percentage dose covering 95% of PTV (D95) was 96.44% for ART versus 95.58% for N-ART (P < 0.0003) for PTV70, and 94.63% for ART versus 93.94% for N-ART (P = 0.0009) for PTV60. Using our treatment setup, only MPS was able to define 2 risk groups for plan deterioration. The high-risk group (HRG) comprises 27 patients with MPS > 1 mm and the low-risk group (LRG) comprises 13 patients with MPS < 1 mm. The mean PTV70 (D95) for ART versus N-ART for the HRG and LRG were 96.44% versus 95.36% (P < 0.0001) and 96.15% versus 96.02% (P = 0.68). The same was true for PTV60 with 94.93% versus 93.36% (P < 0.0033), and 94.62% versus 94.00% (P = 0.104). When compared to ART, 6 out of 40 NART plans had a PTV70 and/or PTV60 (D95) drop exceeding 3% (P < 0.0255), 5 of them in the HRG. The ART plans achieved a significantly lower spinal cord dose maximum (SCMD) of 42.64 Gy versus 44.47 Gy (P < 0.0001). Only 1 patient in this group had SCMD exceeding 46 Gy as compared to 13 in NART plans (P < 0.0012). The improvement in the mean parotid dose with ART in this series did not reach statistical significance (33.35 Gy versus 34.20 Gy, P = 0.063).

Conclusion: ART plans resulted in improved tumor coverage and better spinal cord sparing compared to the corresponding N-ART plans in the present NPC patient series. Further evaluation of the value of the predictive factors will be carried out in a larger sample of patients.

HPV Status May Have Limited Value as a Prognostic Factor in Postoperative Squamous Cell Carcinoma of the Head and Neck Compared to Extramedial Extension and Lymphovascular Space Invasion


Purpose/Objective(s): The significance of human papillomavirus (HPV) as a predictive factor in squamous cell carcinoma of the head and neck (HNSCC) is well described. However, the value of HPV status in patients presenting with advanced disease treated with postoperative neck dissection is less clear. This study aims to evaluate HPV status in patients with advanced squamous cell carcinoma of the head and neck treated with postoperative neck dissection at a single institution.

Materials/Methods: We retrospectively evaluated a cohort of 927 patients treated at our institution between 2009 and 2014 for HNSCC. Of these, 128 were nonmetastatic, treated with definitive surgery with or without adjuvant radiation therapy (RT) or chemoradiation therapy (CRT). Oral cavity (63.3%, n = 81), laryngeal (21.1%, n = 27), oropharyngeal (10.1%, n = 13), and unknown primary or other subsite (5.5%, n = 7) cases were included. Patients were treated with surgery alone (n = 19, 14.8%) or surgery plus adjuvant treatment (RT 38.3%, n = 49; CRT 46.9%, n = 60). Patient, disease, and treatment factors were analyzed as potential prognostic factors in proportional hazard regression models adjusted for site and disease of origin.

Results: Median follow-up for survivors was 18.4 months (range 0.6-66.9). Most patients had locally advanced disease with 63% having pathologically positive nodal disease. The majority (78%) of the 110 patients with known HPV status were negative. Of the 81 node-positive patients undergoing a neck dissection, 62% demonstrated extranodal extension (ECE), and 42% demonstrated lymphovascular space invasion (LVI). At 2-year follow-up (18 [14.1%]) experienced locoregional treatment failure (LRF), and 12 (9.4%) experienced DF without LRF. Positive margins related to poorer disease-free survival (DFS) and overall survival (OS). ECE, perineural invasion, and LVI positivity predicted poorer LRF, DFS, and OS. HPV status alone did not predict LRF, DFS or OS, but an interaction analysis revealed that, compared to HPV-positive/ECE-negative patients, both HPV-positive and HPV-negative patients with ECE experienced significantly poorer OS (85.7% vs 60% and 47%, respectively; P < .018). When all risk factors were considered simultaneously, LVI emerged as a significant predictor of OS (hazard ratio [HR] = 4.06, 95% confidence interval [CI], 1.72-9.57, P = .001) with ECE showing marginal significance for prediction of OS (HR = 2.184, 95% CI, 0.95-4.891, P = .058).

Conclusion: Although HPV status plays a major role in the affecting outcomes of nonoperative HNSCC, its influence on patients in the postoperative setting appears limited compared to traditional postoperative risk factors such as ECE and LVI. Further prospective analysis with a longer follow-up period is warranted.


191

Long-Term Outcomes for Head and Neck Cancer Patients With N3 Neck Disease

A. Wieland, M.E. Witek, A.P. Wojciechowski, T. Kennedy, G.K. Hartig, and P.M. Harari, University of Wisconsin, Madison, WI

Purpose/Objective(s): The aim of the present study was to evaluate clinical outcomes for patients with squamous cell carcinomas of the head and neck presenting with N3 nodal disease.

Materials/Methods: Following identification of eligible cases from our institutional review board–approved head and neck cancer database, we performed a retrospective analysis of patients with N3 nodal disease between 1989 and 2014. We limited this review to patients who received curative intent therapy at 1 institution and had squamous cell carcinoma histology. Primary sites included oropharynx (57%), unknown primary (20%), hypopharynx (10%), larynx (7%), oral cavity (3%), and nasopharynx (3%). Treatment of the primary tumor included chemoradiation therapy (43%), radiation therapy (29%), and surgery (15%). Neck dissection was performed in 90% of patients. Overall survival, locoregional control, and rates of distant metastases were defined.

Results: Mean age was 59 years (range 41-85). Median follow-up was 23.4 months (range 1.2-226.8). Overall survival at 1, 3, and 5 years was 73%, 44%, and 35%, respectively. Locoregional control was 84%, 67%, and 63%, respectively. Distant metastases-free survival at 1, 3, and 5 years was 78%, 61%, and 58%, respectively.

Conclusion: Head and neck cancer patients with N3 nodal disease historically have a poor long-term prognosis. However, approximately 30% of patients are long-term survivors, particularly when effective locoregional control is achieved. Factors that correlate with more favorable long-term outcome are reviewed from this study and from the published N3 head and neck literature. It appears worthy to approach most N3 patients with curative intent in the absence of distant metastases at presentation.

192

Retrospective Analysis of Cisplatin Nephrotoxicity in Patients With Head and Neck Cancer Receiving Outpatient Treatment With Concurrent High-Dose Cisplatin and Radiation Therapy

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Purpose/Objective(s): Cisplatin remains the pivotal chemotherapy in squamous cell carcinoma of the head and neck (SCCHN), with nephrotoxicity considered the dose-limiting toxicity. The purpose of our study was to propose an outpatient high-dose cisplatin (op-HD-cis) protocol aimed at preventing nephrotoxicity and to analyze the results of its use in patients with SCCHN treated with concurrent radiation therapy (RT).

Materials/Methods: We retrospectively evaluated 82 patients with SCCHN treated with op-HD-cis concurrent with RT at our institution. Acute kidney injury (AKI) and chronic kidney disease (CKD) were defined by Kidney Disease Improving Global Outcomes criteria. Associated factors were identified using analysis of covariance models for categorical variables and adjusted Pearson correlations for continuous variables.

Results: The incidence of AKI during treatment was 34.2%. With a median follow-up of 25.7 months, the average decrease in eGFR was 12.57 ml/min/1.73m² (SD = 18.58). At 1-year and at last follow-up, 5.4% and 4.4% of patients had eGFR <60 ml/min/1.73m², respectively. Predictors associated with AKI and CKD were lower baseline weight and creatinine, higher baseline creatinine clearance, smoking, female gender, African American race, hypertension, and increased hydration and magnesium replacement requirements.

Conclusion: We encountered limited early and late nephrotoxicity. Importantly, nephrotoxicity was not the main dose-limiting toxicity. Apparent low baseline serum creatinine in patients with low body weight should not decrease the protocol intensity. Our results emphasize the importance of close monitoring and additional replacement of water and electrolytes as needed. A consistent method of measuring and reporting chemotherapy-induced nephrotoxicity would be a valuable contribution to the literature.


194

Prognostic Indications of p16 and Smoking Status in Predicting the Need for Posttreatment Neck Dissection After Chemoradiation Therapy in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): This study aimed to determine the effect of p16 and smoking status on response to chemoradiation therapy and the need for posttreatment neck dissection in patients with head and neck squamous cell carcinoma (SCC).

Materials/Methods: This study was a retrospective medical records review of patients with head and neck SCC treated with chemotherapy and radiation therapy. Based on ICD-9 and CPT codes, patients with SCC who received definitive chemoradiation therapy were cross-referenced with those also undergoing neck dissection. Preliminary correlations determined age at diagnosis and N stage at presentation should be adjusted in hypothesis tests. Logistic and Cox proportional hazard regression models tested risk group differences in the likelihood of undergoing neck dissection, disease-free survival (DFS), and overall survival (OS).

Results: A total of 152 patients with oral cavity (n=25, 16%), oropharyngeal (n=106, 67.9%), laryngeal (n=20, 12.8%), and unknown primary diagnoses (n=5, 3.2%) were included. Patients were stratified by risk group: 65 (41.7%) were p16 positive (high risk), 46 (29.5%) were p16 positive with a greater than 10 pack-year smoking history (intermediate risk), while 41 patients (26.3%) were p16 positive with a fewer than 10 pack-year history (low risk). Of these, 45 patients (29.6%) underwent a neck dissection after definitive chemoradiation and radiation. After models were adjusted for age, N stage, and total radiation dose, the low (< P = .005) and intermediate (P < .001) risk groups were significantly less likely to undergo neck dissection than were high-risk patients. No significant risk group differences in DFS were observed. High-risk patients demonstrated significantly poorer OS (P = .026). However, model adjustment suggested

193

Presence of Preradiation Therapy Feeding Tube Associated With Poor Prognostic Subset of Postoperative p16-Positive Oropharyngeal Carcinoma

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Purpose/Objective(s): Timing of feeding tube insertion relative to radiation therapy (RT) could be associated with prognosis in patients with head and neck cancers. This study assesses feeding tube insertion time as well as several other clinical variables that are associated with prognoses in postoperative p16-positive oropharyngeal squamous cell carcinoma that undergo adjuvant RT or chemoradiation therapy.

Materials/Methods: Three hundred seventy-six consecutive patients with oropharyngeal cancer were identified from a large prospectively maintained academic institutional database from 1997 to 2009. Two hundred twenty of these had adjuvant RT, and 97 were p16 positive. Of these patients, 42 never had a feeding tube placed (NO-FT), 23 had one placed before RT (B-FT), and 42 had one placed during or after RT (DA-FT). Feeding tubes were not placed prophylactically. Analysis was conducted between these 3 groups for differential tumor, patient, treatment, and feeding tube characteristics, as well as differences in overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS).

Results: Five-year OS for the NO-FT, DA-FT, and B-FT groups was 90%, 86%, and 50%, respectively. Five-year DFS for each group was 88%, 84%, and 43%, respectively. Kaplan-Meier survival curve analysis and log-rank statistical analysis showed statistically inferior OS and DFS for the B-FT group (p < .001). On multivariate analysis, timing of feeding tube placement as well as smoking history was associated with OS and DFS.

Feeding tube insertion prior to RT was associated with higher tumor size and depth, T (but not N) and overall stage, comorbidities, receipt of chemotherapy, and less use of transoral laser microsurgery/transoral bovie surgeries. Additionally, the time from surgery to RT completion was also statistically longer in the B-FT group. The feeding tube was permanent in 52% of patients in the B-FT group versus 16% in the DA-FT group (p = .007).

Conclusion: The presence of a feeding tube at the time of RT consultation, due to associated poor prognostic variables of early feeding tube insertion, can serve as a surrogate marker to identify a subset of p16-positive oropharyngeal cancer patients with a poor prognosis.


199

Prognostic Indications of p16 and Smoking Status in Predicting the Need for Posttreatment Neck Dissection After Chemoradiation Therapy in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): This study aimed to determine the effect of p16 and smoking status on response to chemoradiation therapy and the need for posttreatment neck dissection in patients with head and neck squamous cell carcinoma (SCC).

Materials/Methods: This study was a retrospective medical records review of patients with head and neck SCC treated with chemotherapy and radiation therapy. Based on ICD-9 and CPT codes, patients with SCC who received definitive chemoradiation therapy were cross-referenced with those also undergoing neck dissection. Preliminary correlations determined age at diagnosis and N stage at presentation should be adjusted in hypothesis tests. Logistic and Cox proportional hazard regression models tested risk group differences in the likelihood of undergoing neck dissection, disease-free survival (DFS), and overall survival (OS).

Results: A total of 152 patients with oral cavity (n=25, 16%), oropharyngeal (n=106, 67.9%), laryngeal (n=20, 12.8%), and unknown primary diagnoses (n=5, 3.2%) were included. Patients were stratified by risk group: 65 (41.7%) were p16 positive (high risk), 46 (29.5%) were p16 positive with a greater than 10 pack-year smoking history (intermediate risk), while 41 patients (26.3%) were p16 positive with a fewer than 10 pack-year history (low risk). Of these, 45 patients (29.6%) underwent a neck dissection after definitive chemoradiation and radiation. After models were adjusted for age, N stage, and total radiation dose, the low (< P = .005) and intermediate (P < .001) risk groups were significantly less likely to undergo neck dissection than were high-risk patients. No significant risk group differences in DFS were observed. High-risk patients demonstrated significantly poorer OS (P = .026). However, model adjustment suggested
2233 this result was better explained by age ($P = .004$) and total radiation received ($P = .007$).

2234 **Conclusion:** In this data series, high-risk patients were significantly more likely to undergo a neck dissection after definitive chemoradiation treat-
2235 ment. However, risk group stratification appeared to have no prognostic value when examining DFS or OS among this group of patients with head and
2236 neck SCC.

2237 **Author Disclosure:** Z.J. Cappello: None. M. Eid: None. E. Cash: None. L.
2238 Wilson: None. P. Tennant: None. J. Bumpous: None. K. Potts: None.

2239 195

2240 **Can Aggressive Intravenous Hydration Prevent Cisplatin-Induced Renal Dysfunction?**

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2242 **Purpose/Objective(s):** Renal dysfunction is a well-recognized toxicity from cisplatin chemotherapy, and preemptive intravenous (IV) hydration during cisplatin administration is universally recommended. Subsequent IV hydration is often useful for patients with treatment-induced nausea, vomiting, or dehydration and in those who develop acute cisplatin-induced renal failure, but its role in preventing chronic renal dysfunction is unclear. We retrospectively reviewed a homogeneous cohort of head and neck cancer patients treated with definitive chemoradiation therapy (CRT) using high-dose cisplatin to identify predictors of chronic renal dysfunction and address the preventative value of aggressive IV hydration.

2243 **Materials/Methods:** Between 2013 and 2015, the records of all patients treated with definitive CRT using high-dose intermittent bolus cisplatin (100 mg/m² every 3 weeks) at our institution were reviewed. Data recorded and analyzed included age; race; gender; performance status; smoking history; alcohol use; tumor stage; total cisplatin dose; baseline, peak, and 3-month posttreatment serum creatinine; and additional occasions that IV hydration was given during the course of CRT. Renal dysfunction was defined either as an increase in creatinine of at least 25% over baseline or as any creatinine increase above our institutional norms.

2244 **Results:** We identified 78 patients for review. Their median age was 58 years (range 40-77). Most were male (86%), Caucasian (90%), and had stage IVa disease (96%). There were 42 (54%) former smokers, 18 (23%) active smokers, and 14 (18%) with a history of heavy alcohol consumption. All patients began treatment with normal renal function. Two doses of cisplatin were given to 68 patients (87%); the other 10 patients (13%) received 3 doses. During treatment, 39 patients (50%) experienced a creatinine elevation above normal. Although the 3-month posttreatment creatinine remained greater than 25% above baseline in 13 patients (17%), it was greater than our institutional norms in only 2 (3%). There were 16 patients who did not receive any extra IV hydration. Additional hydration was given on 1 to 18 occasions to the other 62 patients. No pretreatment factors, including cisplatin dose, were identified that could predict for posttreatment renal dysfunction. There was no significant correlation identified between the number of hydration occasions and the percentage change between baseline and 3-month posttreatment creatinine ($P = .54$).

2245 **Conclusion:** Although acute renal failure is common after high-dose cisplatin administration, chronic renal dysfunction is rare. No clinical parameters proved predictive, and aggressive IV hydration after treatment was not helpful.


2247 196

2248 **T3 Squamous Cell Carcinoma of the Glottic Larynx: Primary Radiation Treatment Outcomes**

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2250 **Purpose/Objective(s):** Patients with T3 squamous cell carcinoma of the glottic larynx are commonly treated with organ preservation approaches using radiation or chemoradiation. In this report, we review the University of Wisconsin experience with T3 glottic cancer treated with nonsurgical therapy over the last 23 years.

2251 **Materials/Methods:** Twenty patients with T3 squamous cell carcinoma of the glottic larynx treated with primary radiation between 1992 and 2014 were identified from our institutional review board–approved head and neck cancer database. Median age at diagnosis was 67 years (range: 24-86). TNM staging included 17 patients with T3N0, 2 with T3N1, and 1 with T3N2 disease. All but 1 patient had a history of tobacco use with a median 24 pack-year smoking history. Median tumor volume on pre-treatment computed tomographic scan was 3.4 mL (range: 1.1-9.9). Twelve patients were treated with radiation alone while 8 patients received concurrent chemotherapy with cisplatin (n = 5), lapatinib (n = 2), or cetuximab (n = 1). Median radiation dose was 70 Gy with 10 patients receiving QD radiation and 10 receiving BID or QD/BID hybrid fractionation regimens. Median overall treatment time was 44 days (range: 31 – 49).

2252 **Results:** With a mean follow-up time of 6.2 years, local control rates at 5 and 10 years were 79% and 66%, respectively. Five- and 10-year larynx preservation rates were 74% and 59%. Five patients experienced local failure, with 1 patient failing both locally and regionally, and 1 patient experienced distant only failure in the lung and liver. Median time to locoregional failure was 13.4 months. Ultimately, larynx preservation was achieved in 15 patients (75%). Six patients (30%) had gastrostomy tubes placed during treatment for a median duration of 5 months. Median weight loss during treatment was 6 pounds. Three patients (15%) required hospitalization either during treatment or within the first month after treatment. Of 4 patients (20%) who required a temporary tracheostomy during treatment, only 1 patient maintained a tracheostomy beyond 6 months. Median voice quality at the time of last follow-up per Voice Handicap Index-10 scoring was 15.5 on a 0 to 40 scale (0 = best voice, 40 = worst voice) with range 6 to 27 in our treatment cohort.

2253 **Conclusion:** Patients with T3 glottic cancer treated with primary radiation approaches experienced high rates of local control (79% and 66% at 5 and 10 years) and larynx preservation (74% and 59% at 5 and 10 years). Patient numbers were too small to identify a significant impact of radiation fractionation, overall treatment time, tumor volume, or chemotherapy on outcome. Treatment tolerance and voice quality outcome were favorable for the majority of our T3 glottic cancer patients.

2254 **Author Disclosure:** A.P. Wojcieszyński: None. R. Toya: None. G.K.
2255 Hartig: None. T.M. McCulloch: None. C. Britt: None. T. Gessert: None.
2256 G.D. Avey: None. P.M. Harari: None.

2257 197

2258 **Case Report: Dosimetric Comparison of Oral Cavity Dose With Different Tongue Positions in 5 Patients Treated With Intensity Modulated Radiation Therapy for Oropharyngeal Cancer**

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2260 **Purpose/Objective(s):** To compare radiation dose to oral cavity (OC) with different tongue positions in patients treated with intensity modulated radiation therapy (IMRT) for oropharyngeal cancer (OPC).

2261 **Author Disclosure:** None.
Materials/Methods: Five patients with OPC who were unable to use bite block or tongue blade underwent computed tomographic simulations with neutral tongue position and stuck-out tongue for planning IMRT (IMRT-N and IMRT-S, respectively). Planning objectives were to deliver 70 Gy, 63 Gy, and 56 Gy in 35 fractions to 95% of PTVs using simultaneously integrated boost technique, with mean doses (Dmean) of <26 Gy to the parotid gland, <30 Gy to the submandibular gland, and <36 Gy to the oral cavity (OC). For other organs at risk (OARs), Radiation Therapy Oncology Group (RTOG) recommended dose constraints were applied. Planning was optimized to minimize doses to OARs without compromising coverage of PTVs. Radiation plans with IMRT-N and IMRT-S were compared.

Results: IMRT-N and IMRT-S showed equivalent radiation target coverages with sparing OARs, except OC. Dmean of OC was 34.8±1.6 Gy and 30.7±3.0 Gy with IMRT-N and IMRT-S, respectively (P = .006). OC volume receiving ≥36 Gy (V36) was 34.1±19.0% using IMRT-N compared to 28.0±15.9% with IMRT-S (P = .03). Dmean of oral tongue was 39.6±2.7 Gy and 31.7±3.5 Gy in IMRT-N and IMRT-S, respectively (P = .01). The distance from palate to surface of tongue tend to increase in IMRT-S with 0.9±0.3 cm compared to IMRT-N with 0.1±0.2 cm (P = .003).

Conclusion: In 5 patients with OPC, an IMRT-S significantly reduced radiation dose to oral cavity, specifically oral tongue, compared to IMRT-N without compromising radiation target coverage or other OARs. For the patients with OPC who were unable to use bite block or tongue blade, stuck-out tongue during radiation therapy can provide less OARs. For the patients with OPC who were unable to use bite block or tongue blade underwent computed tomographic simulations with neutral tongue position and stuck-out tongue during radiation therapy can provide less OC.


198

Concurrent Chemoradiation in Oropharyngeal Cancer: Does Omission of 1 or More Cycles of Chemotherapy Diminish Survival or Tumor Control?

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Purpose/Objective(s): Concurrent chemotherapy and radiation improves outcomes in patients with locoregionally advanced oropharyngeal cancer (LA-OPC). The standard regimen of high-dose cisplatin and 70 Gy radiation is associated with significant toxicities, often resulting in a decreased relative dose intensity of radiation and chemotherapy. The effect of such dose reduction on outcomes is unclear. We review our institution’s results to determine factors that predict for improved outcomes in LA-OPC.

Materials/Methods: All patients were treated with concurrent chemoradiation for LA-OPC at an academic medical center from 2007 to 2014. Patient, tumor, and treatment variables were abstracted from the patient records. Overall survival and data regarding relapse were collected. Overall survival and disease-free survival were compared using Kaplan-Meier curves. The log-rank test was used to determine statistical significance.

Results: The 47 patients analyzed had a median age at diagnosis of 56.7 years. The majority were male (89.4%) and had a history of tobacco use (74.5%). Among the 35 patients whose tumors were tested, 30 stained positive for p16. All but 1 patient reviewed had at least stage III disease.

Thirty-six (77%) patients were alive at last follow-up. The median follow-up time for the surviving patients is 2.9 years (range: 0.6-8.2 years). Among those who received cisplatin, there was no significant difference in overall survival or disease-free survival based on receipt of all 3 planned doses versus 1 to 2 doses (P = .93). Only 9 patients received cetuximab; there was no significant difference in overall survival when compared to cisplatin (P = .60). Six patients had a feeding tube placed prior to starting chemoradiation; an additional 20 (43%) required placement of a feeding tube during their chemoradiation course. Patients who lost >10 kg were noted to have a significantly improved overall and disease-free survival (P = .035).

Conclusion: Patients who lost >10 kg weight during therapy had improved outcomes. One possible explanation includes that the development of toxicity correlates with improved response. Omission of 1 or more cycles of cisplatin did not affect outcomes. These findings need to be further elucidated in the setting of larger retrospective series and prospective analyses and, if proven to be true, may have treatment implications.


199

Prognostic Significance of p16 in Squamous Cell Carcinoma of the Larynx and Hypopharynx

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Purpose/Objective(s): To evaluate the prognostic significance of p16 expression in patients with squamous cell carcinoma of the larynx (LSCC) and hypopharynx (HSCC).

Materials/Methods: The records of all patients with locally advanced, nonmetastatic LSCC/HSCC at a single institution were reviewed. P16 (Nkx3-1) protein expression was evaluated by immunohistochemistry (IHC). The Kaplan-Meier method was used to estimate overall survival (OS) and locoregional control (LRC). In select cases, HPV status was evaluated for high-risk and low-risk human papillomavirus (HPV) genotypes by in situ hybridization (ISH).

Results: Thirty-one patients (23 LSCC; 8 HSCC) were identified. Seventeen patients (55%) were p16 negative; 14 (45%) were p16 positive. The primary treatment modality was radiation therapy for 22 patients (71%) and surgery for 9 (29%). Nineteen patients (61%) were evaluated for high-risk HPV and low-risk HPV genotypes by IHC, of whom 2 patients (11%) were positive for high-risk HPV and 1 (5%) was positive for low-risk HPV. For high-risk HPV, the positive predictive value (PPV), sensitivity, and specificity of p16 were 20%, 100%, and 53%, respectively. There was no significant difference in the 2-year actuarial rates of OS (91% vs 64%, P = .34) or LRC (51% vs 46%, P = .69) between the p16-positive and p16-negative patients.

Conclusion: In this small cohort of 31 LSCC and HSCC patients, p16 was not a significant predictor of either LRC or OS. Furthermore, p16 was poorly associated with HPV as identified by ISH.

200

Impact of Weight Loss on Grip Strength in Head and Neck Cancer Patients Receiving Radiation Therapy

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Purpose/Objective(s): Malnutrition is a common complication for head and neck cancer (HNC) patients receiving radiation therapy (RT) or chemoradiation therapy (CRT). The Academy of Nutrition and Dietetics (AND) and the American Society of Parenteral and Enteral Nutrition (ASPEN) define moderate and severe malnutrition as the presence of 2 or more of the following: inadequate energy intake, weight loss, loss of body fat, loss of muscle mass, fluid accumulation, or reduced grip strength. In malnutrition, decreased muscle function may respond more quickly to nutritional deprivation than changes in weight. Research suggests that grip strength is a feasible tool for the bedside assessment of muscle function. The purpose of this study was to implement grip strength assessment as part of the nutrition assessment for HNC patients receiving RT or CRT and to investigate the relationship between grip strength and weight loss before and after 7 weeks of RT.

Materials/Methods: Grip strength, assessed by dynamometry, and weight were recorded the first and last week of RT. Each hand was measured 3 times and the average was calculated. Hand dominance was noted. Subjects were classified as malnourished if they met the AND/ASPEN malnutrition criteria for weight loss and reduced grip strength. Reduced grip strength was defined as a grip strength 2 standard deviations (SD) below the normative standards provided with the dynamometer. Descriptive statistics were used to describe the subject population, changes in grip strength, and changes in weight. Correlation between change in grip strength and change in weight was performed using the Pearson correlation.

Results: Eleven subjects, with a median age of 59 years (53-74), received RT (n = 4) or CRT (n = 7). Mean change in grip strength for the left hand was -1.0±3.8 kg (SD) and for the right hand was -0.7±5.6 kg (SD). The mean weight loss was 6.6±6.4 kg (SD). Decreased grip strength correlated weakly with weight loss for both the left (r = 0.248, 90% confidence interval [CI] -0.205-0.501, P = .462), and right hand (r = 0.180, 90% CI -0.396-0.680, P = .962). Two subjects (18%) at the initial treatment visit and 1 subject (9%) at the last treatment visit qualified as malnourished.

Conclusion: Although this study found no statistical correlation between weight loss and grip strength in the small series of HNC patients receiving RT or CRT, collecting data on grip strength using the dynamometer proved feasible. To more accurately diagnose malnutrition using the criteria of reduced grip strength, further research is needed to establish grip strength reference ranges.


Materials/Methods: A retrospective descriptive case series analysis of patients with parapharyngeal space tumors treated from January 2009 to July 2015 was performed.

Results: Fourteen patients were included: 11 females (76.9%) and 3 males (23.1%) with a mean age of 46.9 years (range 20-75 years). The most common symptom reported at presentation to our clinic was a foreign body sensation in the oropharynx and pain. Navigation-guided surgery was used in 2 cases. Mean size of tumors was 4.7 cm. Complete resection of lesions was performed in all cases, and the only major complication was major bleeding in 1 case (7.1%).

Conclusion: According to the present analysis, the submandibular transcervical approach is an effective and safe technique that allows resection of large parapharyngeal tumors, even those close to the skull base. It has minimal morbidity, prevents morbidity associated mandibulotomy, and allows extension to a transparotid, transmandibular, and even to an infratemporal fossa approach. Navigation is indicated in tumors ≤2 cm. The submandibular transcervical approach should be considered upfront for tumors ≤6 cm, preferentially ≥0.5 cm distant from skull base.


202

WITHDRAWN

203

Prognostic Value of Lymph Node Status Is Greater Than Lymph Node Ratio and AJCC N Staging for Head and Neck Squamous Cell Carcinomas

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Purpose/Objective(s): Changes in the epidemiology of head and neck cancers have created a need for new lymph node prognostics. The lymph node ratio (LNR) has been proposed as an alternative staging system, but this metric has limitations that may attenuate its prognostic value. This study sought to test the prognostic value of the lymph node status (pN) and compare it to the LNR and American Joint Committee on Cancer (AJCC) N staging.

Materials/Methods: The Survival, Epidemiology, and End Results (SEER) database was used to identify surgical cases from 2004 to 2012. The study sample was grouped based on AJCC N stage, LNR, and pN and analyzed using the Kaplan-Meier method and multivariate Cox proportional hazard models. Models were compared using the Akaike Information Criterion (AIC). The sample was also analyzed by site of primary tumor.

Results: We identified 12,437 patients in the SEER database for analysis. Distribution of nodal staging was 5282 N0 patients, 2483 N1 patients, 4454 N2 patients, and 218 N3 patients. Twenty-four percent of patients had an oropharyngeal primary. Kaplan-Meier survival curves showed improved prognostic ability for pN and LNR stagings relative to the AJCC system. Tumors with >5 positive nodes were associated with the worst overall survival (5-year survival rate = 16%). Oropharyngeal tumors had better outcomes for all groupings in all staging systems as compared to those in nonoropharyngeal sites. Using the pN staging system, >5 positive nodes in oropharyngeal tumors was strongly associated with decreased survival (5-year survival rate = 53%), while patients with 0 to 5 positive nodes had similar 5-year survival. Multivariate regression outputs demonstrated more prognostic hazard ratios and a lower AIC for the pN model compared to the AJCC N stage and LNR models (Table 1). Hazard ratios were 1.78 (95% confidence interval [CI], 1.62-1.95) for 1 positive node, 2.53 (95% CI, 2.32-2.75) for 2-5 positive nodes, and 4.64 (95% CI, 4.18-5.14) for >5 nodes.

Conclusion: The pN models demonstrated superior prognostic value compared to the LNR and AJCC N staging in the overall study sample.
and site-specific analyses. Future modifications of the nodal staging system should be based on the lymph node status, with consideration given to a separate system for oropharyngeal cancers. Patients with more than 5 positive nodes have significantly worse survival in all subsites and should be considered for alternative treatment regimens.  

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204  
Dosimetric Predictors of Hypothyroidism After Radical Intensity Modulated Radiation Therapy for Nasopharyngeal Carcinoma

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Purpose/Objective(s): We investigated for dosimetric predictors of hypothyroidism after radical intensity modulated radiation therapy (IMRT) for nonmetastatic nasopharyngeal carcinoma (NPC).

Materials/Methods: Patients with nonmetastatic NPC treated with radical IMRT from 2008 to 2013 were reviewed. They were regularly monitored clinically with serum thyroid function tests before and after IMRT. Univariable and multivariable analyses were performed for demographic and dosimetric predictors of biochemical and clinical hypothyroidism.

Results: A total of 149 patients fulfilled eligibility criteria. After a median follow-up duration of 3.1 years (range, 1.3-8.2 years), 33 patients (22.1%) and 21 patients (14.1%) developed biochemical and clinical hypothyroidism, respectively. Eight patients (24.2%) who had biochemical hypothyroidism developed clinical hypothyroidism later. Univariable and multivariable analyses revealed that volume of the thyroid (P = .002, multivariable), VS60 (the absolute thyroid volume spared from 60 Gy or less) (P < .001, multivariable), and VS45 (P = .001, multivariable) of the thyroid were significant predictive factors of biochemical hypothyroidism. The freedom from biochemical hypothyroidism was longer for those whose VS60 ≥ 10 mL (mean 90.9 months vs 62.6 months; P = .001) and VS45 ≥ 5 mL (mean 91.9 months vs 65.2 months; P = .001). Similarly, multivariable analyses revealed that volume of the thyroid (P = .002, multivariable), VS60 (the absolute thyroid volume spared from 60 Gy or less) (P < .001, multivariable), and VS45 (P < .001, multivariable) of the thyroid were significant predictive factors of clinical hypothyroidism. The freedom from clinical hypothyroidism was longer for those whose VS60 ≥ 10 mL (91.5 months vs 73.3 months, P = .002) and VS45 ≥ 5 mL (91.5 months vs 75.9 months, P = .007).

Receiver-operating characteristics (ROC) analyses revealed that the area-under-the-curve (AUC) value for VS60 was significantly higher than that for VS45 for both biochemical (0.751 vs 0.660; P = .009) and clinical hypothyroidism (0.718 vs 0.667; P = .007), respectively.

Conclusion: VS60 and VS45 of the thyroid significantly predicted post-IMRT hypothyroidism and should be considered important parameters of dose constraints during IMRT optimisation for NPC.


205  
Clinical Presentation of Oropharyngeal Squamous Cell Carcinoma in the Modern Era: Does Risk Stratification Using Human Papillomavirus and Smoking Status Matter?

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Purpose/Objective(s): Patterns of cervical lymph node metastases (LNMs) in patients with oropharyngeal squamous cell carcinoma (OPSCC) have historically been described. Here we compare the distribution of cervical LNMs in the human papillomavirus (HPV) era to historical controls. We also evaluated the influence of HPV and smoking status on the clinical presentation of OPSCC.

Materials/Methods: All patients with OPSCC presenting to our institutional multidisciplinary clinic from January 2010 to June 2015 were reviewed from a prospective database. Subsite, stage, smoking status, and involved anatomical nodal levels were tabulated. Variance in clinical presentation was examined using X2, Kruskal-Wallis, Mann-Whitney, and logistic regression analyses.

Results: Of 291 patients, HPV/p16 status was available for 243. Preliminary analyses confirmed that patients could be grouped based on anatomical site (Group 1: tonsil, base of tongue [BOT], vallecula, n = 217; Group 2: oropharyngeal wall, palate, and other n = 26) and risk level (low risk: HPV/p16 positive and ≤ 10 pack-year history of smoking, n = 78; intermediate risk: HPV/p16 positive and > 10 pack-year history of smoking, n = 82; high risk: HPV/p16 negative, n = 80). Overall, 188 patients (77.3%) had at least 1 cervical LNM at time of presentation (99.4% ipsilateral, 16.5% contralateral). Locally advanced tumor stages were uncommon at presentation (22.2% T1, 37.0% T2, 10.7% T3, 2.5% T4a, and 2.5% T4b); however, advanced nodal disease was more common (22.6% N0, 14.8% N1, 7.0% N2a, 39.1% N2b, 11.9% N2c, and 4.5% N3). Patients who were current smokers were more likely to present with metastases to level IIa than were nonsmokers (odds ratio [OR] = 4.56, P = .032). Rates of HPV/p16 positivity (P < .001), never having smoked (P = .016), and cervical LNM (P = .023) were significantly higher for patients in Group 1. Low-risk Group 1 patients presented with nodal stage N2a at a much higher than expected frequency (P = .007), and high-risk patients presented with tumor stage T4 at a much higher than expected frequency (P = .003). Previous smokers with a BOT subsite were more likely to have clinically positive ipsilateral necks than nonsmokers (OR = 1.8, P = .038). There were no significant differences in T stage or N stage based on HPV/p16 positivity or smoking (P > .05). Furthermore, distribution of cervical LNMs was not associated with HPV/p16 positivity, risk group, or anatomical group (P > .05). When data were compared to historical series, no significant differences were seen in the patterns of cervical lymph node metastases for patients with OPSCC.

Conclusion: HPV/p16 positivity, smoking status, risk group, and anatomical group influenced the clinical presentation of patients with OPSCC. Historical series describing the patterns of cervical LNMs in patients with OPSCC remain clinically relevant.


206  
Demographics, Disparities, and Survival in Young Patients With Oral Cavity Squamous Cell Carcinoma: A Population-Level Analysis of 3828 Cases

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Purpose/Objective(s): To characterize and identify prognosticators in oral cavity squamous cell carcinomas (OCSCC) in young patients. To determine whether type of hospital and insurance status correlates with survival.

Materials/Methods: We conducted a retrospective review of the National Cancer Data Base from 1998 to 2012 of OCSCC in patients younger than...
45 years of age. Relevant demographic, tumor, and survival variables were extracted for analysis. Hospitals were divided into community cancer programs (100-500 annual cancer cases) and comprehensive community or academic/research programs (≥500 annual cancer cases). Cox regression was used to identify predictors of survival.

Results: We identified 54,565 OSCC patients, 7.6% of whom are younger than 45 years of age (n = 3828). Of these patients, 80% were between 35 and 44 years of age. More males were affected (65.7%) than females. Caucasians represented 86.3% of cases, followed by African Americans (9.5%) and patients of “other” races (4.2%). Private insurance (65.6%) was most common, with Medicaid (17.6%), uninsured (11.7%), and Medicare (5.1%) comprising the rest. Overall survival at 2 and 5 years was 76% and 66%, respectively. The oral tongue subsite was most common (55.4%), followed by floor of mouth (FOM; 28.5%), gingiva/retromolar trigone (15.4%), and buccal mucosa (0.7%). An increasing incidence of oral tongue cancers was seen, while FOM cancers showed a decreasing trend over the study period. A minority of cases was treated at low-volume community cancer centers, which saw more stage I-II disease. Uninsured and Medicaid patients had more advanced stage III-IV disease (P<0.01), while those with private insurance had more early-stage disease. Further analysis including treatment, insurance, demographics, and survival was performed. cStage I-II patients without private insurance were more likely to receive some form of chemotheraphy, Ethnicity, insurance status, income, age group, pathologic stage, and positive surgical margins are significant prognosticators on univariate analysis. In multivariate analysis, high pathologic stage, non-private insurance, treatment at a low-volume community center, and positive margins remained predictors of worse survival.

Conclusion: In young patients with oral cavity cancers, differences in treatment, presentation, and survival were seen in those with health disparities. In addition to staging and surgical margins, treatment at low-volume community cancer centers and nonprivate insurance status predicted worse survival.

Author Disclosure: K. Zhan: None. E.A. Nicollie: None. T. Day: None.

208
Patient Immunosuppression and the Association With Cancer-Specific Outcomes After Treatment for Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): Patients (pts) with a history of immunosuppression such as hematologic malignancy or transplant have previously been shown to have an increased risk of a second malignancy and worse cancer-specific outcomes particularly with respect to oral cavity cancers. We aimed to determine the impact of immunosuppression on recurrence and survival after treatment for squamous cell carcinoma of the oropharynx (OPSCC).

Materials/Methods: We analyzed 336 pts with OPSCC treated with definitive intensity modulated radiation therapy (IMRT) to a median dose of 70 Gy (median 2 Gy/fraction) at a single institution. We identified all pt comorbidities at the initial consultation prior to therapy. Pts were considered to be immunosuppressed if they had a history of hematologic malignancy, stem-cell or solid-organ transplant, or AIDS. The association of immunosuppression with overall survival (OS) and recurrence was assessed with single and multivariable Cox proportional hazard regression models. Predictors that were significant in the univariate model with a P value of ≤0.05 were included in the multivariable model. The Fine & Gray method was used to adjust for competing risks.

Results: The primary cohort comprised 336 pts with OPSCC of whom 85% were male, the median age was 57.3 years, and primary sites were tonsil (49.4%), base of tongue (46.7%), and other (3.9%). Most pts were HPV positive (72.3%) with stage IVA being the most common American Joint Committee on Cancer stage (71.5%) followed by IVB (9.2%) and other. Pts received upfront concurrent chemoradiation (58%) or sequential therapy (38.4%). 3.6% received radiation alone. With a median follow-up of 3.8 years, pts with a history of immunosuppression had a 3-year OS of 71.4% with a cumulative incidence of local-regional failure (LRF) and distant failure of 32.1%. They had worse OS (adjusted hazard ratio [HR] 3.95, 95% confidence interval [CI] 1.13-13.80), worse recurrence-free survival (adjusted HR 3.72; 95% CI 1.18-11.75), and increased risk of LRF (unadjusted HR 3.80; 95% CI 1.31-11.09; adjusted HR 3.27; 95% CI 0.97-11.01) and increased risk of distant failure (adjusted HR 3.72; 95% CI 1.18-11.73) compared with the primary cohort of pts.

Conclusion: Patients with a diagnosis associated with immunosuppression prior to definitive treatment for OPSCC have worse OS and recurrence-free survival and increased rates of local and distant failure after treatment. This clinical finding lends support to exploring the role of optimal immune function for cancer clearance and survival after treatment for oropharyngeal cancer.


209
WITHDRAWN

210
Compliance to Radiation Therapy for Head and Neck Cancer in a Safety-Net Health System

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Purpose/Objective(s): To identify variables associated with compliance to radiation therapy (RT) for treatment of head and neck cancer in a safety-net health system.

Materials/Methods: We systematically screened electronic health record data from a large safety-net health system serving over 300,000 patients annually between October 2012 and August 2015 and identified 181 patients who were treated with radiation therapy (RT) in a curative approach for American Joint Committee on Cancer stage I-IV head and neck cancer. The number of days of missed treatments and reasons given for them by the patients were identified. Demographics, access to care, toxicity, drug use, comorbidities, psychiatric diagnosis, and treatment variables were analyzed for impact on compliance. Disease-free (DFS) and overall survival (OS) of patients with more than or fewer than 5 days of missed treatments were compared using Kaplan-Meier analyses.

Results: A total of 181 patients (mean age 54.8 years) were identified who completed RT with curative intent, and 141 (77.9%) of these patients received chemotherapy (CT). Of these patients, 45 (31.9%) patients received induction CT, and 136 (96.4%) received concurrent CT. There were 166 patients (90.0%) who completed all fractions of RT, and 43 patients (23.8%) completed their RT with no missed days. There were 9240 total treatment days (mean of 51.1 treatment days), of which 844 (9.1%) were missed or delayed treatment days. Patient-offered reasons for the delay were classified as: failure to coordinate care (n=34, 4.0%), transportation issues (n=54, 6.4%), acute toxicity (n=229, 25.9%), remained treatment (n=20, 2.4%), comorbidities (n=107, 12.7%), delays related to PFG feeding tubes (n=18, 2.1%), tolerance to set-up (n=32, 3.8%), patient initiated (n=209, 24.8%), and unknown (n=150, 17.8%). Not owning a vehicle was associated with missing more days due to transportation issues (P=0.04). Male gender (P=0.017) and weight loss during radiation (P=0.029) were associated with more total missed days of radiation. Variables that were associated with 5 or more missed treatment days were the lowest Karnofsky Performance Score Status achieved during RT (P=0.002), maximum pain score during RT (P=0.042), skin sensation toxicity (P=0.008), history of methamphetamine abuse (P=0.009) (but not other substances), and multiagent induction CT (P=0.027). In patients whose RT treatment was completed with fewer than or exactly 5 days of delay, DFS was improved by 9.4 months (22.5 vs 13.1, P=0.012), and OS was improved by 7.0 months (28.2 vs 15.3, P=0.001).

Conclusion: This study concurs with past studies that missing treatments is detrimental to overall survival. Therefore, it is prudent in a safety-net hospital to identify specific barriers to treatment compliance in order to design optimal interventions, such as a questionnaire that identifies high-risk patients so that we can intervene by allocating resources appropriately in order to improve outcomes.

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211
Free Open Source REDCap Software to Track EORTC QLQ-30 and H&N-35 Quality of Life Scores and Allow Real-Time Clinical Management of Individual Patients

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Purpose/Objective(s): Treatment for head and neck cancer involves a combination of therapies that are highly toxic impacting both quality of life (QOL) and overall recovery period. The purpose of this project is to prospectively monitor QOL in a cohort of head and neck cancer patients while integrating QOL findings into patient care.

Materials/Methods: QOL is currently being tracked in a head and neck radiation medicine clinic using the European Organization for Research and Treatment of Cancer (EORTC) Quality of life (QLQ)-30 and EORTC head and neck module (H&N)-35 questionnaires which was translated into a digital platform using a Research Electronic Data Capture (REDCap) survey format. Patients complete the survey at the beginning of treatment, end of treatment, and at each follow-up appointment (3 months, 6 months, 1 year). The REDCap survey program build enables automatic computation of scores upon patient completion. Results are therefore available for immediate review by the clinician.

Results: A total of 561 QOL surveys have been completed by 200 patients to date. Patients have completed surveys up to a period of 20 months following treatment.

Conclusion: Prospectively tracking QOL before, during, and after treatment provides clinicians with a more comprehensive understanding of factors related to changes in their patients’ QOL scores, allowing them to provide immediate treatment or appropriate referrals. Using a digital platform (REDCap Surveys) is a novel method for tracking and managing QOL factors in real time in a head and neck cancer population.


212
Basal Cell Adenocarcinoma of the Major Salivary Glands: A Population-Level Study of 509 Cases

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Purpose/Objective(s): We sought to better characterize the demographic, tumor, and long-term survival characteristics of basal cell adenocarcinoma (BCAC) of the major salivary glands with the National Cancer Data Base (NCDB), the world’s largest cancer database.

Materials/Methods: We conducted a retrospective review of the National Cancer Data Base (NCDB) from 1998 to 2012 for all cases of major salivary gland basal cell adenocarcinoma (BCAC) with histologic code 81477. Relevant demographic, tumor, and survival variables were extracted for analysis. Cox univariate and multivariate regression analysis was used to identify predictors of survival.

Results: Out of 36,224 major salivary gland cancers in the NCDB, we found 509 cases of BCAC (1.4%), 88% of which were in the parotid glands, 11.2% submandibular, and 0.8% in the sublingual glands. Age at diagnosis ranged from 18 to 92 years (average 64). No gender preference was found (50.7% male). Most tumors were 2 to 4 cm in size (47.3%). Regional (11.9%) and distant metastases (1.8%) were uncommon. Occult nodal disease was rare (5.7%). Of available grade information, 22.4% were labeled high grade (9% of all cases). Survival between low- and high-grade
lymph node metastases are common. Distant and regional metastasis are predictors of worse survival. Conclusion: Basal cell adenocarcinoma is a rare salivary malignancy with a good prognosis, traditionally understood as a low-risk malignancy. The presence of “high-grade” tumors may suggest a more aggressive variant, although survival was not significantly different. Overall, regional and distant metastases were uncommon. Radiation with surgery may help for higher T-stage disease. Old age and high T stage were significant predictors of worse survival.

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more likely to occur in the ≥75 years of age group (45.6% vs 19.2%, P<0.01). Odds of being treated with radiation were less in sOC compared to dnOC cancer (OR: 0.79, confidence interval [CI]: 0.66-0.96, P<0.05). sOC cancer patients were less likely to receive radiation with a prior diagnosis of breast cancer (OR: 0.60, 95% CI: 0.39-0.95, P<0.05). No differences in surgical intervention were seen between sOC and dnOC cases. Median OS was longer in sOC in comparison to sOC cases (61 vs 43 mo) (hazard ratio [HR]: 1.19, 95% CI: 1.13-1.27, P<0.01). Oral cancer-related survival was worse in sOC compared to dnOC cases (HR: 1.16, 95% CI: 1.1-1.20).

Conclusion: Elderly age is more common in sOC versus dnOC cancer, and patients with sOC cancer receive radiation less frequently than do those with dnOC cancer. Although sOC tumors were more likely to be limited to local disease, survival was worse in sOC compared to dnOC cancer. Future research should seek to understand whether treatment decisions for the sOC are driving this difference in survival.


216

Demographics of Individuals Presenting to Community Oral Screenings as Compared to Head and Neck Cancer Patients Seen in an Academic Multidisciplinary Clinic

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Purpose/Objective(s): Community oral screening for head and neck cancer is widely promoted, although the utility of such screening is largely unknown. We sought to characterize the demographics of individuals presenting for free community oral cancer screenings as compared to the demographics of head and neck cancer patients seen in an academic multidisciplinary clinic.

Materials/Methods: Demographics of the screened population were collected retrospectively from information provided voluntarily by subjects at the time of screening. All subjects older than 18 years of age screened in calendar years 2012 and 2013 were included. Patient demographics and cancer type were collected retrospectively from a prospectively maintained database of patients seen in an academic head and neck cancer multidisciplinary clinic during the same time period. The discrete characteristics are compared using a X² test and continuous characteristics are compared using a t test for normally distributed data and Wilcoxon rank sum test for nonnormally distributed data.

Results: A total of 519 screened subjects and 491 cancer patients met inclusion criteria. The gender distribution of the screened population differed significantly from that of the cancer patient population, with males representing 74.08% of cancer patients but only 32.11% of the screened population (P<0.001). Screened subjects were also significantly younger than the cancer patients (median age 52 years and 61 years respectively, P<0.05). The cancer patients were 3 times more likely than screened individuals to reside in a zip code classified as rural by the Office of Management and Budget (18.13% vs 5.03%). Referral rate of screened individuals (including referral to dentistry, dermatology, or otolaryngology) did not differ significantly by gender, age, or screening location (hospital, state fair, community health fair, or baseball game). In this cohort of patients, male cancer patients were more likely than female patients to present to the multidisciplinary clinic with a diagnosis of squamous cell carcinoma. Other diagnoses including cutaneous malignancies, thyroid cancer, and salivary gland cancers comprised 40.2% of presenting diagnoses in female cancer patients.

Conclusion: Individuals presenting voluntarily for community oral cancer screenings are demographically distinct from patients diagnosed with head and neck cancer and evaluated at an academic multidisciplinary clinic.


217

Squamous Cell Carcinoma of the Buccal Mucosa: Clinical Outcomes of Patients Treated at a Tertiary Care Hospital in Pakistan

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Purpose/Objective(s): Squamous cell carcinoma (SCC) of the buccal mucosa is one of the commonest oral cavity cancers in South East Asia. It is usually associated with the use of tobacco, gutka, and betel quid. There is a dearth of data on behavior and outcomes of these tumors, not only from this region but also worldwide. The aim of our study is to share the demographics, prognostic factors, and clinical outcomes of these patients.

Materials/Methods: Retrospective chart review was conducted after approval from the ethical review committee. All patients with localized/locally advanced buccal mucosa SCC presenting and receiving treatment at our institute between January 2006 and December 2013 were included. Patients with lesions originating from other oral structures extending into buccal mucosa and who did not complete their treatment at the institute were excluded. Demographic data, patterns of clinical presentations, risk factors, surgical pathology, and details of treatment were reviewed. SPSS v19 was used to perform statistical analysis.

Results: A total of 220 patients were included. One hundred seventy-six (80.4%) were males and 43 (19.6%) were females. Mean age at presentation was 48 years (range: 24-83). One hundred eighty-five (84%) patients were users of tobacco and betel quid. Nonhealing oral ulcer was the main presenting symptom in 161 patients (73.5%) followed by cheek swelling in 41 patients (19.3%). All patients underwent surgery of which 157 (71.7%) received adjuvant treatment. Pathological stage/margin status was found to be independent prognostic factors affecting survival. One hundred eleven (50.4%) of these patients relapsed. Eighty (72.1%) of those had loco-regional recurrence while 31 (27.9%) developed distant metastasis. The main sites of metastasis were lungs (51%) and bones (16%).

Conclusion: Squamous cell carcinoma of the buccal mucosa is a common malignancy in our region which is strongly correlated with tobacco/betel quid abuse. Despite optimal treatment more than half of the patients in our study relapsed. Further studies are required to characterize and optimize management of this malignancy.


218

Accuracy of 3-Tesla Magnetic Resonance Imaging for the Initial Evaluation of Tongue Carcinoma

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Purpose/Objective(s): With a higher signal-to-noise ratio than 1.5 T, in theory, our study aims to further define 3T MRI’s role in the initial evaluation of oral tongue cancer.

Materials/Methods: In this prospective study, 29 patients with histologically proven squamous cell carcinoma of the tongue underwent preoperative 3T MRI (2009-2012); 25 patients were included and 4 patients were excluded. Using 3T MRI scans of the head and neck, tumor thickness was measured or reconstructed, and cervical lymph node metastases were evaluated.

Results: Mean tumor thickness did not significantly differ between measured (18.2±7.3 mm) or reconstructed (17.9±7.2 mm) images.
805
Compared with histology findings, mean measured thickness was 8.3 mm higher by MRI while mean reconstructed thickness was 5.51 mm greater (P<0.001). Correlation between MRI depth of invasion and cervical metastases was confirmed of 21 patients with 3T MRI showing cervical nodal metastases, 20 had undergone neck dissection. While no patients with a 3T-MRI depth of invasion <5 mm had cervical metastases, 11 of 21 patients with thickness >5 mm did at surgery. 3T MRI had 83% sensitivity and 82% specificity for detecting positive cervical lymph node metastases.

253 Conclusion: We identified 3T MRI's effectiveness in evaluating the extent of squamous cell tongue carcinoma. With accuracy provided by direct measurement of tumor thickness, reconstructions are unnecessary. 3T MRI has a higher sensitivity, specificity, and negative predictive value than 1.5T MRI when predicting nodal stage. 3T MRI was useful for detection of malignant adenopathy with extracapsular spread.

257 Author Disclosure: Y. Patil: None.

219
259 Predicting Outcomes Using Pre- and Posttreatment PET/CT in Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck

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263 Materials/Methods: One hundred thirty-seven patients with LASCCHN underwent pretreatment PET/CT with repeat imaging obtained 3 months after therapy. Both the primary tumor and dominant lymph node were assessed for size in grade. On some patients, volumetric assessment was obtained using 3D reconstruction. On some patients, volumetric data were collected using commercial software to segment primary tumor targets. Linear growth rates were calculated from the serial scans. Demographic, treatment, and outcome information was obtained from patient charts. Recursive partitioning analysis was used to identify cut points associated with outcomes. Kaplan-Meier calculations were used to evaluate disease control and overall survival (OS). Comparisons between groups were made using Wilcoxon tests. Cox regression, univariate, and multivariate analyses were also performed.

269 Results: Median follow-up was 59 months (range 7-118). The majority of patients (60%) underwent concurrent chemoradiation, 18% underwent definitive radiation, and 22% underwent induction chemotherapy followed by radiation or chemoradiation. Mean pretreatment PET/CT was 0.16±0.23 mL/day. Recursive partitioning analysis identified velocity cut point of 0.2 mL/day associated with local recurrence. Patients with TGV=0.2 mL/day had significantly worse 5-year local control (LC; P<0.0001) and OS (P<0.0001) than patients with lower TGV, as shown in Table 1 below.

274 TGV >0.2 mL/day 23 68% 48% TGV <0.2 mL/day 70 97% 80%

278 Univariate analysis also showed that higher TGV predicts worse LC (hazard ratio [HR] 13.0; 95% confidence interval [CI] 3.1-87.5, P=0.003) and OS (HR 3.8; 95% CI 1.7-8.5, P=0.001). Multivariate analysis of age, sex, ethnicity, T stage, overall American Joint Committee on Cancer stage, and human papillomavirus status suggested that higher TGV is an independent predictor of LC (HR 11.6; 95% CI 2.2-59.0, P=0.003) and OS (HR 3.0; 95% CI 1.2-7.6, P=0.02).

283 Conclusion: Oropharyngeal squamous TGV>0.2 mL/day is a substantive negative prognostic indicator for LC and OS. This novel quantitative CT-based volumetric assessment of tumor growth velocity suggests a simple methodology for stratification of oropharyngeal squamous cell cancer patients into a distinct risk group for which treatment and screening strategies could be optimized.


299

220 Impact of Pretreatment Volumetric Tumor Growth Velocity on Oncologic Outcomes in Oropharyngeal Squamous Cell Cancer

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292 Materials/Methods: We performed a retrospective analysis of 3-dimensional TGV in patients with oropharyngeal cancer treated with radiation at a single institution between 2004 and 2008. Ninety-three patients met inclusion criteria of squamous histology; 2 pretreatment CTs with radiographically visible tumors, and scan time gap of more than 2 weeks. Volumetric data were collected using commercial software to segment primary tumor targets. Linear growth rates were calculated from the serial scans. Demographic, treatment, and outcome information was obtained from patient charts. Recursive partitioning analysis was used to identify cut points associated with outcomes. Kaplan-Meier calculations were used to evaluate disease control and overall survival (OS). Comparisons between groups were made using Wilcoxon tests. Cox regression, univariate, and multivariate analyses were also performed.

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317 Conclusion: Oropharyngeal squamous TGV>0.2 mL/day is a substantive negative prognostic indicator for LC and OS. This novel quantitative CT-based volumetric assessment of tumor growth velocity suggests a simple methodology for stratification of oropharyngeal squamous cell cancer patients into a distinct risk group for which treatment and screening strategies could be optimized.

Purpose/Objective(s): Squamous cell carcinoma (SCC) of the larynx is routinely treated with radiation (XRT) alone or concurrently with chemotherapy (CRT) with the goals of disease cure and organ preservation. Many patients, however, develop local recurrence after XRT or CRT and require salvage laryngectomy. There is controversy regarding the role of neck dissection in salvage laryngectomy as the frequency of occult nodal disease in clinically N0 patients has been reported to be from 3% to 17%, with a higher rate in T4 (34%) and supraglottic tumors (28%). Positron emission tomography–computed tomography (PET-CT) is increasingly used in laryngeal SCC to evaluate treatment response, detect recurrence, and aid in staging. The objective of this study was to evaluate the predictive value of PET-CT in identifying occult nodal metastasis in patients undergoing salvage laryngectomy.

Materials/Methods: A retrospective review of 46 clinically N0 patients with no nodal disease on physical exam or other imaging modalities (CT or magnetic resonance) who underwent salvage laryngectomy with neck dissection from January 1, 2002 to December 31, 2014 was performed. Patients were included if a PET-CT was performed prior to surgery. Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR−), sensitivity (Se), and specificity (Sp) were calculated. PET-CT results were classified as positive (metastasis), negative (no metastasis), and equivocal.

Results: The PPV, NPV, LR+, LR−, Se, Sp were 75% (95% CI, 19.4%–99.4%), 78.6% (95% CI, 63.2%–89.7%), 4.4, 0.2, 59.2% for PP and PE groups (P < 0.001). Likewise the 5-year disease-specific survival (DSS) and overall survival (OS) were also significantly higher for PN patients; 92.6% and 88.1% for PN, 49.9% and 41.2% for PN, and both 58.7% for PE (P < 0.001 for both DSS and OS).

Conclusion: PET-CT has a reasonable specificity but poor sensitivity in detecting occult nodal disease. The PPV of 78.6% makes PET-CT an imperfect predictor of nodal disease in the setting of recurrent laryngeal cancer.


223

The Long-Term Predictive Value of Posttreatment Positron Emission Tomography—Computed Tomography Imaging in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): 18F-fluorodeoxyglucose–positron emission tomography (PET) scans can be a helpful tool in managing head and neck squamous cell carcinoma. The purpose of this study is to evaluate the predicative significance of a negative posttreatment PET scan performed on long-term outcomes.

Materials/Methods: One hundred twenty-nine patients who received radiation therapy with or without chemotherapy at our institution from 2002 to 2011 and had posttreatment PET/CT imaging were retrospectively reviewed under an institutional review board–approved protocol. Median age at diagnosis was 58 years (range: 25 - 81 years), and there were 97 males and 32 females. Primary site was oral cavity (3%), oropharynx (68%), hypopharynx (8%), larynx (18%), and unknown (3%), and the following disease stages were present: stage I (7%), stage II (8%), stage III (27%), and stage IV (58%). The median dose delivered was 70 Gy (range 66-72 Gy). Ninety were treated with concurrent chemotherapy. The median time from the end of therapy to PET/CT was 4.1 months. Posttreatment PET/CT scans were simply categorized as negative (no residual FDG avidity), positive (residual avidity or increased FDG avidity at initial or new sites), or equivocal based on initial radiological report.

Results: Median follow-up was 52 months (range: 4 - 142 months). By response on posttreatment PET, 71 patients were classified as negative, 45 as positive, and 13 equivocal. Overall disease recurrence (local, locoregional, or distant) was identified in 5 patients (7%) in the PET-negative (PN) group, 24 patients (53%) in the PET-positive (PP) group, and 5 patients (38%) in the PET-equivocal (PE) group. For disease recurrence, a negative posttreatment PET scan had a negative predictive value of (NPV) of 95%. Most recurrences occurred within 2 years of treatment (87.5%). The median time for recurrence was 20.5 months, 6.6 months, and 12.2 months, respectively for the PN, PP, and PE groups. The 2-year recurrence-free survival was highest for PN patients; 95.6% compared to 47.7%, and 59.2% for PP and PE groups (P < 0.001). Likewise the 5-year disease-specific survival (DSS) and overall survival (OS) were also significantly higher for PN patients; 92.6% and 88.1% for PN, 49.9% and 41.2% for PN, and both 58.7% for PE (P < 0.001 for both DSS and OS).

Conclusion: For posttreatment PET findings of negative, positive, and equivocal, the long-term outcomes were 92.6% and 88.1% for PN, 49.9% and 41.2% for PN, and both 58.7% for PE (P < 0.001 for both DSS and OS).

Purpose/Objective(s): Radiation therapy (RT) for nasopharyngeal carcinoma (NPC) is often effective at curing disease but can injure the surrounding organs at risk, including the muscles responsible for swallowing, with possible resultant short-term or long-term dysphagia. However, no study has tracked serial (ie, acute and late) quantitative dose-response magnetic resonance imaging (MRI) parameter kinetics in a uniform NPC dataset. We aim to characterize serial MRI signal intensity (SI) changes in dysphagia-associated volumes of interest (VOIs) as a function of the radiati therapy dose.

Materials/Methods: In this retrospective study, we extracted data on 77 patients with stage III-IV NPC who had been treated with curative intensity modulated RT (IMRT). The mean T1- and T2-weighted MRI SIs were recorded for the superior pharyngeal constrictor (SPC) and soft palate (SP) at baseline, early-after IMRT, and last follow-up, with normalization to reference structures receiving <5 Gy. RT dose grids were restored for dose response analysis. Statistical methods included a nonparametric analysis test and recursive partitioning analysis (RPA).

Results: The median time to early post-RT follow-up was 4 months, and the median time to late post-RT follow-up was 41 months. The mean dose to the SPC was 62.4 Gy (standard deviation [SD], 8.7 Gy), and the mean dose to the SP was 66.8 Gy (SD, 7.3 Gy). All structures had a significant increase in T2 SIs early after treatment compared to baseline, irrespective of the mean dose given (SPC and SP, 0.47±0.12 and 0.56±0.12 at baseline vs 0.73±0.18 and 0.82±0.17, respectively, P<0.0001 for both). At last follow-up, the increase in T2 SI subsided completely for SPC and partially for SP. The T1 SI did not change significantly in early follow-up images of both structures; on late follow-up, patients with mean doses >62.25 Gy had significant decrease in the corresponding T1 SI for SPC (1.6±0.4 vs 1.3±0.4, P=0.007) compared to baseline but decreased nonsignificantly for SP (1.7±0.5 vs 1.6±0.5, P=0.09). No significant changes in T1 SI were noted with doses below 62.25 Gy for both structures. Continuous RPA showed a cutoff value of magnitude 0.37 for alterations in T1 SI, with a Dmean of 63.8 Gy (95% confidence interval [CI], 61.6-66.0) for those with decrease >0.37 compared to 56.7 Gy (95% CI, 52.2-61.1) for those not achieving threshold. A sigmoidal fit was used to create a normal tissue complication probability curve for T1 alteration as a function of dose (observed R2=0.928).

Conclusion: Serial MRI acquisitions enable the identification of both early and late radiation-induced changes in swallowing structures after definitive IMRT for NPC. Decreased SI on late T1 images may indicate muscle fibrosis and is associated with higher RT doses to the SPC, while increased SI on early T2 images is associated with acute edema that subsides after therapy.


Prospective Comparative Study of Diffusion-Weighted MRI Versus FDG-PET for Detection of Recurrence After (Chemo)radiation for Head and Neck Squamous Cell Carcinoma

Purpose/Objective(s): High-dose (chemo)radiotherapy for head and neck squamous cell carcinoma (HNSCC) may result in late edema and necrosis, resembling recurrent disease. FDG-postion emission tomography/ computed tomography (PET/CT) has a high negative predictive value for recurrent disease; however, it is limited by the positive predictive value. The diagnostic accuracy of conventional magnetic resonance imaging (MRI) with diffusion-weighted (DW) MRI to detect a local recurrence has been compared with the standard FDG-PET/CT.

Materials/Methods: Seventy-four patients clinically suspected of local recurrence after (chemo)radiation for laryngeal, hypopharyngeal or oropharyngeal cancers were prospectively included in this study and underwent an MRI including diffusion-weighted imaging (DW-MRI) and an FDG-PET/CT. Qualitative assessment of DW-MRI and FDG-PET/CT was performed by an experienced radiologist resp. nuclear physician blinded for the other modality. Reference standard was the absence of a biopsy-proven local recurrence within 6 months following imaging.

Results: Four patients were excluded due to contraindications or disruption of the MRI (eg, claustrophobia or patient stature). Seventy-three percent (51 of 70) of the FDG-PET/CTs were positive compared to only 46% (32 of 70) of the DW-MRI. FDG-PET/CT had a diagnostic accuracy of 72% compared to 73% for MR-DWI. The negative predictive value of FDG-PET/CT was 94% compared to 71% for MR-DWI. The positive predictive value of FDG-PET/CT was 64% compared to 75% for DW-MRI. See Table 1 for the complete results.

Conclusion: In this study, DW-MRI showed superior positive predictive value but inferior negative predictive value compared to FDG-PET/CT. False negative results will cause delay in the detection of recurrence and therefore will potentially influence the chance of successful salvage surgery. Therefore, based on these results, we consider FDG-PET/CT to be superior to MR-DWI in the follow-up of HNSCC after (chemo)radiotherapy. With improved technical performance DW-MRI techniques which will decrease artefacts and enhance contrast, may enable DWI to resemble FDG-PET/CT negative predictive value without compromising the higher positive predictive value of DWI.

Author Disclosure: J. Driessen: None. C. Terhaard: None. M. Philippens: None. W. Grolman: None.

Assessment of Laryngeal Motion Dynamics Using 4D-Computed Tomography and Dynamic Magnetic Resonance Imaging

Purpose/Objective(s): With increasing interest in reduced-volume intensity modulated radiation therapy (IMRT) and intrafraction image guidance for early glottic cancer, we sought to better understand laryngeal motion. The aim of our study was to determine the dynamics of laryngeal motion during the course of a radiation treatment using combined 4-dimensional computed tomography (4D-CT) and cine-magnetic resonance imaging (MRI) information.

Materials/Methods: This prospective study included patients with T1-2N0 glottic cancer treated with radical radiation therapy. Dynamic sagittal MRI was obtained pretreatment and midtreatment to assess for inadvertent swallowing frequency and respiratory motion. Pre- and midtreatment 4D-CT allowed for assessment of larynx excursion during swallowing and breathing as well as evaluation of gross tumor volume, clinical target volume (CTV), and planning target volume (PTV) coverage during motion. In addition, bone registration of simulation CT with pre- and
midtreatment 4D-CT allowed for assessment of larynx resting position shift compared to simulation CT. Student t and Fisher tests were used for statistical analysis.

Results: Twenty patients were included. Pretreatment median swallowing frequency over 2 minutes was 1 time (0-5) without instruction versus 0 (0-1) with instruction not to swallow, \( P = .03 \). Midtreatment median frequency was 0, with or without instruction. On 4D-CT, median amplitude of deglutition was 22 mm (14-30), 0 mm (0-3), 6 mm (3-9), and 0 mm (0-3) in the superior, inferior, anterior, and posterior directions, respectively; these correlated well with amplitudes seen on MRI. Median swallowing duration was 2.4 (1.3-3.1) seconds. Assuming 1 deglutition during a 2-minute treatment and a 1-cm craniocaudal PTV, the CTV would spend a median of 1.7 seconds (0-2) outside of the 95% isodose volume. Median amplitude of respiratory laryngeal motion was 4 mm (2-6) and 2 mm (1-2) in the SI and anteroposterior (AP) directions. There were no statistically significant differences between pre- and midtreatment amplitudes. Midtreatment 4D-CT identified a shift in larynx resting position compared to simulation CT in 40% of cases (median 4 [4-8] mm in SI and 3 [2-4] mm in AP).

Conclusion: Our study supports minimal occurrence and minimal dosimetric impact of swallowing during treatment; PTV volumes need not account for the entire swallowing motion. Respiratory motion up to 6 mm was identified and should be taken into account when considering reduced volume IMRT planning. A larynx shift, potentially related to an anatomy change, occurs during treatment in a significant proportion of patients and warrants for the use of laryngeal cone beam CT match rather than bone match. Our data will help define PTV margins for a future phase 2 study of single vocal cord IMRT.


227

Correlating Clinical Outcomes With Changes in Tumor Volume and 18F-FDG PET Characteristics During Radiation Therapy for Head and Neck Squamous Cell Carcinoma (HNSCC)

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Purpose/Objective(s): To assess the predictive value of 18F-FDG positron emission tomography/computed tomography (PET/CT) parameters during induction chemotherapy (IC) for response to radical chemoradiation therapy (CRT) in head and neck squamous cell carcinoma (HNSCC).

Materials/Methods: This is an ongoing prospective, single-institution study in which patients underwent 18F-FDG-PET/CT with thermoplastic shell immobilization before and 2 weeks following each cycle of IC (first cycle, IC1; second cycle, IC2). Following IC, patients received radical CRT (65 Gy in 30 fractions) over 6 weeks with concomitant chemotherapy on days 1 and 29. Treatment response was assessed at 3 months from completion of CRT with clinical examination, magnetic resonance imaging, and 18F-FDG-PET/CT. Patients with evidence of residual or progressive disease were classified as nonresponders. Reductions in tumor SUVmax (maximum standard uptake value) and MTV (metabolic tumor volume with a pre-determined SUV threshold of 3.5) following IC were compared between responders versus non-responders with Mann-Whitney U test. The significance threshold was set at \( P < .05 \).

Results: Twenty patients with stage III/IVA HNSCC were included in this preliminary analysis. The median age was 63 years (47-79). All patients underwent 2 cycles of IC except 3 patients who stopped after 1 cycle due to poor tolerance. One patient did not receive concomitant chemotherapy due to persistent myelosuppression. In 17 evaluable patients, there was no significant difference in the changes from baseline between IC1 and IC2 for MTV (\( P = .80 \)) and SUVmax (\( P = .10 \)).

Abstract 227; Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response (n=62)</th>
<th>Incomplete response (n=72)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>ΔGTVp</td>
<td>−46 (−55, −40)</td>
<td>−46 (−81, 13)</td>
<td>.9</td>
</tr>
<tr>
<td>ΔGTVn</td>
<td>−36 (−44, −28)</td>
<td>−21 (−40, 11)</td>
<td>.43 (−49, 29)</td>
</tr>
<tr>
<td>ΔSUVmax</td>
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<td>−31 (−46, −13)</td>
<td>.39 (−45, 33)</td>
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<tr>
<td>ΔSUVmax</td>
<td>−35 (−45, −28)</td>
<td>−28 (−63, 12)</td>
<td>.37 (−47, 31)</td>
</tr>
<tr>
<td>ΔSUVmean</td>
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<td>−28 (−46, 7)</td>
<td>−28 (−38, 20)</td>
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<tr>
<td>ΔSUVmean</td>
<td>−30 (−35, 23)</td>
<td>−28 (−50, 12)</td>
<td>−31 (−36, 20)</td>
</tr>
</tbody>
</table>

Discussion: Although this study is limited by sample size, the results suggest that lower pretreatment SUVmax and SUVmean of GTVp, SUVmax of GTVn, and nodule tumor volume are associated with improved outcome. Analyses are ongoing to assess whether metabolic tumor volume and other SUV parameters predict for clinical outcomes.

229
Prognostic Value of 18-Fluorodeoxyglucose in Independent Training and Validation Sets of Patients With HNSCC Largely Explained by Association With Tumor Volume

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Purpose/Objective(s): Training and validation sets of patients with Head and Neck squamous cell cancer (HNSCC) were generated by the model in the test set were 90%, 81%, 61%, and 30%. A simpler model, ignoring FDG uptake, provided equivalent prognostication.

Conclusion: The prognostic value of the original model was validated in the independent validation set, but the effect size associated with FDG uptake is overestimated if tumor volume is not appropriately accounted for.


230
Dynamic Optical Contrast Imaging as a Novel Modality to Rapidly Distinguish Oral Squamous Cell Carcinoma From Surrounding Normal Tissue

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Purpose/Objective(s): Head and neck cancers are debilitating diseases for which patient prognosis depends heavily on complete tumor resection. Currently, it is the surgeon’s fingers and eyes that determine the location of tissue margins. An intraoperative instrument that can significantly improve the accuracy of margin detection over current methods will improve outcomes for cancer patients by minimizing removal of normal functional tissue while also ensuring complete tumor removal. The objective herein is to demonstrate the utility of dynamic optical contrast imaging (DOCI) in reliably and accurately delineating tumor tissue from surrounding normal tissues.

Materials/Methods: Oral squamous cell carcinoma (OSCC) specimens and surrounding tissues from the surgical bed were collected; fluorescence decay images were acquired using a wide-field DOCI system. Samples from 55 patients were subsequently processed for standard histological assessment by head and neck pathologists. Mean relative fluorescence decay signatures were calculated for tumor, fat, muscle, and collagen tissues. Statistical analyses were performed using the Wilcoxon signed rank test.

Results: Qualitative analysis of DOCI images revealed microscopic characterization sufficient for tissue type identification comparable to histology. Quantitative analysis revealed a statistically significant difference (P<0.05) between tumor and collagen among 10 of 10 wavelength bands analyzed, between tumor and muscle in 10 bands, and between fat and tumor in 2 bands.

Conclusion: This study demonstrates a novel imaging modality capable of rapidly and significantly distinguishing OSCC from surrounding normal tissue. Such an intraoperative tool would be transformative: allowing for an intraoperative capacity to delineate tumor tissue from nontumor tissue, thus maximizing the efficacy of tumor resection and minimizing damage to adjacent structures, thus improving patient outcomes.

231
Primary Tumor and Nodal Regression Rates: The Prognostic Value of Volumetric Image Guided Radiation Therapy for Head and Neck Cancer
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Purpose/Objective(s): The objective of this study is to evaluate weekly primary tumor regression rates (PTRR) and nodal tumor regression rates (NTRR) of head and neck cancers (HNC) during radiation (RT) as a prognostic indicator of oncologic outcomes and survival. Image guided radiation therapy (IGRT), specifically computed tomography (CT)-on-Rails (CToR), increases the accuracy of daily RT and additionally affords the opportunity for intratreatment response evaluation.

Materials/Methods: A single-institution retrospective review from 2008 to 2013 was completed for patients with HNC who received RT with CToR. Forty-three patients with 70 measurable targets, 43 primary lesions and 27 metastatic lymph nodes, met inclusion criteria. Patients without radiographically evident primary tumors and those with surgical intervention prior to RT were excluded.

Results: The analysis included 43 patients with a median age of 56 years (21-78), and 91% of them were male. The majority of patients were diagnosed with oropharynx cancers (63%), 26% nasopharynx and 11% sinonasal. Fifty-eight percent of patients received definitive chemoradiation, 25% treatment plan modification may be warranted 19%) were purely cystic or had a cystic component. Many of the highly cystic nodes demonstrated an initial increase in size, likely secondary to RT induced inflammation, before later regression.

Conclusion: CToR enables accurate GTV tracking during treatment which carries prognostic value. PTRR of ≥25% at midtreatment can be used as an indicator for LC, RFS, and OS. NTRR does not appear to carry the same prognostic value as PTRR due to variations in nodal architecture, an initial paradoxical size increase, especially in cystic nodes, and treatment response often continuing up to 4 months post-RT. The clinical implication of TRR appears to be of most value when tracking the primary lesion, and specifically if PTRR <25% treatment plan modification may be warranted given a higher likelihood of treatment failure.


232
Comparison of Tumor Volume Delineation on Magnetic Resonance/Positron Emission Tomography Versus Standard Computed Tomography for Head and Neck Cancer: Is There Added Value?
K. Wang,1 B. Mullins,1 A. Falchook,1 J. Lian,1 M.J. Dance,1 W. Lin,2 T. Sills,1 B. Huang,1 and B.S. Chera2
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Purpose/Objective(s): To determine how radiation-induced mucositis affects radiotracer uptake at pretreatment planning CT and immediately after radiation therapy (RT) in head and neck cancer (HNC) patients. Materials/Methods: Patients with locally advanced HNC were enrolled in an institutional review board–approved phase I trial to determine the feasibility of using PET/CT to guide treatment dose escalation. Patients were treated with accelerated regimen, 2.27 Gy per fraction to 68.1 Gy in 30 fractions over 6 weeks. Concurrent cisplatin was given every 3 weeks. PET scans using 2 types of tracers, [18F]FDG and [18F]FLT, were obtained at fraction 15 (n=21) and 13.6 mL (SD 10.3), respectively. PTRR of metastatic lymph nodes, met inclusion criteria. Patients without radiotherapy to neck were excluded. The objective of this study is to evaluate weekly primary tumor regression rates (PTRR) and nodal tumor regression rates (NTRR) of head and neck cancers (HNC) during radiation (RT) as a prognostic indicator of oncologic outcomes and survival. Image guided radiation therapy (IGRT), specifically computed tomography (CT)-on-Rails (CToR), increases the accuracy of daily RT and additionally affords the opportunity for intratreatment response evaluation.

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233
Radiation-Induced Mucositis Does Not Increase Radiotracer Uptake on PET/CT Imaging in Head and Neck Cancer Patients
S. Song,1 J. Zweit,1 M.J. Fratkin,1 J.F. Williamson,1 and D. Holdorf1
1Virginia Commonwealth University Health System, Richmond, VA 2Virginia Commonwealth University, Richmond, VA, United States

Purpose/Objective(s): To determine how radiation-induced mucositis affects radiotracer uptake on positron emission tomography/computed tomography (PET/CT) scan during and immediately after radiation therapy (RT) in head and neck cancer (HNC) patients.

Materials/Methods: Patients with locally advanced HNC were enrolled in an institutional review board–approved phase I trial to determine the feasibility of using PET/CT to guide treatment dose escalation. Patients were treated with accelerated regimen, 2.27 Gy per fraction to 68.1 Gy in 30 fractions over 6 weeks. Concurrent cisplatin was given every 3 weeks. PET scans using 2 types of tracers, [18F]FDG and [18F]FLT, were obtained at fraction 15 (n=21) and 13.6 mL (SD 10.3), respectively. PTRR of metastatic lymph nodes, met inclusion criteria. Patients without radiotherapy to neck were excluded. The objective of this study is to evaluate weekly primary tumor regression rates (PTRR) and nodal tumor regression rates (NTRR) of head and neck cancers (HNC) during radiation (RT) as a prognostic indicator of oncologic outcomes and survival. Image guided radiation therapy (IGRT), specifically computed tomography (CT)-on-Rails (CToR), increases the accuracy of daily RT and additionally affords the opportunity for intratreatment response evaluation.

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233
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S. Song,1 J. Zweit,1 M.J. Fratkin,1 J.F. Williamson,1 and D. Holdorf1
1Virginia Commonwealth University Health System, Richmond, VA 2Virginia Commonwealth University, Richmond, VA, United States

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mucositis in imaging interpretation, as FLT, unlike FDG, does not highlight metabolic or inflammatory activity of the tissue. A total of 9 PET scans were planned per patient (4 FLT-PET and 5 FDG-PET scans). Acute mucositis was recorded according to Common Terminology Criteria for Adverse Events version 4. PET scans were read by the same radiologist. Maximal standard uptake value of FDG-PET at each timepoint was compared with FLT-PET. Activity of both FLT- and FDG-PET was also matched to the mucositis score to determine the correlation between PET activity and the severity of mucositis.

Results: Three patients were enrolled in the first phase of the feasibility study. A total of 26 PET scans were obtained (missing was an FLT scan in 1 patient at week 2). All patients completed treatment according to the protocol. All patients developed mucositis, which nearly peaked at the end of week 4. Both FDG and FLT PET activity significantly decreased at week 2 and reached the lowest level at week 4. FDG-PET did not show activity in areas with the severe mucositis at and around the primary site, same as FLT-PET (see table). Interestingly, FLT- as well as FDG-PET activity slightly increased at week 2 after RT at the mucosal sites while mucositis subsided to less than grade 2. At minimal follow-up of 1 year, all patients were without treatment failure.

Conclusion: This study demonstrates that radiation-induced mucositis in oral cavity or oropharynx does not increase FDG or FLT uptake during radiation therapy.


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234

PET/CT in CT Simulation: Significance of a Standardized Positioning Protocol for Head and Neck Radiation Therapy Planning

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Purpose/Objective(s): Diagnostic imaging scans, such as PET/CT and MRI, provide a valuable tool for radiation therapy treatment planning (RTP) for head and neck (H&N) cancer. Information from diagnostic scans can be incorporated into the RTP process by performing a dedicated diagnostic scan in the treatment position or by coregistering an existing scan with the simulation scan. The former approach should minimize differences in anatomical positioning that may hinder accurate coregistration. The purpose of this study was to use the claval incline to quantify differences in H&N positioning between patients undergoing diagnostic PET/CTs positioned with versus without the RTP immobilization mask.

Materials/Methods: Twenty patients who received intensity modulated radiation therapy for H&N cancer from 2011 to 2015 at our institution were selected for this retrospective review. Ten patients underwent diagnostic PET/CT using the mask created during simulation (Group A) while 10 patients underwent PET/CT without the mask (Group B). A 5-point Ortho Effict thermoplastic mask, size B head support, base plate, and, occasionally, a block or wedge were used for immobilization. Clival incline was measured for each simulation and PET/CT group using MIRADA software by a single user.

Results: Mean clival incline for Group B was 61.44° (standard deviation [SD], 8.30°; standard error mean [SEM], 2.62°), while clival incline for Group A was 72.25° (SD, 7.78°; SEM, 2.46°). Comparing the simulation CT to the PET/CT, mean clival incline difference was 12.61° in Group B (SD, 5.62°; SEM, 1.78°), and 1.48° (SD, 1.026°; SEM, 0.32°) in Group A. Both these differences between the groups were statistically significant, P = .008 and P = .001, respectively, using t test analysis for the equality of means.

Conclusion: Based on these results we reach 2 conclusions: (1) when no mask is used (when PET/CT technologists position patients without guidance from radiation oncology staff), there is a different approach to positioning; PET/CT technologists favor a more neutral to flexion position, while we favor a neutral to extended position. (2) Using the simulation mask for the PET/CT greatly reduces the difference in head position when compared to its respective simulation scan. This allows for a more robust registration. Given these data, when possible, patients should have PET/CT performed using the immobilization mask created for simulation. However, as this is not always feasible, dosimetric and clinical studies are warranted to further explore the implications of a standardized neck positioning protocol for both H&N simulations and PET/CT scans.

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235

Does Routine Surveillance PET/CT at 3 Months Have Value After Laryngectomy (L) Followed by Radiation therapy (RT) for Locoregionally Advanced Laryngeal Cancer? T. Yuan,1 J.M. Watkins,2 S.L. Mont,3 M. Marquardt,2 A. Hoover,3 W. Sun,2 J. Batti,1 N. Pagdah,1 and C.M. Anderson;2 Cancer Center of Guangzhou Medical University, Guangzhou, China, 2University of Iowa Hospitals & Clinics, Iowa City, IA, 3The University of Kansas Hospital, Kansas City, KS

Purpose/Objective(s): While positron emission tomography/computed tomography (PET/CT) has demonstrated value following definitive chemoradiation therapy in the setting of locoregionally advanced laryngeal cancer (LC), its routine use in surveillance following laryngectomy (L) + radiation therapy (RT) remains to be determined. This study explores the diagnostic value of PET/CT 3 months following L+RT.

Materials/Methods: This institutional review board–approved retrospective review included patients who underwent curative-intent L with adjuvant RT for initial presentation of LC, with 3-month post-RT surveillance PET/CT performed in the absence of suspected active disease. The positive and negative predictive values for locoregional disease (PETV/ negativity) were calculated based upon the 3-month PET/CT head and neck findings, as correlated with clinical or pathologic outcomes during the 12 months after the scan. Patients with PET/CT performed <60 or >130 days post-RT or who had <12 months of potential post-PET oncologic follow-up were excluded.

Results: Between 2004 and 2014, 18 patients were eligible for the present analysis; 3 had partial laryngectomy and 15 had total laryngectomy. The median age at diagnosis was 56 years (range 48-73), and pathologic stage was III, IVA, and IVB for 3 (17%), 4 (22%), and 1 (6%) patients, respectively. All patients started adjuvant RT at a median of 45 days post-L (31-72), with median dose 66 Gy (60-70) and 10 patients (56%) also received concurrent platinum-based chemotherapy. PET/CT was performed at a median of 98 days post-RT completion (69-127), with 4 patients (22%) demonstrating positive locoregional findings. At a median follow-up of 31.9 months (10.3-75.5) post-PET/CT, 11 patients were alive (10 without recurrence, 1 with active disease) and 7 patients had died (5 with recurrent LC, 4 of 5 with distant recurrence only, 1 of 5 with regional and distant recurrence). The sensitivity, specificity, PPV, and NPV for surveillance 3-month PET for locoregional disease were 100%, 80%, 25%, and 100%, respectively. Occult distant metastases were discovered on 3-month PET/CT in 4 of 18 patients (22%), all of whom had lung metastases.

Bone and liver mets were additionally discovered in 1 of these 4 patients. The remaining patient who died of LC recurred in the lungs 38.1 mo after...
DCE-MRI can detect dose-dependent alterations in mandibular bone vascularity as measured by K\textsubscript{trans}.

Thirty-two patients undergoing EBRT treatment for laryngeal cancer patients. We demonstrate, in a prospective imaging trial, that DCE-MRI can provide indications for risk-adapted treatment strategies. Here, we analyze tumor textural features from pretreatment 18\textsubscript{F}-fluorodeoxyglucose (FDG) PET scans as related to clinical outcomes in patients treated with definitive radiation therapy (RT) for laryngeal cancer.

Purpose/Objective(s): Seventy-five consecutive patients with laryngeal squamous cell carcinoma treated with definitive RT with available pretreatment PET/CT scans at our institution were retrospectively evaluated.

Materials/Methods: Thirty-two patients undergoing EBRT treatment for head and neck cancer underwent prospective DCE-MRI imaging prior to, midway through, and following chemoradiation therapy. DCE-MRI scans were coregistered to dosimetric maps to correlate EBRT dose and change in mandibular bone vascularity as measured by K\textsubscript{trans}.

Results: All patients had successful completion of treatment. We identified 3 patterns of vascularity changes associated with EBRT. One group of patients demonstrated a dose-dependent increase in K\textsubscript{trans} midway during (n=9) and following completion (n=5) of treatment. One group of patients demonstrated a dose-dependent decrease in K\textsubscript{trans} midway during (n=8) and following completion (n=6) of treatment. One group of patients demonstrated no change in K\textsubscript{trans} midway during (n=13) and following completion (n=20) of treatment. Overall, the frequency of dose-dependent changes in mandibular vascularity abated from the midpoint to the endpoint of the treatment regimen.

Conclusion: We demonstrate, in a prospective imaging trial, that DCE-MRI can detect dose-dependent alterations in mandibular bone vascularity during and following chemoradiation therapy and measures a biomarker of acute mandibular injury and recovery temporal kinetics.

Purpose/Objective(s): Statistical image features from computed tomography (CT) and positron emission tomography (PET) scans are currently being explored for their potential to predict clinical outcome and thus provide indications for risk-adapted treatment strategies. Here, we analyze tumor textural features from pretreatment 18\textsubscript{F}-fluorodeoxyglucose (FDG) PET scans as related to clinical outcomes in patients treated with definitive radiation therapy (RT) for laryngeal cancer.

Materials/Methods: Seventy-five consecutive patients with laryngeal squamous cell carcinoma treated with definitive RT with available pretreatment PET/CT scans at our institution were retrospectively evaluated.

Results: With a median follow-up of 31.4 months, the 3-year LC, PFS, and overall survival (OS) were 66% (53%-79%), 49% (36%-62%), and 75% (64%-87%), respectively. Out of the calculated image features, only SUV\textsubscript{peak} value from pretreatment PET scans may hold important information for LC, suggesting that the SUV\textsubscript{peak} value may hold important information about potential regional or distant spread. Dividing the patient population based on the median SUV\textsubscript{peak} value shows a split of the Kaplan-Meier survival curves, although not statistically significant with a log-rank P value of 0.82. KPS=70 was the only parameter significantly related to OS (P=0.0002).

Conclusion: The SUV\textsubscript{peak} value from pretreatment PET scans may hold important information about the risk of distant and regional spread for laryngeal cancer patients. We are currently working on gathering additional patient data to validate these findings.
239

Prognostic Significance of FDG-PET/CT Metabolic Parameters After
Induction Chemotherapy in Squamous Cell Carcinoma of the Head and
Neck

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Purpose/objective(s): Previously, we reported that the absolute metabolic tumor volume (MTV) measured on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) after 2 cycles of induction chemotherapy (IC) and the percent reduction of MTV are prognostic for tumor recurrence in patients with squamous cell carcinoma of the head and neck (SCCHN). In this study, we updated the analysis to include patients from an additional IC protocol to evaluate the prognostic significance of MTV and related PET parameters in a larger cohort.

Materials/Methods: From 2009 to 2013, 60 consecutive patients with SCCHN (T1 excluded) were enrolled in 2 single-institution prospective single-arm phase 2 trials. From 2009 to 2010, 30 patients were treated with APCE (nab-paflaxil, cisplatin, 5-FU, and cetuximab x3 cycles). From 2012 to 2013, another 30 patients were treated with APFx3 cycles. IC was scheduled to be followed by concurrent chemoradiation with cisplatin and 70 Gy at 2 Gy per fraction for both trials. Of the 60 patients, 54 had evaluable FDG-PET/CT studies obtained both before and after 2 cycles of IC. The primary tumors were contoured using a gradient-based method software tool. Total body weight was used to calculate SUVs. SUVmax, SUVmean, MTV, and total glycolytic activity (TGA = SUVmean*MTV) of the pre- and post-IC scans as well as the percent changes in these parameters were calculated. Wilcoxon rank sum testing was used to compare the parameters of patients with any tumor recurrence to those without. A likelihood-based approach was used to identify the optimal cutpoints with regard to recurrence-free survival and determine the associated P values.

Results: The primary tumors were oropharynx (38; 31 of 37 were p16+ by IHC), larynx (11), hypopharynx (4), and oral cavity (1). Tumor stages were as follows: T2 (15), T3 (19), T4a (18), and T4b (2). At the median follow-up of 2.9 years, 5 patients (9%) had tumor recurrence: 3 local, 2 regional, and 2 distant metastases (1 patient had all 3 types of recurrences). Of the patients with recurrence, 4 had oropharynx and 1 had larynx cancer. Compared to the patients without recurrence, those with recurrence had higher post-IC MTV (P <.011) and TGA (P =.008) and had smaller post-IC reductions in MTV (P =.008) and TGA (P =.016). Factors that increased the risk of tumor recurrence included a postinduction MTV of more than 4 cm3 (P <.001, absolute risk [AR] 24% vs 0%), a postinduction TGA of more than 16 SUVmean*cm3 (P <.001, AR 29% vs 0%), and a decrease in MTV of less than 63% (P <.001, AR 28% vs 0%), and a decrease in TGA of less than 63% (P =.002, AR 21% vs 0%).

Conclusion: MTV and the TGA of the tumor on FDG-PET/CT after IC, as well as the percent reduction in these parameters after therapy, are prognostic for tumor recurrence.


240

Redefining Osteoradionecrosis With the Use of Cone Beam
Technology

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Purpose/objective(s): Osteoradionecrosis (ORN) has been defined in multiple ways; however, this diagnosis is generally made when exposed bone in a previously irradiated field is documented. This review of head and neck cancer patients who have been irradiated has incorporated the use of cone beam computed tomography (CBCT) scans to uncover ORN that is not visible on routine physical examination. Combining these radiographic findings with other characteristics in patients who have been diagnosed with ORN, there appear to be subsets of ORN.

Materials/Methods: The charts of 45 patients with head and neck cancer who had received radiation therapy and been diagnosed with ORN were retrospectively reviewed. Specific characteristics looked at included the location of ORN, patient’s sex, dose to area of breakdown of bone, finding on CBCT scan, and timing of diagnosis after radiation. Utilizing these 5 characteristics, it became clear that there were subsets of ORN that correlated with a patient’s prognosis with respect to their ORN and the best approach in terms of managing this condition.

Results: Three subsets of patients with ORN were identified: (1) spontaneous ORN (SpO), (2) subclinical ORN (SubO), and (3) traumatic ORN (TO). Patients with SpO always developed ORN in the posterior aspect of the mylo-hyoid ridge of the mandible, were male, received between 6500 and 7000 centiGray, and occurred within 12 months after radiation. Patients with SubO did not have exposed bone but, instead, radiographically on CBCT scan, they had clear evidence of breakdown in their mandibular bone, this was not specific to males or females, on occasion they received less than 6500 centiGray, and occurred beyond 12 months out from radiation. Patients with TO developed ORN as a result of iatrogenic medical means (ie, following a biopsy in the previously irradiated field) or by an invasive dental procedure (ie, extraction or periodontal surgery in an area previously irradiated). Depending on the timing and management of one’s treatment for ORN, patients with SpO had the best prognosis while those with TO had the worst. Prognosis of those with SubO was in between.

Conclusion: This review suggests that rather than treating all patients with ORN the same way, there appears to be a benefit with placing them into 1 of 3 subsets of ORN: SpO, SubO, or TO. Doing so will help the treating radiation oncologist and dentist in caring for this individual’s symptoms and counseling them in how best to deal with this potentially devastating complication of therapy both emotionally and psychologically.


241

Anatomic and Dosimetric Changes in Patients With Head and Neck
Cancer Treated With a Tri-60Co Teletherapy/Magnetic Resonance
Imaging Device

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Purpose/Objective(s): Prior studies have quantified the anatomic changes in head and neck cancer patients during a course of intensity modulated radiation therapy (IMRT) by analyzing serial images acquired using onboard computed tomography (CT). A novel tri-60Co teletherapy system equipped with a 0.35 T magnetic resonance imaging (MRI) allows MRI-based image guided IMRT. We sought to determine the feasibility of quantifying the anatomic and dosimetric changes of the primary gross tumor volumes (GTVs) and the parotid glands using daily pretreatment MRIs among patients with head and neck squamous cell carcinoma (HNSCC) treated with this MRI/IMRT device.

Materials/Methods: Six patients with HNSCC were treated with the MRI/IMRT system to 66.00 to 69.96 Gy in 33 fractions. Pre-IMRT MRIs on days 1, 5, 10, 15, 20, 25, 30, and 35 were imported into a contouring interface. Primary GTVs and parotids were contoured on each MRI and volumes were quantified. The center of mass (COM) shifts for these structures were assessed relative to the COM on day 1 in the medial-lateral direction. Daily dose delivery data were imported into the contouring interface, and doses to the GTVs and parotids were assessed.
based on daily contours. Statistical significance was determined by the 2-tailed t test, while correlations were assessed by the Spearman coefficient.

**Results:** Primary GTVs decreased significantly in volume over the course of IMRT (median % volume loss, 38.7%; range, 29.5-72.0%; P < 0.05) at a median rate of 1.2% per fraction (range, 0.92%-2.2% per fraction). Both ipsilateral and contralateral parotid glands underwent significant volume loss (P < 0.05). Median percentage of volume loss of ipsilateral parotid glands was 31.1% (2.3%-45.9%), and median rate of volume loss was 0.97% per fraction (0.07%-1.4% per fraction). Contralateral parotids experienced a median percentage of volume loss of 21.8% (4.0%-40.5%) and median shrinkage rate of 0.68% per fraction (0.13%-1.3% per fraction). Both ipsilateral and contralateral parotids shifted medially during IMRT. Weight loss correlated significantly with parotid gland volume loss and medial COM shift (P < 0.05). Dose received by the primary GTVs and parotids did not significantly change during treatment. Median difference between administered median dose at fraction 33 and planned dose per fraction was 0.008 Gy (+0.06-0.18 Gy) for ipsilateral and 0.01 Gy (+0.12-0.27 Gy) for contralateral parotids.

**Conclusion:** Integrated on-board MRIs from a tri-18O-Co teletherapy system can be used to accurately contour and analyze primary GTVs and parotid glands over the course of IMRT. COM shifts and significant volume reductions of the primary tumors and parotids were observed, confirming the results of CT-based studies. The enhanced resolution of the MRIs acquired may facilitate online adaptive re-planning in the future. Despite anatomic changes during IMRT, significant dosimetric shifts were not always apparent.

**Author Disclosure:** G. Raghavan: None. A.U. Kishan: None. M. Cao: None. Y. Yang: None. A.M. Chen: None.

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**Validation Is Crucial in Head and Neck Translational Imaging**

**Research**

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**Purpose/Objective(s):** Delineation of the tumor, based on imaging, is the weakest link in radiation therapy. The value of new and existing imaging techniques should be demonstrated by comparison with the ground truth: histopathology. Total laryngectomy (TLE) specimens are an appropriate model, since the resected tissue remains cohesive.

**Materials/Methods:** For 27 patients who received primary TLE because of T3/T4 laryngeal or hypopharyngeal cancer, ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET), computed tomography (CT), and magnetic resonance imaging (MRI) images were made in a radiation mask before surgery. The specimens were fixed and sliced, and whole-mount hematoxylin-eosin (H&E) stained sections were obtained. These were used to digitally reconstruct the specimen in 3 dimensions, which was registered to the CT, MRI, and FDG-PET scan. H&E sections, CT, and MRI were delineated by 3 observers. For the FDG-PET scan, automatic delineations were obtained with a Gaussian mixture model. MRI was delineated in 2 sessions, the first according to clinical practice. The second session involved excluding regions with high signal intensity on T1 weighted MRI. This is a retrospective, institutional review board–approved analysis of 52 cases of OPC recurrence from the year 1997 to 2015 at Mayo Clinic Rochester, MN. These cases failed after being treated with surgery followed by adjuvant radiation therapy with or without chemotherapy. Time to failure was determined following adjuvant radiation treatment. Local, nodal, or distant failure patterns were categorized based on clinical or imaging evaluations.

**Results:** Among the 52 cases with disease recurrence, the mean time to recurrence following adjuvant treatment was 10.7 months (median 8 months). Distant, regional, and local failure comprised 79%, 13%, and 8% of the cohort, respectively. A total of 36 patients (69%) failed within the first year following completion of treatment: 3 local, 5 nodal, and 28 distant. Among the patients that failed, 12 were detected clinically, whereas 24 were detected by imaging modalities. CT detected 8 cases while PET was successful in detecting 16 cases. The mean time to clinical detection was 5 months (3 local [25%], 2 nodal [17%], 7 distant [58%]), while the mean time to detection by imaging was 6.2 months (1 local [4%], 5 nodal [21%], 18 distant [75%]). In the imaging category, the mean time of recurrence detection was 7.5 months by CT scan and 5.5 months by PET. Early local failures are generally detected by physical exam (25% vs 4%). However, imaging exam was superior at detecting nodal and distant failure (17% vs 21% in nodal and 58% vs 75% in distant). PET detected distant failures earlier than CT by an average of approximately 2 months.

**Conclusion:** Imaging modalities remain the optimal tool for detecting disease recurrence following adjuvant radiation treatment. Surveillance and follow-up in OPC patients undergoing adjuvant therapy warrants early imaging for regional and distant disease detection.

**Acknowledgment(s):** *Authors M. Shuja and M. Rosado contributed equally to this abstract.

244

Functional Outcome of Total Glossectomy and Anterolateral Thigh Free Flap (ALTF) Reconstruction: Long-Term Follow-up Result

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Purpose/Objective(s): In advanced tongue cancer, wide excision and reconstruction is indispensable. After reconstruction, functional problems like speech and swallowing can occur, and tongue volume and height are important factors related to this functional problem. The purpose of this study was to evaluate the relationship between reconstructed tongue volume and functional outcome in advanced tongue cancer patients who received total or near total glossectomy.

Materials/Methods: From January 2004 to December 2013, tongue cancer patients who received total or near total glossectomy and reconstruction with anterolateral thigh free flap (ALTF) in St. Mary Hospital in Seoul, Korea, were involved in this study. All patients had postoperative computed tomography or magnetic resonance imaging scans at 6 months and 2 years, and reconstructed tongue volume was calculated by summation of all 2-dimensional areas of the reconstructed tongue. Speech ability was scored from 0 to 100 points by a professional speech language pathologist. Swallowing ability was scored from 1 to 7 by the latest Modified Barium Swallow test or esophagogram.

Results: From a pool of 25 patients, 19 patients who followed up were involved in this study. Tongue volume was reduced about 19% from 6 months to 2 years following surgery. There was a statistical difference between tongue volume and 2 years following surgery (P = 0.01), and more tongue volume led to less weight change. Patients with a larger tongue volume loss showed larger weight loss, but there was no statistical significance. Speech and swallowing ability were related to tongue volume at 6 months and 2 years following surgery, and this was statistically significant.

Conclusion: There was a statistically significant relation between reconstructed tongue volume and postoperative functional outcome.

Author Disclosure: Y. Choi: None. M. Kim: None.

245

The Prognostic Utility of 18F-FDG-PET Metabolic Tumor Response Following Chemoradiation Therapy for Locally Advanced Head and Neck Cancer

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Purpose/Objective(s): To characterize 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) metabolic tumor response (MTR) findings and the associated prognosis following chemoradiation therapy (CRT) for locally advanced head and neck cancer (HNC).

Materials/Methods: A retrospective study of the pre- and posttreatment FDG-PET scans of 47 individuals who underwent CRT for stage III-IV HNC between 2003 and 2011 was undertaken. FDG-PET was usually performed before therapy and 2 to 3 months after completion of CRT. Interpretation of images by visual analysis was either a positive or negative scan indicating incomplete or complete MTR respectively.

Results: Thirty-nine patients (83%) exhibited complete resolution of tumor and 8 individuals (17%) had incomplete or absent MTRs. At a median follow-up of 36 months, the overall locoregional failure and distant metastases rates were 17%. The 2-year survival rates in people with complete and incomplete disappearance of the neoplasms were 92% and 57%, respectively (P = 0.02); the corresponding 2-year disease-free survival rates were 97% and 25% (P = 0.01). After adjusting for patient age, primary and regional disease stage, site and volume of the neoplasm, number of chemotherapy drugs used, and the presence or absence of significant comorbidity, tumor response was the only significant independent predictor of prognosis.

Conclusion: FDG-PET imaging, aside from documenting MTR >2 months after CRT, may also be useful for its prognosis predictive potential in patients with locally advanced HNC.

important to prevent long-term changes in tissues occurring with LE. “Seeing” lymphatic vessels and function could guide manual lymphatic drainage therapy to alleviate fluid accumulation.

**Materials/Methods:** Lymphatic anatomy and function (pumping) were visualized using near-infrared fluorescence lymphatic imaging (NIRFLI) with a customized imaging system. Intraorbital and intradermal injections of indocyanine green (ICG) delivered microdose amounts (less than 300 micrometres total per subject) of the fluorescent dye. Seven study subjects were imaged before surgery, before radiation, and then longitudinally at approximate 3-month intervals, for a total of 7 imaging sessions per study subject. Of note, 1 subject received no radiation.

**Results:** Head and neck lymphatic vessels were readily visualized in all subjects. Dermal lymph backflow was noted in all subjects who received radiation. 1 of these subjects developed temporary edema, and another of these subjects developed lymphedema. The subject who received no radiation did not develop dermal backflow or lymphedema.

**Conclusion:** Radiation treatment may impart a greater risk of H&N lymphatic abnormalities. NIRFLI allowed early detection of changes in lymphatic vessel usage and function after H&N cancer treatment.

**Author Disclosure:** H.S. Naqvi: None. R.J. Karni: None. I. Tan: None. J. Rasmussen: None. M. Aldrich: None. J. Morrow: None. E. Sevick: None.

**Related Articles:**

1. **248 Combined Radiation and PD-L1 Blockade Improved Tumor Control in Mouse Head and Neck Squamous Cell Carcinoma (HNSCC)**

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**Purpose/Objective(s):** Expression of the negative immune regulatory molecule, programmed death-ligand 1 (PD-L1) by tumor cells is associated with T cell dysfunction, attenuated antitumor immune responses, and poor clinical outcomes. Blocking the interaction between PD-L1 and its receptor, programmed death-1 (PD-1), expressed on activated CD8+ cytotoxic T lymphocytes (CTLs) enhances antitumor activity. Radiation induces cell death and is known to release in the release of tumor-associated antigens capable of triggering antitumor responses as well as enhancing antigen presentation. Radiation therapy (RT) is a commonly used treatment for locally advanced or recurrent HNSCC. In the current study, we examined the effect of radiation on major histocompatibility complex class I (MHC-I) and PD-L1 expression on HNSCC cell lines, and whether the combination of RT and PD-L1 blockade will improve tumor control.

**Materials/Methods:** Seven human (UCP1-SCC-90, UDS2C2, UMSCC-1, UMSCC-6, UMSCC-22B, UMSCC-47, and 93W147T), and 3 mouse (Meer, MTE, and PAM212) HNSCC cell lines were examined for expression of MHC-I antigens and PD-L1 by flow cytometry after irradiation with 1, 6, and 10 Gy, and at different timepoints (0, 12, 24, 72, and 96 h, and 7 days). The antitumor effect of RT combined with anti-PD-L1 antibody was evaluated in a subcutaneous mouse Meer HNSCC tumor model.

**Results:** Both human and mouse HNSCC cell lines constitutively expressed PD-L1. Irradiation increased the expression of MHC-I and PD-L1 in a dose and time-dependent manner. This trend was observed in all cell lines. Irradiation induced both MHC-I and PD-L1 expression 3 to 4 fold between days 4 and 7, compared to nonirradiated cells. In the mouse model, treatment with combined RT and anti PD-L1 antibody resulted in complete tumor eradication in 10 of 16 mice (62.5%). Median survival of untreated control mice (n=10) was 33 days (range, 25-41 days), that of mice receiving XRT alone (n=6) was 50 days (range, 36-71 days), and animals treated with the combination of XRT and anti-PD-L1 (n=8) survived a median of 101 days (range, 67-101+ days).

**Conclusion:** Radiation increased expression of both MHC-I and PD-L1 on tumor cells in a dose- and time-dependent manner. The combination of radiation and anti-PD-L1 improved survival of mice bearing subcutaneous Meer HNSCC compared to mice treated with radiation, or anti-PD-L1 alone. The combination radiation therapy and PD-L1/PD-1 blockade deserve further investigation in HNSCC.

250
Synergistic Combination of PD-1 and EGFR Antibodies: A Proposed Phase 1 Clinical Trial Using Nivolumab and Cetuximab
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Purpose/Objective(s): Cetuximab induces head and neck cancer cell death through ADCC mediated by NK cells. NK cells when activated by the Fc exposed region of cetuximab bound to EGFR increase production of IFN-gamma. The high levels of IFN-gamma produced dendritic cell maturation and also increase CD8 T cell expression of PD1. The combination of an EGFR mab with a checkpoint (PD1) inhibitor may be synergistic through an enhancement of CD8 T cell activation and dendritic cell engagement which will increase cancer cytolyis. Based on this preclinical data, we proposed a phase 1 clinical trial exploring the combination of cetuximab plus nivolumab in recurrent head and neck cancer patients. The goal of the trial is to identify the maximally tolerated dose (MTD) and the recommended phase 2 dose (RP2D). Secondary endpoints would be the assessment of response rate, progression-free survival (PFS), and overall survival (OS).

Materials/Methods: Patients with recurrent head and neck cancers will be eligible. We recommended a phase 1 clinical trial with a 3+3 dose escalation design as described here: (1) dose Level 1: cetuximab 200 mg/m² IV loading dose followed by weekly cetuximab 125 mg/m² IV nivolumab 1.5 mg/kg IV every 14 days; (2) dose Level 2: cetuximab 300 mg/m² IV loading dose followed by weekly cetuximab 187.5 mg/m² IV nivolumab 2.25 mg/kg IV every 14 days; and (3) dose Level 3: cetuximab 400 mg/m² IV loading dose followed by weekly 250 mg/m² IV nivolumab 3 mg/kg IV every 14 days.

Results: Since cetuximab as single agent has a response rate of 10% to 20% as a single agent in metastatic head and neck cancer, we anticipate a response rate of 30% with the proposed combination therapy. Since the agents do not have overlap toxicity, we do not anticipate major toxicities.

Conclusion: PD-1 and EGFR Ab therapy may be synergistic, and further exploration in a clinical setting is proposed on this abstract.

Author Disclosure: J.Y. Lee: None. E. Sapia: None. A. Eisbruch: None.

251
Shorter Reirradiation Intervals for Head and Neck Cancer Are Associated With Severe Long-Term Toxicity
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Purpose/Objective(s): Reirradiation to the head and neck for recurrent disease or a second primary malignancy is increasing in frequency. A retreatment interval cutoff of 6 months is often cited when considering reirradiation, as studies have demonstrated a correlation between retreatment interval and survival. However, treatment-related toxicity can be substantial after reirradiation, and little is known regarding its determinants. We sought to identify factors that correlate with severe long-term toxicity.

Materials/Methods: We reviewed treatment plans and outcomes of patients who underwent intensity modulated radiation therapy (IMRT)-based reirradiation to the head and neck at a single institution from 2008 to 2015 with data available for both the initial and reirradiation course. Graded (Common Terminology Criteria for Adverse Events version 4.0) treatment-related acute and long-term toxicities were analyzed. Patient-, tumor-, and treatment-related variables including retreatment interval were analyzed as predictors of outcomes such as locoregional control, overall survival, and toxicity. Univariate analysis was performed with 2-tailed t tests, covariates were assessed with multiple regression modeling, and survival was assessed by the Kaplan-Meier method.

Results: Seventy-one reirradiation patients were identified with a median retreatment dose of 68 Gy. Reirradiation followed resection in 27 patients (38%), and concurrent chemotherapy was delivered to 42 patients (59%). After a median follow-up of 26 months, 21 (30%) were alive and free of disease. For all patients, median overall survival was 22 months and median locoregional control was 31 months. Of the 62 of 71 patients that survived longer than 3 months after reirradiation, 16 patients (26%) experienced severe long-term toxicity (≥ grade 3), with 12 (75%) suffering PEG tube—dependent dysphagia. The median treatment interval in patients who experienced severe toxicity after reirradiation was 20 months (9-167) compared to 53 months (8-304) in patients who did not (P = .017). On multivariable analysis, only retreatment interval was significant in predicting severe toxicity. Neither concurrent chemotherapy nor surgery prior to reirradiation was associated with severe long-term toxicity. Using the median retreatment interval at which patients experienced severe long-term toxicity (20 months) as the threshold, median survival was 8 months versus 27 months, favoring longer intervals (P = .04).

Conclusion: In a cohort treated with modern IMRT-based reirradiation to the head and neck, rates of severe long-term toxicity was 26%. To our knowledge, this is the first report showing that shorter retreatment intervals are significantly associated with severe long-term toxicities. The increase in severe toxicity should also be considered in addition to poor survival in patients with short reirradiation intervals.

Author Disclosure: J.Y. Lee: None. E. Sapia: None. A. Eisbruch: None.

252
Patterns of Failure in Human Papillomavirus (HPV)-Positive Versus HPV-Negative Oropharyngeal Cancer
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Purpose/Objective(s): Human papillomavirus positivity in oropharyngeal squamous cell carcinomas (OSCC) generally confers a more favorable prognosis. However, a limited number of patients still develop recurrent and distant disease posttreatment. We sought to better understand failure patterns and survival in HPV-positive (HP+) versus HPV-negative (HP-) patients using data from a single institution’s experiences with OSCC.

Materials/Methods: We identified all OSCC patients in our head and neck database of 546 patients who had developed local and/or distant failures, and retrospectively analyzed their treatment, survival, and failure patterns with regards to their HPV status. Thirty-three such patients were identified and analyzed. The HPV status of all patients was determined either by p16 immunostaining or polymerase chain reaction. When available, the HPV genotype was specified for a given patient. All patients were treated with intensity modulated radiation therapy (IMRT) with/without chemotherapy, or IMRT with/without chemotherapy adjuvantly with surgery. Primary endpoints included locoregional failure, distant failure, sites of distant failure, and overall survival (OS) since time of failure. The Kaplan-Meier method was used to calculate survival among the patients.

Results: The mean age of our patients was 58.8 years. Thirty (91%) were male, and 3 (9%) were female. Within this group, 20 (61%) patients were HPV+ and 13 (39%) HPV-. HPV genotypes were available for 12 patients: 10 HPV16, 1 HPV33, and 1 HPV35. Primary sites included 15 base of tongue (45.5%), 13 tonsils (39.3%), and 5 oropharynx nonspecified site (15.1%). Median follow-up time since local or distant failure for all patients was 16.2 months. Median OS following local failure was not significantly different between the 2 cohorts (17 months for HPV+ vs 14 months for HPV-, P = .23). However, HPV+ patients who failed distantly lived significantly longer than HPV- patients who failed distantly (median 42 months vs 11 months, P = .004). Two-year OS after distant metastasis was 65% for HPV+ patients versus 0% for HPV- patients. Notably, HPV+ patients were more likely to develop distant metastases to sites other than the lung and bones (Table 1).

Conclusion: Following distant recurrences, HPV positivity indicates a much more favorable prognosis with the potential for long-term survival. By contrast, for patients with OSCC who fail locally, prognosis may not be driven by HPV status. Lastly, in HPV+ patients who are undergoing
follow-up scans to assess for distant metastasis, imaging of the chest alone may not be sufficient given the anatomic range of metastatic sites in patients who are HPV+.

253
Role of EphB4 in Radiosensitization of Head and Neck Squamous Cell Carcinoma
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Purpose/Objective(s): Head and neck squamous cell carcinomas (HNSCCs) afflict over half a million patients annually worldwide. In the absence of disease at distant sites, salvage treatment may provide durable disease control in only approximately 15% of such patients. Our research goal is to improve radiation therapy for aggressive HNSCCs by identifying novel targets for radiosensitization. The EphB4 receptor is ubiquitously expressed in HNSCCs and has been shown to promote tumorigenic and invasive properties of HNSCCs but the effect of EphB4 on cellular radiosensitization has not been investigated. We hypothesize that knockdown of EphB4 receptor will enhance radiosensitization of HNSCCs by inhibiting EphB4 targets involved in radioresistance.

Materials/Methods: To fulfill our objective, we used EphB4-targeting siRNA and performed clonogenic assays in HNSCC cell lines to determine the in vitro radiosensitization effect following EphB4 knockdown. Effects of EphB4-siRNA on cell cycle progression, DNA damage response, and cell death pathways were also investigated.

Results: We observed a decrease in the survival fractions in HNSCC cell lines following knockdown of EphB4 at increasing doses of radiation. Cell cycle analysis showed an enhanced G2 arrest of HNSCC cells following EphB4 knockdown and radiation exposure. In addition, we observed an increase in the expression of p-H2AX, a DNA damage marker protein, in HNSCC cells suggesting activation of DNA damage response pathway following EphB4 knockdown and radiation exposure. This was further accompanied by DNA fragmentation and modulation of key apoptotic markers. Studies are currently underway to determine the effect of EphB4 inhibition on radiosensitization in an in vivo patient-derived xenograft model of HNSCC.

Conclusion: Our findings support the hypothesis that EphB4 promotes resistance of HNSCCs to ionizing radiation and its targeted inhibition will therefore result in enhanced radiosensitization. In conclusion, the successful completion of this study will allow us to design functional analyses of EphB4 targets responsible for radioresistance. From translational point of view, these targets could serve as the basis for development of combined therapy, prognostic biomarkers, or patient selection strategies in future clinical trials.


254
Phase 2a Study of Cetuximab and Dasatinib in Patients With Cetuximab-Resistant Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)
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Purpose/Objective(s): Activation of Src family kinases (SKFs) leads to resistance to EGFR inhibitors in preclinical models of HNSCC. Dual EGFR-SFK targeting has been proposed as a way to overcome cetuximab resistance in R/M HNSCC. We evaluated the combination of cetuximab and SKF inhibitor dasatinib in patients (pts) with cetuximab-resistant R/M HNSCC.

Materials/Methods: This was a single-arm, 2-stage phase 2a/2b design evaluating the open-label combination of cetuximab (250 mg/m²/week) and dasatinib (150 mg/day) in pts with cetuximab-resistant R/M HNSCC defined as progressive disease (PD) after prior cetuximab in definitive or R/M setting. An all-comers design was selected to target an improvement in the overall response rate (ORR). At the end of the first stage there were no responses among 12 pts, and the trial was stopped for futility. Baseline serum was queried for candidate biomarkers mechanistically associated with Src activation to identify preliminary relationships with clinical benefit (defined as stable disease [SD] ≥12 weeks).

Results: Fourteen pts were enrolled from 2012 to 2013. Four pts (29%) had human papillomavirus-positive oropharyngeal cancers. The median age was 62 years (range 51-72); median time from previous cetuximab treatment was 4.7 months (range 0.9-7). The most common grade 3 adverse events (AEs) were infection (14%) and pleural effusion (14%); no grade 4 AEs were observed. There were no objective responses in the first 12 response-evaluable pts, and the trial was suspended after 14 accruals. Biomarker analysis compared pts who experienced SD≥12 weeks (36%, N=5) with pts who had PD (64%, N=9). Among 5 predefined candidate biomarkers, we observed a significant association between low baseline serum interleukin 6 (IL6) and clinical benefit. IL6 is the ligand for JAK2 and a key activator of STAT3, a known mechanism of acquired resistance to dasatinib. Five pts with SD (duration 5-15 months) had median serum IL6 of 5 pg/mL versus 34 pg/mL for pts with PD (Wilcoxon test P = 0.028).

We hypothesized that baseline IL6/JAK/STAT3 activation represents a de novo mechanism of resistance to dasatinib. Based on this finding the second stage of the trial was revised to a phase 2b biomarker-enrichment design enrolling pts with undetectable serum IL6.

Conclusion: The combination of cetuximab and dasatinib in an unselected population had no objective responses and was stopped early for futility. However, a biomarker was discovered in pts who derived clinical benefit: low baseline serum IL6. Baseline IL6/JAK/STAT3 activation may prevent dasatinib rescue of clinical cetuximab resistance. Thus, the trial is now proceeding as an independent, Bayesian, biomarker-selected phase 2b study in pts with undetectable IL-6. Clinical trial information: NCT01488318.


255
Reirradiation of Recurrent and Second Primary Head and Neck Cancer With Proton Therapy
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Purpose/Objective(s): To fulfill our objective, we used EphB4-targeting siRNA and performed clonogenic assays in HNSCC cell lines to determine the in vitro radiosensitization effect following EphB4 knockdown. Effects of EphB4-siRNA on cell cycle progression, DNA damage response, and cell death pathways were also investigated.

Results: We observed a decrease in the survival fractions in HNSCC cell lines following knockdown of EphB4 at increasing doses of radiation. Cell cycle analysis showed an enhanced G2 arrest of HNSCC cells following EphB4 knockdown and radiation exposure. In addition, we observed an increase in the expression of p-H2AX, a DNA damage marker protein, in HNSCC cells suggesting activation of DNA damage response pathway following EphB4 knockdown and radiation exposure. This was further accompanied by DNA fragmentation and modulation of key apoptotic markers. Studies are currently underway to determine the effect of EphB4 inhibition on radiosensitization in an in vivo patient-derived xenograft model of HNSCC.

Conclusion: Our findings support the hypothesis that EphB4 promotes resistance of HNSCCs to ionizing radiation and its targeted inhibition will therefore result in enhanced radiosensitization. In conclusion, the successful completion of this study will allow us to design functional analyses of EphB4 targets responsible for radioresistance. From translational point of view, these targets could serve as the basis for development of combined therapy, prognostic biomarkers, or patient selection strategies in future clinical trials.

Purpose/Objective(s): To report clinical outcomes of head and neck reirradiation with proton therapy.

Materials/Methods: Between 2004 and 2014, 61 patients received curative-intent fractionated proton reirradiation, 90.2% for disease involving skull base structures and 80.3% recurrent T4, at a median of 23 months from the most recent prior course of radiation. The most frequent histologies were squamous cell (54.2%), adenoid cystic (11.0%), and undifferentiated (8.2%) carcinoma. Fourteen patients (23.0%) had carcinomas of cutaneous origin. Salvage surgery prior to reirradiation was undertaken in 47.5% of patients. Gross residual disease was present in 70.5% of patients. For patients with microscopic residual disease, the median dose of reirradiation was 66 Gy (relative biological effectiveness [RBE]) for gross disease, 70.2 Gy (RBE). The median cumulative lifetime dose of fractionated radiation was 136 Gy (range 96-203.2 Gy). Concurrent chemotherapy was used in 27.9%.

Results: The median follow-up time was 15.2 months; it was 28.7 months in patients remaining alive. The 2-year overall survival (OS) estimate was 32.7% (95% confidence interval: 20.2%–45.2%), and median OS was 16.5 months. The 2-year estimate of the risk of developing local failure was 23.6%, of developing regional nodal failure 4.0%, and of developing distant metastases 42.0%. In multivariable analysis, the presence of a gastrostomy tube prior to reirradiation, gross residual disease, and an increasing number of prior courses of radiation therapy were associated with greater hazard ratio for death, while the presence of a gastrostomy tube prior to reirradiation, gross residual disease, and a dose of reirradiation <60 Gy were associated with a greater hazard ratio for local failure. The median percent weight loss at completion of reirradiation was 2% (range 10% weight gain to 10% loss). Acute toxicity of maximum grade 2 occurred in 47.5%, grade 3 in 13.1%, and grade 5 in 1.6%. Late toxicity of maximum grade 2 occurred in 22.6%, grade 3 in 15.1%, grade 4 in 5.7%, and grade 5 in 3.8%. There were a total of 3 treatment-related deaths.

Conclusion: Despite a preponderance of unfavorable characteristics including advanced-stage recurrent disease, a high frequency of microscopic perineural invasion, and an absence of more favorable disease sites such as the larynx, our cohort outcomes are comparable to other series of patients with higher LRF risk after reirradiation. Additional data are needed to identify which patients are most likely to benefit from aggressive efforts to achieve local disease control and to evaluate the potential benefit of proton therapy relative to other modalities of reirradiation.

Author Disclosure: M.W. McDonald; None. O. Zolali-Meybodi; medical student; Indiana University School of Medicine. S.J. Lehner; medical student; Indiana University School of Medicine. A.A. Cohen-Gadol; None. M.G. Moore; None.

256

Patterns of Failure After Salvage Surgery and Intensity Modulated Radiation Therapy Reirradiation for Recurrent Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): Surgical salvage is the preferred treatment for patients with recurrent head and neck squamous cell carcinomas (HNSCC) after radiation therapy (RT). Adjunct reirradiation is reserved for those with adverse features, but the optimal reirradiation volume remains unclear given the potential for severe treatment toxicity. Here we evaluated the patterns of locoregional failure (LRF) after salvage surgery and post-operative intensity modulated RT (IMRT) reirradiation for patients with recurrent HNSCC.

Materials/Methods: The records of recurrent HNSCC patients who underwent surgical salvage followed by adjuvant IMRT reirradiation at our institution were reviewed. Patterns of LRF were determined by 2 methods: (1) visual comparison (“eyeball method”) of the IMRT treatment plan and diagnostic computed tomography (CT) scan utilizing anatomic landmarks; and (2) use of deformable image registration (DIR) between treatment planning CT and diagnostic CT. Failures were defined as in-field if completely within the high-dose clinical target volume (CTV-HD), marginal if <1 cm from the CTV-HD, and of out of field if ≥1 cm from the CTV-HD or subclinical dose CTV (CTV-SD). All recurrences were verified by biopsy or radiological progression. Logistic and Cox regression analyses were performed to identify predictors for LRF.

Results: Fifty-nine patients were analyzed with a median follow-up of 22 months after reirradiation (range 1-115 months) and median dose of 60 Gy (range 60-70 Gy). Of these, 27 patients (46%) had documented LRF with a median time to LRF of 5 months after reirradiation (range 1-16 months). By visual comparison, 7 patients failed in-field (26%), 9 failed marginally (33%), and 11 failed out of field (40%). Utilizing DIR, 57% of the in-field failures received <95% of the CTV-HD prescription dose, and 78% of the marginal failures received <95% of the CTV-SD prescription dose. Of the in-field and marginal failures, 56% occurred within 1 cm of the surgical flap. Of the out-of-field failures, 55% recurred in the first or second echelon nodal station, and 27% recurred on the contralateral side. On correlative analysis, a first recurrence in a pharyngeal mucosal site vs nodal, soft tissue, or bone sites) after initial radiation therapy predicted for higher LRF risk after reirradiation (P<0.05). The use of chemotherapy, CTV dose or volume, or time to first recurrence did not correlate with LRF risk, although a trend for increased LRF risk was observed for those with PNI or positive margins after salvage surgery.

Conclusion: The majority of locoregional failures after surgical salvage and adjuvant IMRT reirradiation for recurrent HNSCC were within or <1 cm from the CTV-HD and occurred within 6 months of reirradiation.

Author Disclosure: G.V. Martin; None. V. Takiar; None. J. Phan; None.
were asked to consider a shorter time interval between radiation courses (ie, 6 months vs 2 years from previous radiation therapy). On multivariate analysis, the number of cases treated per year and number of years in practice significantly influenced treatment recommendations for unresectable recurrent disease ($P = 0.09$ and $P = 0.06$, respectively). For a postoperative salvage scenario (case 2), only the number of years in practice significantly predicted treatment recommendations ($P = 0.016$).

There was significant variation in treatment recommendation with regard to radiation therapy technique, choice of systemic therapy, fractionation schedules, radiation therapy doses, definition of radiation therapy target, and frequency of image guidance.

**Conclusion:** Recommendations for salvage therapy of recurrent head and neck cancer vary considerably in terms of reirradiation approaches and systemic therapy recommendations among radiation oncologists in the US. These findings may be of utility in patient counseling and the design of prospective clinical trials comparing salvage therapy modalities.

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**258**

**Association of a Claims-Based Marker of Functional Impairment With Treatment Patterns and Cost in Metastatic Squamous Cell Carcinoma of the Head and Neck (mSCCHN)**

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**Purpose/Objective(s):** Information on patients’ performance status (PS) is important to characterizing treatments and health care costs in the real world setting; however, this information cannot be directly ascertained from administrative claims data. The objective of this analysis was to evaluate the JEN Frailty Index (JFI), a marker of functional impairment that can be derived from claims data and potentially used as proxy for PS, in order to describe outcomes among mSCCHN patients.

**Materials/Methods:** The JFI has been found to be significantly related to concurrent and future need for long-term care services; it has been utilized by Centers for Medicare & Medicaid Services and has been evaluated in studies of multiple sclerosis and Alzheimer’s disease. In the current study, treatment pattern data for patients with mSCCHN were evaluated using categories of low, medium, and high JFI, with high JFI corresponding to high impairment and by extrapolation, to poor PS. The associations between JFI and treatment patterns as well as monthly total Medicare costs were assessed. This study population was derived from the 2005-2009 Surveillance, Epidemiology, and End Results (SEER) cancer registry, linked to Medicare claims for 2002-2010. SCCHN was categorized as metastatic based on either determination of stage IVC disease at diagnosis or the existence of secondary or distant cancer diagnoses in Medicare claims.

**Results:** A total of 4616 patients with mSCCHN were eligible for study inclusion. Approximately 60%, 40%, and 41% of the total population received radiation, surgery, or systemic therapy, respectively. Twenty-nine percent of the total population had high JFI scores at 3 months post-metastatic diagnosis. The percentage of patients with high JFI scores fluctuated over time: 5% one year prior to diagnosis, 34% 6 to 8 months after diagnosis, and 16% at 18 months postdiagnosis. In patients with observed deaths, the proportion with high JFI expanded in the 36 months prior to death, rising from 22% to 51% during the last observation month.

Of the 1902 patients who received systemic therapy, only 18% had high JFI scores at the time of treatment initiation. There was a trend toward administering cetuximab monotherapy rather than platinum-containing regimens in first- and second-line treatment for patients with high JFI scores. Multivariate regression analyses found a cost impact associated with high JFI score during the observation period (9.13-fold increased cost relative to low JFI, $P < .0001$).

**Conclusion:** The JFI was used as a proxy for PS. Patterns of systemic therapy use and cost of care varied according to JFI strata in mSCCHN patients. This study supports the opportunity and need for further validation of the JFI as a proxy for PS in observational claims-based oncology research.


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**259**

**Elective Neck Management for Squamous Cell Carcinoma Metastatic to the Parotid-area Lymph Nodes**

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**Purpose/Objective(s):** To determine if radiation therapy to the regional lymphatics is a suitable alternative to elective neck dissection in patients who undergo parotidectomy for squamous cell carcinoma metastatic to the parotid lymph nodes.

**Materials/Methods:** We retrospectively reviewed the medical records of 107 patients consecutively treated from November 1969 to March 2012 for squamous cell carcinoma metastatic to the parotid lymph nodes with a clinically and radiographically node-negative neck. Primary therapy consisted of parotidectomy in all cases. We compared regional control in 2 subgroups: 42 patients treated with elective neck dissection and radiation therapy and 65 patients treated with elective neck radiation therapy alone.

**Results:** The median time of follow-up was 5.5 years (range, 0.3-30 years) for all patients and 11 years for living patients (range, 1.8-26 years). There was 1 neck recurrence in each subgroup: elective neck dissection and RT, 1/42 (2%); and elective radiation therapy alone, 1/65 (1.5%). No patient experienced a complication related to neck radiation therapy.

**Conclusion:** Elective neck radiation therapy to a dose of approximately 50 Gy is a suitable alternative to elective neck dissection in patients with squamous cell carcinoma metastatic to the parotid lymph nodes.


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**260**

**Linear Accelerator-Based Stereotactic Ablative Radiation Therapy Reirradiation for Unresectable Recurrent Head and Neck Cancer**

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**Purpose/Objective(s):** To report our early institutional experience utilizing linear accelerator (Linac)-based fractionated stereotactic ablative radiation therapy (HN-SABR) for reirradiation of unresectable recurrent head and neck tumors.

**Materials/Methods:** From 2013 to early 2015, 26 patients with biopsy-confirmed head and neck cancer recurrence after radiation therapy were treated with HN-SABR and retrospectively analyzed. Patients with <3 months follow-up were excluded. Patients were treated for isolated
Results: Twenty-one patients (81%) had squamous cell carcinoma. All patients received 5 fractions delivered every other day. Twenty-three patients (88%) received a prescribed dose of 45 Gy, 2 patients (8%) received 40 Gy, and 1 patient received 47.5 Gy. Twenty-two patients (86%) received concurrent weekly cetuximab. With a median follow-up time of 6.2 months (range 3.1-20.7 months), the 6-month overall survival, disease-free survival, and locoregional control rates were 79%, 73%, and 91%, respectively. Five patients failed in the head and neck. One had persistent disease in-field after tongue base treatment, 1 recurred in the soft tissue adjacent (<1 cm) to the treated skull base, 1 occurred in an inferior adjacent nodal station after isolated neck treatment, and 2 failed in the ipsilateral neck after oropharynx treatment. No local failures were observed in 9 patients treated for isolated retropharyngeal recurrence (median follow-up of 7.8 months; range 4.2-19.4 months). There were 3 deaths, all due to metastatic disease. There were 5 acute grade 1 adverse events (3 odynophagia, 1 mucositis, and 1 dysgeusia), 2 grade 2 events (1 mucositis and 1 odynophagia) that required intermittent nonnarcotic analgesics, and no acute grade 3 toxicity. Five patients (23%) developed grade 1-2 cetuximab-related folliculitis. One patient developed edema of his oropharyngeal flap 10 days after treatment of the bilateral retropharyngeal nodes to 47.5 Gy.

Conclusion: Linac-based SABR utilizing VMAT for head and neck reirradiation appears safe, tolerable, and effective. Longer follow-up is needed to assess late treatment toxicity and tumor control durability.


262
Evaluation of Weekly Paclitaxel, Carboplatin, and Cetuximab in Head and Neck Cancer Patients With Incurable Disease

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Purpose/Objective(s): Weekly paclitaxel, carboplatin, and cetuximab (PCC) has been found to be efficacious and well tolerated in patients with incurable squamous cell carcinoma of the head and neck (SCCHN) with good performance status (PS) when used as induction chemotherapy. Use of PCC in incurable SCCHN in patients with poor PS or in a noninduction setting is an area that warrants further evaluation. Current recommendations for incurable disease consist of a platinum-based regimen with fluorouracil and cetuximab. Studied in patients with PS of 0 to 1, the fluorouracil-based regimens were associated with significant toxicities. Therefore, weekly PCC may offer an appealing, less toxic alternative for incurable patients with poor PS.

Materials/Methods: This retrospective analysis evaluated 41 patients with very advanced or metastatic head and neck cancer who had received PCC (paclitaxel 80 mg/m², carboplatin AUC 2, and a cetuximab 400 mg/m² loading dose, followed by 250 mg/m² weekly) for up to 6 cycles between April 2008 and September 2014. Maximal response achieved and proportional control rates were 39% and 65%, respectively. Patients who underwent salvage surgery prior to radiation treatment had significantly better locoregional control, progression-free survival, and overall survival rates (P<0.05). Severe (grade 3+) late complications were observed in 21 patients (50%). No significant prognostic factors for severe late toxicity were found on univariate analysis.

Conclusion: Our results showed similar locoregional control rates to historical controls for patients undergoing reirradiation of recurrent and second primary head and neck cancer. The observed rates of severe late toxicity were significant. Further studies are necessary to optimize locoregional control while reducing treatment-related morbidity.

263

Reirradiation With Simultaneously Integrated Boost (SIB) in Patients With Local Recurrence of Squamous Cell Carcinoma of the Head and Neck: Own Experience
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Purpose/Objective(s): Locoregional recurrence is a major cause of death in patients with squamous cell carcinoma of the head and neck (HNSCC). At the moment, there are no clear recommendations and standards regarding the timing, total doses, and dose tolerance of normal tissues to re-exposure. Based on limited studies on the reirradiation with high total doses, we evaluated the tolerability of high-dose reirradiation with simultaneous integrated boost.

Materials/Methods: Fourteen patients with histologically confirmed locoregional recurrence of HNSCC received reirradiation. Median time after primary radiation therapy course was 60 months. The treatment volumes and total doses were formed as follows: gross tumor volume (primary lesion and involved lymph nodes, delineated on computed tomography [CT], magnetic resonance imaging, and 18F-fluorodeoxyglucose positron emission tomography/CT) + clinical target volume (0.5-1.0 cm) + planning target volume (PTV; 0.3-0.5 cm) was treated to the total dose equivalent to 66 to 70 Gy of conventional fractionation, the upper neck (if indicated, levels I-III + PTV 0.5 cm) to 60 Gy, the lower neck (if indicated, levels IV-V + PTV 0.5 cm) — equivalent to 50 Gy. Single doses to these volumes were 2.14 to 2.21 Gy, 2.0 Gy, and 1.8 Gy, respectively. Radiation treatment was once a day, 5 days a week, 6 weeks long (30 fractions). A treatment planning system was used (intensity modulated radiation therapy [IMRT]), and patients were treated with 2 linear accelerator models. According to the literature, in a year after primary irradiation, almost complete recovery of normal tissue tolerances is observed. Tolerances of the eye, lens, optic nerves and chiasm, brain stem, spinal cord, parotid gland, intact mucosa of the mouth and pharynx were not exceeded. Patient positioning accuracy was controlled by kV-imaging daily and cone beam CT weekly.

Results: Three of 14 patients received the full course of radiation therapy without a break. Radiation toxicity manifested with grade 2 oral and pharyngeal mucositis and grade 2 radiation epidermitis. After 1 month, almost complete relief of radiation mucositis and dermatitis was observed. One patient took a break of 7 days after the 25th fraction due to the development of grade 3 mucositis and grade 3 dysphagia.

Conclusion: Using the technique of SIB with IMRT during curative reirradiation of recurrent HNSCC is available with maintaining satisfactory tolerability.

either from postoperative complications or early secondary recurrence. The aim of the study was to identify clinical factors that might predict early failure and/or worse outcome after salvage laryngectomy in patients initially treated with definitive CRT for advanced laryngeal cancer.

Materials/Methods: This was a retrospective chart review of salvage laryngectomies performed for advanced laryngeal squamous cell carcinoma at a single academic institution. An existing prospectively collected database of head and neck cancer patients was queried to identify patients who had undergone salvage laryngectomies. Additional pertinent information on the identified patients was gathered from manual chart review for analysis after institutional review board approval was obtained. Patients were separated into groups based on how quickly they recurred after primary therapy with CRT: group 1 was defined as patients that relapsed in less than 1 year, and group 2 consisted of patients that recurred after the 1-year mark. Survival in each group was estimated using the Kaplan-Meier method, and differences between curves were assessed by the log-rank test.

A multivariable Cox proportional hazards model was used to estimate the hazard ratio, adjusted for age and initial stage at diagnosis. Results: The 2 groups were homogeneous with respect to age, sex, race, and disease location/severity. The Kaplan-Meier analysis indicated that laryngeal cancer patients with a recurrence less than 1 year after definitive chemoradiation (group 1) fared poorer than those with later recurrences ($P = .06$). After adjusting for patient age and stage at diagnosis, patients in group 1 still experienced poorer outcomes, although the results were not significant (hazard ratio $= 2.30$, $95\%$ confidence interval: $0.79-6.73$).

Conclusion: Patients with larynx cancer who initially undergo CRT who relapse in less than a year have lower overall survival and are less likely to benefit from a salvage total laryngectomy.


266

Novel Preclinical In Vitro and In Vivo Model Systems for Adenoid Cystic Carcinoma of the Salivary Gland

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Purpose/Objective(s): Adenoid cystic carcinoma (ACC) is one of the most malignant salivary gland cancers with a high incidence of both local and distant (lung and bone) metastases. In order to study this tumor type, a reliable model system is critical. Patient-derived mouse xenografts (PDX) have been shown to maintain the histology and gene expression profile of the primary tumor, making them a valid model system. However, PDX models suffer from high cost for generation and maintenance, low take rate (30%-50%), lack of manipulation, and high throughput capability. Lack of authenticated cell line has compromised studies of ACC basic biology and drug development.

Materials/Methods: A new conditionally reprogrammed (CRC) method described previously combines the use of irradiated mouse fibroblasts and a ROCK inhibitor to induce the rapid and long-term growth of normal and tumor cells without any additional immortalization. We have used this technology to establish cell cultures using PDX tissue materials from 5 different individuals. We also established an in vivo zebrafish models system to study migratory and metastatic behavior of tumor cells using 2-day post fertilization embryos. We used transgenic zebrafish (flk:GFP) expressing green reef coral fluorescent protein in the vascular endothelial system to study migratory and metastatic behavior of tumor cells. We also established an in vivo zebrafish models system to study migratory and metastatic behavior of tumor cells using 2-day post fertilization embryos.

Results: We have stable cultures from 5 individual PDX tumors using CRC technology. One ACC cell line, ACC11, has shown to maintain the MYB-NF1B translocation, mutations in FGFR2 and ATM genes and overexpression of Myb-NF1B fusion protein similar to the tumor of origin (PDX tumor). We also established an in vivo zebrafish xenograft model system for ACCs, using ACC11 as a prototype, we showed that these cells are migratory and possess metastatic potential as a fraction of tumor cells moved from the yolk sac to the tail via vascular invasion within 3 days postinjection. Similar results were obtained when PDX tissue material for ACC11 was transplanted directly to the yolk sac. In contrast, injection of a non-ACC salivary gland cell line did not show any movement of cells even after 7 days of post injection.

Conclusion: We have successfully established a toolkit consisting of an in vitro (cell line) and an in vivo (Zebrafish) model system for biological and translational research.

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Patent/License Fees/Copyright: Propagenix. Advise on scientific directions; Propagenix.

267

WITHDRAWN

268

The Cancer Genome Atlas Data Suggest Only a Modest Role for TP53 in Head and Neck Squamous Cell Carcinoma Prognostication

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Purpose/Objective(s): Identifying combinations of clinical variables and biomarkers best related to outcome is important for informing clinical decisions and for designing trials. Early studies could not distinguish human papillomavirus (HPV)-positive from HPV-negative head and neck squamous cell carcinoma (HNSCC), so it is now important to determine which combinations of prognostic variables are best related to outcome in these types of HNSCC. The Cancer Genome Atlas (TCGA) provides a rich set of clinical and molecular data on HNSCC; the mix of cases is representative of higher stage disease. Taking HPV status into consideration, we combined TCGA survival analysis with best-subset and LASSO variable selection to identify combinations of prognostic variables most closely associated with outcome.

Materials/Methods: Ten prognostic variables potentially related to outcome had sufficient TCGA data for analysis (259 cases, 114 deaths): age, gender, smoking history, T and N classifications, TNM stage, tumor grade, TP53 mutation status, HPV status (32 HPV positives including 1 TP53 mutant), and mutant-alone tumor heterogeneity (MATH). Best-subset selection examined the relation of all combinations of variables to overall survival in Cox proportional hazards models. LASSO selection added individual variables sequentially as Cox model complexity was increased to allow for model building. To avoid overfitting, model complexity was penalized by the Akaike Information Criterion in best-subset analysis, and by the sum of the absolute values of regression coefficients in LASSO.

Results: Surprisingly, best-subset selection omitted TP53 mutation status as a prognostic variable. Age ($P < .001$), smoking history ($P = .0015$), MATH ($P = .005$), HPV status ($P = .008$), and N classification ($P = .01$) was the combination of variables best related to outcome. The pattern of sequential variable selection by LASSO provided an explanation for this omission. TP53 mutation was the first variable selected by LASSO for inclusion in the 259-case Cox model, followed by smoking history. As MATH, HPV status, N classification, and age entered the model, however, the
contribution of TP53 status diminished. Variable selection by LASSO was particularly striking in HPV-negative cases, as 5 other variables (smoking history, N classification, MATH, tumor grade, and age) were included in the model before TP53.

**Conclusion:** Although TP53 mutation was identified long ago as a prognostic variable in HNSCC, these results suggest that its prognostic value might be modest outside of its acting as a surrogate for HPV status. These results should be interpreted cautiously, as they are based on a single data set and not from a prespecified clinical study. Nevertheless, despite its importance in the biology of HNSCC, the role of TP53 mutation as a prognostic variable in HPV-negative HNSCC may need to be reconsidered in future studies, particularly as novel biomarkers are evaluated.

**Author Disclosure:** J.W. Rocco: Patent/License Fees/Copyright; Massachusetts General Hospital (MGH). Development and discussion of clinical trial ideas; NCI. comments and reviews on clinical trial ideas; NCI. E.A. Mroz: Patent/License Fees/Copyright; Massachusetts General Hospital (MGH).

### 269

**miR-203 Inhibits Human Papillomavirus Oral Tumor Growth by Suppressing Proliferation in Differentiated Tumor Cells**

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**Purpose/Objective(s):** In order to facilitate viral replication, the human papillomavirus (HPV) oncogene E7 stimulates differentiated keratinocytes in the suprabasal epithelial layers to initiate DNA synthesis. Here, we studied the extent to which HPV oncopgenes caused proliferation in differentiated tumor cells and the pathways governing this process.

**Materials/Methods:** Tamoxifen treatment of triple transgenic KHR mice induced expression of the HPV oncopgenes E6 and E7 and a mutant KrasG12D oncoprotein to cause oral tumor development. As a control, we used HPV-negative KR mice that developed oral tumors in which proliferation was limited to the basal stem cell compartment. To study how a regulator of epithelial differentiation, miR-203, impacted primary tumor growth, we generated a dual inducible mouse model, KHR-203, where doxycycline (DOX) induced miR-203 expression independent of HPV and KrasG12D oncoproteins. Gene expression was assessed using Affymetrix Mouse Gene 1.0 ST arrays, quantitative RT-PCR, and in situ hybridization (ISH). The proliferation markers Mcm7, PcnA, and BrdU as well as the keratinocyte differentiation marker CK10 were assessed by immunohistochemistry or immunofluorescence.

**Results:** Compared to HPV-negative KR tumors, HPV-positive KR tumors grew faster (tumor volume at d24: 387.1 ± 74.3 mm^3 for KR tumors vs 140.1 ± 66.9 mm^3 for KR tumors; P < 0.001). KHR oral tumors had more cells expressing proliferation markers M cm7 (81.5 ± 2.2% of KR vs 23.8 ± 0.7% of KR tumors; P < 0.001) and PcnA (76.8 ± 1.4% of KR vs 31.9 ± 1.4% of KR tumors; P < 0.001). Furthermore, KR tumors, but not KR tumors, had partially differentiated CK10^+ cells incorporating BrdU, indicating that proliferation occurred in partially differentiated cells. Expression profiling demonstrated that 112 genes and 1 miRNA, miR-203, were differentially expressed between HPV-positive and HPV-negative tumors. qRT-PCR confirmed that miR-203 was downregulated 1.9-fold in HPV-positive tumors (P < 0.01), and ISH demonstrated that loss of miR-203 occurred primarily in the suprabasal layers. In KHR-203 oral tumors, DOX treatment induced miR-203 expression and suppressed HPV-positive tumor growth (tumor volume at d24: 147.3 ± 18.9 mm^3 for DOX-treated vs 426.1 ± 25.3 mm^3 for vehicle-treated tumors; P < 0.001). The decrease growth of DOX-treated tumors was associated with decreased proliferation in differentiated tumor cells as measured by percentages of Mcm7-positive cells (P < 0.001) and PcnA-positive cells (P < 0.001).

**Conclusion:** HPV oncopgenes accelerated oral tumor growth by inducing proliferation of partially differentiated tumor cells that was regulated by miR-203. Our results suggest that restoring the miR-203 pathway in primary tumors may antagonize HPV oncopgenes to inhibit cell proliferation and tumor growth.

**Author Disclosure:** M.T. Spiotto: None. J. Bechill: None. R. Zhong: None.

### 270

**A Regimen Combining the Wee1 Inhibitor AZD1775 With Histone Deacetylase Inhibitor Vorinostat is Highly Active Against Head and Neck Squamous Cell Carcinoma Harboring High-risk TP53 Mutations**

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**Purpose/Objective(s):** The cure rate for patients with advanced head and neck squamous cell carcinoma (HNSCC) remains poor due to resistance to standard therapy primarily consisting of chemoradiation. Since mutation of TP53 in HNSCC occurs in 60% to 80% of nonhumanpapillomavirus (HPV)-associated cases and is in turn associated with resistance to these treatments, novel therapeutic approaches are needed to overcome drug resistance and improve survival outcomes in patients with advanced HNSCC. Wee-1 is a kinase that has been linked to DNA damage-induced G2/M arrest, owing to its ability to inactivate cyclin-dependent kinase 1 (CDK1) through phosphorylation of the Tyr15 residue. Our laboratory has shown that the Wee-1 kinase inhibitor AZD1775 sensitizes HNSCC cells harboring high-risk p53 mutations to cytotoxic therapies both in vitro and in vivo. Vorinostat is a small molecule inhibitor of histone deacetylase (HDAC) that has been shown in vitro and in vivo to have promising anticancer activity. Treatment with vorinostat alone shows preferential cytotoxicity for mutant p53 HNSCC cells. This finding supports the rationale to use vorinostat-based regimens to achieve maximum synthetic lethality in HNSCC with p53 mutations. In this study, we evaluated the efficacy of a regimen combining vorinostat and AZD1775 in HNSCC cells with a variety of p53 mutations.

**Materials/Methods:** Clonogenic survival assays were performed to examine the in vitro sensitivity of several TP53 mutant HNSCC cell lines following treatment with vorinostat and AZD1775. Cell cycle and western blotting analyses were performed to investigate cellular mechanisms. An orthotopic mouse model of oral cancer and HNSCC patient-derived xenografts (PDX) were used to evaluate in vivo efficacy of the drugs.

**Results:** Vorinostat synergized with AZD1775 in vitro and reduced cell survival of mutant p53 HNSCC cells. Interestingly, addition of vorinostat had no effect on AZD1775 responses in the wild-type p53 HNSCC cells. It appears that the reduction in cell survival with vorinostat or combination treatment is mediated through apoptosis. Treatment of HNSCC cells with vorinostat and AZD1775 increased p21 induction and promoter activity independent of p53 expression. Interestingly, shRNA knock-down of p21 did not attenuate the lethal effect of combined treatment, suggesting that p21 might be necessary but not sufficient for vorinostat-mediated cell death in these cells. Finally, coadministration of vorinostat with AZD1775 resulted in significant tumor growth inhibition and prolonged animal survival in an orthotopic mouse model of oral cancer and HNSCC patient-derived xenografts.

**Conclusion:** A regimen combining AZD-1775 with vorinostat is highly active in preclinical models of p53 mutant head and neck cancer.


### 271

**E2F1 Mediates Human Papillomavirus (HPV) Oncogene Toxicity and Suppresses HPV Oral Tumor Growth**

M.T. Spiotto,1 R. Zhong,2 J.M. Mcleotek,3 and J. Bechill; 1University of Chicago, Chicago, IL, 2The University of Chicago, Chicago, IL

**Purpose/Objective(s):** The cure rate for patients with advanced head and neck squamous cell carcinoma (HNSCC) remains poor due to resistance to standard therapy primarily consisting of chemoradiation. Since mutation of TP53 in HNSCC occurs in 60% to 80% of nonhumanpapillomavirus (HPV)-associated cases and is in turn associated with resistance to these treatments, novel therapeutic approaches are needed to overcome drug resistance and improve survival outcomes in patients with advanced HNSCC. Wee-1 is a kinase that has been linked to DNA damage-induced G2/M arrest, owing to its ability to inactivate cyclin-dependent kinase 1 (CDK1) through phosphorylation of the Tyr15 residue. Our laboratory has shown that the Wee-1 kinase inhibitor AZD1775 sensitizes HNSCC cells harboring high-risk p53 mutations to cytotoxic therapies both in vitro and in vivo. Vorinostat is a small molecule inhibitor of histone deacetylase (HDAC) that has been shown in vitro and in vivo to have promising anticancer activity. Treatment with vorinostat alone shows preferential cytotoxicity for mutant p53 HNSCC cells. This finding supports the rationale to use vorinostat-based regimens to achieve maximum synthetic lethality in HNSCC with p53 mutations. In this study, we evaluated the efficacy of a regimen combining vorinostat and AZD1775 in HNSCC cells with a variety of p53 mutations.

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**Results:** Vorinostat synergized with AZD1775 in vitro and reduced cell survival of mutant p53 HNSCC cells. Interestingly, addition of vorinostat had no effect on AZD1775 responses in the wild-type p53 HNSCC cells. It appears that the reduction in cell survival with vorinostat or combination treatment is mediated through apoptosis. Treatment of HNSCC cells with vorinostat and AZD1775 increased p21 induction and promoter activity independent of p53 expression. Interestingly, shRNA knock-down of p21 did not attenuate the lethal effect of combined treatment, suggesting that p21 might be necessary but not sufficient for vorinostat-mediated cell death in these cells. Finally, coadministration of vorinostat with AZD1775 resulted in significant tumor growth inhibition and prolonged animal survival in an orthotopic mouse model of oral cancer and HNSCC patient-derived xenografts.

**Conclusion:** A regimen combining AZD-1775 with vorinostat is highly active in preclinical models of p53 mutant head and neck cancer.


### 271

**E2F1 Mediates Human Papillomavirus (HPV) Oncogene Toxicity and Suppresses HPV Oral Tumor Growth**

M.T. Spiotto,1 R. Zhong,2 J.M. Mcleotek,3 and J. Bechill; 1University of Chicago, Chicago, IL, 2The University of Chicago, Chicago, IL
Purpose/Objective(s): The human papillomavirus (HPV) expresses the viral oncoprotein E7 that inhibits the retinoblastoma protein (RB1). RB1 mediates contradictory cell growth and cell death pathways via E2F family members. Here, we assessed the extent to which HPV oncopgenes caused toxicity as measured by mouse survival and tumor growth.

Materials/Methods: iHPV mice contained a LoxP-Stop-LoxP (LSL)-iE6E7 transgene in which conditional E6E7 expression is regulated by Cre recombinase. We constitutively expressed HPV oncoproteins by breeding iHPV transgenic mice to CMV-Cre transgenic mice expressing Cre recombinase under a CMV promoter (CMV-HPV mice). We induced HPV oncoprotein expression in adult mice using RosaHPV mice containing the iHPV transgene and a Rosa-CreER<sup>tam</sup> transgene expressing a tamoxifen-regulated (TAM) regulated Cre recombinase in all tissues. We studied primary oral tumors using triple transgenic KHR mice containing a K14-CreER<sup>tam</sup> transgene, a LSL-iE6E7 transgene and a LSL-Kras<sup>G12D</sup> transgene that formed HPV-positive oral tumors after TAM treatment. We assessed the role of E2F1 on survival and oral tumor formation using RosaHPV-E2F1<sup>+/+</sup> mice and KHR-E2F1<sup>−/−</sup> mice, respectively, that contained a homozygous E2F1 deletion. HPV oncoprotein expression and E2F1 target gene expression was assessed by quantitative RT-PCR.

Results: Induction of HPV oncoproteins caused embryonic lethality as CMV-HPV double transgenic mice were born at significantly lower frequencies compared to mice carrying single transgenes (P < 0.0001).Tamoxifen treatment of adult RosaHPV (RosaHPV+TAM) mice caused recombination of the LSL-iE6E7 transgenes and HPV oncoprotein expression in all organs tested. Furthermore, RosaHPV+TAM mice had decreased survival compared to vehicle treated RosaHPV mice (median survival: 50d for RosaHPV+TAM vs not reached for RosaHPV-TAM; P < 0.0001). Decreased survival in RosaHPV+TAM mice was associated with focal necrosis in hepatocytes and pancreatic tissues and the activation of the E2F1 target genes. Deletion of E2F1 increased survival of RosaHPV+TAM mice indicating that E2F1 mediated HPV oncoprotein toxicity (median survival: not reached for RosaHPV-E2F1<sup>−/−</sup> vs 49 days for RosaHPV-E2F1<sup>+/+</sup> mice vs 30 days for RosaHPV-E2F1<sup>−/−</sup>; P = 0.0001). Compared to tumors with homozygous loss of E2F1, KHR tumors with homozygous loss of E2F1 grew faster and had more proliferating tumor cells as measured by Pcm antiimmunohistochemistry (tumor volume at d18: 453.7 mm<sup>3</sup> for KHR-E2F1<sup>+/+</sup> vs 139.7 mm<sup>3</sup> for KHR-E2F1<sup>−/−</sup>; P = 0.004).

Conclusion: Our results indicate that HPV oncoproteins activated the E2F1 pathway to cause toxicity in normal mice and to suppress oral tumor growth. These results suggest that selective modulation of the E2F1 pathway, which is activated in HPV tumors, may facilitate tumor regression.


273

Cetuximab Has Antiviral Activities in Human Papillomavirus (HPV)-Infected Cells and HPV-Associated Tumors

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Purpose/Objective(s): Human papillomaviruses (HPVs) are small DNA viruses with species specificity and strict tropism for squamous epithelium. Oncogenic HPV16 is associated with up to 72% of HPV-positive (HPV+) oropharyngeal squamous cell carcinomas (OPSCC). Patients with locally advanced, HPV+ OPSCC have more favorable outcomes than those with HPV-negative (HPV-) cancers when treated with radiation and cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR). EGFR overexpression is a hallmark of HPV- head and neck cancer, whereas EGFR expression is low in HPV+ cancer. Thus, the molecular mechanisms underlying prognostic advantage in the context of cetuximab radiation are unclear. This clinical paradox led us to hypothesize that HPV oncoproteins augment EGFR signaling independent of EGFR expression level, establishing a positive feedback loop wherein enhanced signaling upregulates viral gene transcription. As a corollary, we postulated that interrupting this loop would blunt viral oncoprotein levels, restore tumor suppressor functions, and sensitize the cells to apoptotic stimuli from DNA damaging agents.

Materials/Methods: We employed syngeneic HPV- and HPV16+ cell lines. To determine the effect of EGFR stimulation on viral transcription, cells were incubated with 10 ng/mL EGFR. Viral E6, E7, and E1/E4/E5 transcript levels were quantified by RT-qPCR. We pretreated cells with cetuximab and measured (1) EGFR pathway inhibition by detection of p-EGFR Y-1173 and Y-1068, and downstream p-ERK1/2; (2) early viral transcripts by RT-qPCR; and (3) cellular surrogates of oncoprotein activity (p53, p21, pRB and p16) by immunoblot. To determine whether cetuximab enhances apoptotic response to DNA damage, we evaluated cell viability after varying schedules of cetuximab and cisplatin. We studied cetuximab’s activity in xenograft models using HPV16+ tumor cell lines.

Results: In cells harboring episomal HPV16 genomes, EGFR stimulation significantly upregulated, while cetuximab suppressed viral oncogene...
levels. The latter was accompanied by restored tumor suppressor p53 and pRB functions. Cell viability was not reduced by either cetuximab or cisplatin alone. However, viability decreased when cetuximab and cisplatin were combined—with greatest effect when cetuximab was delivered prior to cisplatin. Finally, cetuximab reduced viral oncogene transcript levels and inhibited tumor growth in HPV+ xenografts.

**Conclusion:** Cetuximab displays anti-HPV activity, reducing viral oncogene expression, diminishing viral load, and restoring tumor suppressor function. Moreover, cetuximab sensitized HPV+ cells to DNA damage by cisplatin, which may be attributed, in part, to return of apoptotic function. Cetuximab's anti-HPV action may explain its effectiveness in the context of definitive cetuximab radiation for locally advanced HPV-positive OPSCC.


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**274**

**The Relationship Between CD44, EGFR, and c-MET Expression in Patients With Locally Advanced p16-Positive and p16-Negative Head and Neck Squamous Cell Carcinoma**

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**Purpose/Objective(s):** CD44 is a cell surface glycoprotein known to be a cancer stem marker in head and neck squamous cell carcinoma (HNSCC). It is involved in tumor growth, metastasis, and self-renewal. c-MET is a marker of poor prognosis and may have stem cell capacity in HNSCC. Combined CD44/c-MET signaling can drive repopulation in cell culture. The relationship between c-MET and CD44 expression in HNSCC patient tissue is unknown. We examined the association between CD44 and c-MET in relation to p16 and the epithelial growth factor receptor (EGFR) in a cohort of HNSCC patients treated with chemoradiation.

**Materials/Methods:** Immunohistochemical staining of CD44, p16, EGFR, and c-MET was performed on a tissue microarray consisting of tumors from 103 locally advanced HNSCC patients treated with definitive chemoradiation. Tissue cores were graded by 2 blinded pathologists. p16 was graded as positive (3+ or 2+ in ≥50% of tumor cells) or negative. Positive EGFR expression was defined as any 3+ or 1+/2+ in ≥50% of tumor cells. High c-MET expression was defined as any 3+ and CD44 high expression was defined as 2+/3+ in ≥50% of tumor cells. CD44 expression was correlated with p16, EGFR, and c-MET, locoregional control (LRC), distant metastases (DM), disease-free survival (DFS), and overall survival (OS). Univariate and multivariate analyses (MV A) were performed.

**Results:** CD44 high expression was present in 37% of patients. Fifty-two percent of patients were p16 positive, including 78% of oropharynx tumors. Fifty-four percent of patients were positive for EGFR, and 36% were classified as high c-MET expression. High CD44 expression was associated with higher T stage (P = .01), nonoropharynx primaries (P < .001), p16-negative (P < .001), and EGFR-positive tumors (P < .001). High CD44 expression was highly correlated with c-MET expression with greatest effect when cetuximab was delivered prior to cisplatin. Finally, cetuximab reduced viral oncogene transcript levels and inhibited tumor growth in HPV+ xenografts.

**Conclusion:** Cetuximab displays anti-HPV activity, reducing viral oncogene expression, diminishing viral load, and restoring tumor suppressor function. Moreover, cetuximab sensitized HPV+ cells to DNA damage by cisplatin, which may be attributed, in part, to return of apoptotic function. Cetuximab’s anti-HPV action may explain its effectiveness in the context of definitive cetuximab radiation for locally advanced HPV-positive OPSCC.

276

XPA – A Biomarker With Potential Prognostic Value in Patients With Oropharyngeal Head and Neck Squamous Cell Carcinoma
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Purpose/Objective(s): Platinum-based chemotherapy resistance has been under investigation for a long time, looking at the nucleotide excision repair (NER) pathway, which is responsible for DNA adduct repair. One of the participating proteins in that pathway is XPA. There is little information about this protein regarding its prognostic value in patients with head and neck squamous cell carcinoma (HNSCC). Therefore, we investigated XPA expression as a prognostic factor by retrospectively looking at overall survival, time to recurrence, and correlation with clinical parameters.

Materials/Methods: Tissue microarrays were constructed from 453 cases of HNSCC including 222 oral (49%), 126 pharyngeal (27.8%), and 105 laryngeal (23.2%) tumors. Two hundred ninety-three tumor blocks were evaluable for XPA immunohistochemistry. Expression levels were dichotomized into a high and low XPA expressing group followed by a comparison of age, gender, TNM status, grading, and UICC stage. Outcomes for overall survival and time to recurrence were analyzed by using the Kaplan-Meier method and performed for different subsites of the head and neck.

Results: Analysis of overall survival and time to recurrence showed no difference between both expression levels of XPA in the overall patient cohort. However, superior overall survival in patients with oropharyngeal SCC and a high XPA expression could be observed (P = .0386). Looking at SCCs of the oral cavity, a trend toward an inferior overall survival in patients with a high XPA expression was seen, whereas investigations in the hypopharynx and larynx showed no significant differences between high and low XPA expressing tumors. Looking generally at gender, M stage, and grading, no statistical correlation was found. Analyzing T and N stage in all tumors, a trend toward a lower XPA expression in advanced tumors (>pT4 P = .0543 and >pN1 P = .0546) could be seen. This trend was confirmed by statistical lower expression of XPA in patients with UICC stage IV looking at the overall patient cohort (P = .035).

Conclusion: The shown results suggest that XPA might be a novel predictive marker for overall survival in patients with oropharyngeal SCC with a superior survival in tumors with a high XPA expression. Furthermore, this study shows that subsites in the head and neck will have to be looked at separately in the future to determine the predictive value of biomarkers for therapy outcome and pretreatment risk stratification of patients. To increase statistical power of this study and to evaluate the effect on platinum-based chemotherapy resistance, further studies with even larger patient cohorts will be needed and are ongoing.

Author Disclosure: S. Prochnow: None. A. Muenscher: None. R. Knecht: Advisory Board of Merck; Advisory Board of Merck. W. Wilczak: None. T. Clauditz: None.

277

MGMT Hypermethylation—Missing Piece of the Puzzle in Primary Head and Neck Squamous Cell Carcinoma?
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Purpose/Objective(s): A specific mechanism explaining the higher chemoradiation responsiveness of human papillomavirus (HPV)-positive head and neck squamous cell carcinoma (HNSCC) and the modulation of this effect by tobacco exposure remains unidentified. Promoter hypermethylation (HM) of the DNA-repair O6-Methylguanine (O6-MG)-DNA-methyl-transferase (MGMT) gene is an independent predictor of response to chemoradiation and survival in gliomas and lymphomas. We are investigating the role of MGMT in HNSCC in the context of tobacco exposure and HPV status.

Materials/Methods: After exclusion of patients with no pathology, cytology only, and outside slides, primary HNSCC patients suitable for this ongoing investigation were identified from the institutional cancer database after we secured institutional review board approval. Tumor was extracted from paraffin blocks using laser-capture microdissection. DNA was extracted from the tumor followed by bisulfite treatment, methyl-specific PCR, and pyrosequencing using a commercially available kit. In pilot, HPV status was ascertained with the help of p16 immunohistochemistry. Age, gender, site, stage, and tobacco use was extracted from patient charts.

Results: As a part of this ongoing investigation, we provide the interim report on 100 cases with both MGMT and p16 status. MGMT-HM was seen in 35% of patients (35 of 100). The distribution of HNSCC tumors with respect to HPV status, tobacco use, and MGMT-HM is shown in Table 1. Tobacco status did not influence HPV status (45% [33 of 73] of tobacco-associated cancers vs 56% [15 of 27] of tobacco-unassociated cancers were p16 positive; P = 3; Fisher exact test). HPV status did not influence MGMT status (35% [17 of 48] p16 positive cancers vs 35% [18 of 52] p16 negative cancers had MGMT-HM; P = 1.0; Fisher exact test). However, tobacco use was found to be significantly associated with MGMT status (29% [21 of 73] tobacco-associated cancers vs 52% [14 of 27] tobacco-unassociated cancers had MGMT-HM; P = .0369; Fisher exact test). Furthermore, tobacco use influence MGMT status particularly in the HPV-positive subgroup (27% [9 of 33] tobacco-associated/p16-positive cancers vs 53% [8 of 15] tobacco-unassociated/p16-positive cancers had MGMT-HM; P = .04; X² test).

Conclusion: At least one-third of HNSCC patients have MGMT-HM. To our knowledge, this is first study to report an association between tobacco use and MGMT status, especially in HPV-positive HNSCC.


278

Variations in Genome Structure Between Follicular Variant and Highly Aggressive Papillary Thyroid Cancer
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Purpose/Objective(s): Structural genome instability is a cardinal feature of cancer. Genomic structural variations (SVs), including insertions, deletions, inversions, copy number alterations, and translocations, acquired during malignant transformation may alter gene expression, resulting in tumor growth, invasion, and metastasis. However, the short reads of 50-200 base pairs (bp) used by many next-generation sequencing technologies lead to systematic errors in identifying and localizing SVs within the genome. To understand how SVs contribute to invasion or metastasis we...
are using a novel high-throughput genome mapping technology to map tumor genomes isolated from thyroid cancer patients. This system images single DNA molecules up to >1,000,000 bp in size, which permits accurate identification and localization of SVs in the genome. Using this technology, we have constructed the first genomic map of follicular variant papillary thyroid cancer (PTC) isolated from patient tissue. Our current efforts focus on mapping the genome of a highly invasive, metastatic PTC. We hypothesize that the invasive PTC genome will contain unique SVs compared to the follicular variant PTC genome.

**Materials/Methods:** High molecular weight DNA was extracted from the blood (germline), primary thyroid tumor, and lymph node metastases of a patient with highly aggressive PTC. Similarly, DNA was extracted from germline, thyroid tumor, and adjacent normal thyroid tissue from a patient with follicular variant PTC. The DNA was fluorescently labeled at specific 7-bp sequences, background stained, and loaded onto the genome mapping instrument. Single DNA molecules ranging in length from 150,000 bp to >1,000,000 bp were imaged and used to assemble genome maps via the genome mapping analysis pipeline. Maps were assembled at >80x coverage for germline and normal tissue and >100x coverage for tumor tissue. SVs were visualized using software. Unique SVs in tumor samples were identified.

**Results:** In the follicular variant PTC, we identified 185 putative insertions and deletions unique to the tumor genome. The average size across the 69 putative deletions identified in the follicular variant PTC was 7120 bp with a range of 982 to 70,602 bp. Among 116 putative insertions in the follicular variant PTC the average size was 14,820 bp with a range of 1002 to 299,045 bp. Analysis of the invasive PTC genome map is forthcoming.

**Conclusion:** These data indicate that SVs may be a significant source of variation in tumor genomes. Importantly, this study represents the first effort to compare maps of patient-derived solid tumor genomes and will increase our understanding of how changes to the genome structure mediate tumor growth, invasion, and metastasis.


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**279**

The DEK Oncogene Can Be Detected in the Plasma of Head and Neck Cancer Patients and May Be Correlated With Tumor Immune Response and Prognosis

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**Purpose/Objective(s):** Head and neck cancer remains the sixth most common cancer worldwide. Although infection with human papillomavirus (HPV) has emerged as a favorable prognostic factor, no plasma biomarkers currently exist to predict tumor response and/or relapse. One candidate plasma biomarker is encoded by the human DEK gene. DEK is an apoptosis and differentiation inhibitor and overexpression results in oncogenesis. DEK knockdown results in decreased growth and apoptosis of cancer cells. DEK mRNA and protein are highly up-regulated in tissue specimens from several tumor types, including head and neck squamous cell carcinoma (HNSCC), breast cancer, and melanoma, and antibodies to DEK are detected in patients with autoimmune disease. High levels of tumor DEK mRNA are correlated with advancing stage and poor survival. However, our previous work has demonstrated that DEK protein is present in HNSCC tissue specimens regardless of stage or HPV infection. Additionally, in vitro data have suggested that tumor-associated macrophages secrete DEK protein. Therefore, we sought to determine whether plasma DEK protein may have a different value than tissue levels leading to the hypothesis that DEK may be present in the plasma of cancer patients and may be correlated with patient outcome.

**Materials/Methods:** Peripheral blood was collected from patients with newly diagnosed or untreated HNSCC and age-matched normal healthy controls. Plasma was separated from the samples and subjected to DEK-specific ELISA (Cusabio, Wuhan, China). Plasma DEK levels were compared to normal controls, tumor stage, age, and smoking status. Plasma DEK levels were also compared to inflammatory markers in the plasma and tissue.

**Results:** DEK was indeed found to be present in the plasma of both healthy control subjects and those with head and neck cancer. DEK was decreased in head and neck cancer patients compared to healthy patients and inversely correlated with IL-6 in the plasma. Immune infiltration (defined by presence of CD8+ T cells) of the tumor also appeared to be correlated with high DEK plasma levels.

**Conclusion:** Interestingly, although DEK expression is increased in head and neck cancer tissue, plasma DEK levels are decreased in patients with cancer compared to controls and are further decreased with advancing stage. DEK plasma levels are inversely correlated with IL-6 levels, suggesting that high plasma DEK levels may be correlated with a better prognosis. Furthermore, high DEK levels in the plasma may predict superior immune infiltration of tumors. Further analyses are ongoing to determine whether DEK levels predict response to various treatment modalities, correlate with the body’s immune response, and whether DEK presence in the plasma will predict residual disease and/or early relapse. These data will be important to verify DEK plasma measurements as a clinically useful test and may give insight to future personalized and targeted treatment strategies for HNSCC.


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**280**

M3814, a DNA-dependent Protein Kinase Inhibitor (DNA-PKI), Potentiates the Effect of Ionizing Radiation (IR) in Xenotransplanted Tumors in Nude Mice

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**Purpose/Objective(s):** Agents that generate breaks in DNA are among the most widely used classes of cancer therapeutics. These agents induce different forms of DNA damage, including double-strand breaks (DSBs), which are the most lethal if left unrepaired. M3814 targets tumor cell growth and survival by inhibiting a critical DNA damage repair mechanism. The antitumor effect of M3814 is dependent on the functionality of DNA repair and checkpoint signaling in cancer cells, which have a lowered ability to cope with DSBs, leading to cell death. Hence, the rationale of DNA-PK inhibition is to increase the amount of DSB DNA damage generated by IR. The objective of the series of nonclinical experiments was to demonstrate that IR together with M3814 was more efficacious than IR alone.

**Materials/Methods:** The efficacy of M3814 in combination with IR was evaluated in 6 human xenograft models (HCT116, FaDu, NCI-H460, A549, Capan-1, BxPC3) in mice representing 4 different cancer types (colon, head and neck, lung, and pancreas). Tumor cells were injected s.c. into nude mice, and treatment started when palpable tumors were established (>100-200 mm³). M3814 was given orally at different doses (25-300 mg/kg) 10 min prior to IR. IR was applied using a radiation therapy device for small rodents calibrated to deliver 2 Gy. Autophosphorylation of DNA-PK (serine2056) in FaDu tumor lysates was measured at 80x phosphorylation of DNA-PK (serine2056) in FaDu tumor lysates was measured at 1,000,000 bp in size, which permits accurate identification and localization of SVs in the genome. Using this technology, we have constructed the first genomic map of follicular variant papillary thyroid cancer (PTC) isolated from patient tissue. Our current efforts focus on mapping the genome of a highly invasive, metastatic PTC. We hypothesize that the invasive PTC genome will contain unique SVs compared to the follicular variant PTC genome.

**Results:** In the follicular variant PTC, we identified 185 putative insertions and deletions unique to the tumor genome. The average size across the 69 putative deletions identified in the follicular variant PTC was 7120 bp with a range of 982 to 70,602 bp. Among 116 putative insertions in the follicular variant PTC the average size was 14,820 bp with a range of 1002 to 299,045 bp. Analysis of the invasive PTC genome map is forthcoming.

**Conclusion:** These data indicate that SVs may be a significant source of variation in tumor genomes. Importantly, this study represents the first effort to compare maps of patient-derived solid tumor genomes and will increase our understanding of how changes to the genome structure mediate tumor growth, invasion, and metastasis.

Results: In combination with IR, M3814 showed efficacy in all of the 6 mouse models of human cancer as demonstrated by a strong potentiation of the effect of IR. In all models, a dose of 2 Gy administered daily for 1 week in combination with M3814 induced statistically significant tumor growth inhibition compared to IR alone. In 2 models, FaDu and NCI-H460, M3814 induced tumor regression. In the FaDu model, no tumor regrowth (duration of the experiment >100 days) was observed in the combination arm with IR (2 Gy per fractions, 6 weeks, 5 days per week: total dose 60 Gy) at the doses of 25 and 50 mg/Kg. In the IR only arm, no tumor responses were observed. These effects were a likely consequence of inhibiting DNA-PK activity, as shown by measuring the autophosphorylation of DNA-PK in FaDu tumor tissue. M3814, alone or in combination with IR, did not induce significant weight loss or visual signs of toxicity in the mice in any study.

Conclusion: M3814 is active in nonclinical experiments in combination with IR. Strong antitumor activity was observed in several xenograft models with complete regressions of tumors upon application of the established clinical IR schedule of 2-Gy fractions for 6 weeks in the FaDu model (squamous cell carcinomas of the head and neck). Clinical evaluation of M3814 is ongoing.


281
A Phase 2 Study Evaluating Axitinib in Patients With Unresectable, Recurrent, or Metastatic Head and Neck Cancer

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Purpose/Objective(s): Data on axitinib, a small molecule tyrosine kinase inhibitor with selective inhibition of VEGFR 1, 2, 3, as well as inhibition of potential downstream effectors of the EGFR pathway: Gefitinib and VEGFIR in HNSCC, treatment with axitinib holds promise as a rational targeted therapy. We conducted a phase 2 trial to investigate the clinical activity of this agent in patients with unresectable, recurrent, and/or metastatic head and neck squamous cell carcinoma (HNSSC) range between 10% and 30% with single-agent regimens. Hence, new rational therapies are needed. Axitinib is a small molecule tyrosine kinase inhibitor with selective inhibition of VEGFR 1, 2, 3, as well as inhibition of potential downstream effectors of the EGFR pathway: Gefitinib and VEGFIR in HNSSSC, treatment with axitinib holds promise as a rational targeted therapy. We conducted a phase 2 trial to investigate the clinical activity of this agent in patients with unresectable, recurrent, and/or distant metastatic HNSSC. Our hypothesis was that treatment with axitinib would result in improvement in 6-month progression-free survival (PFS) compared to historical controls.

Materials/Methods: Patients with unresectable, recurrent, or metastatic HNSSC were included in this open-label, single-arm, phase 2 trial. Primary endpoint was 6-month PFS. All patients received single-agent axitinib with planned dose escalation based on tolerability. Treatment-related adverse events were graded according to the Common Terminology for Adverse Events version 3.0. Treatment response was evaluated by Response Evaluation Criteria in Solid Tumors version 1.0. A planned interim efficacy analysis was performed after enrollment of 30 patients. A simulation study performed to evaluate efficacy as determined by PFS did not demonstrate superiority of axitinib, and the trial was prematurely closed.

Results: Forty-two patients were registered, of whom 30 were evaluable for response. While treatment was well tolerated, with no severe bleeding events, only 19 patients were able to achieve full planned dose. The disease control rate was 76.7%, with a median PFS of 3.7 months (95% confidence interval [CI]: 3.5-5.7) and overall survival of 10.9 months (95% CI: 6.4-17.8). Exploratory analysis demonstrated that patients with a smaller sum of diameter of target lesions experienced improved response rates and better PFS and overall survival. Exploratory cumulative rates were performed on patient serum, and it was noted that the change in IL-8 after the first dose of axitinib was associated with response to therapy (P = .04).

Conclusion: Although limited by premature closure based on a perceived lack of response, single-agent axitinib should be considered for further evaluation based on its acceptable toxicity profile and favorable median overall survival compared to standard therapies. We observed cystic degeneration and mild tumor volume increase after initiation, suggesting likely treatment effect and clinical benefit. Future studies are needed to define whether other radiologic definitions of response are more appropriate in defining response to TKI or anti-VEGF therapy in head and neck cancer.


282
Morphoproteomics Identifies the EZH2 Pathways as a Potential Therapeutic Target of Human Papillomavirus–Associated Oropharyngeal Cancer

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Purpose/Objective(s): Human papillomavirus (HPV) has been identified as an etiopathogenic factor in oropharyngeal cancer. The HPV E6 and E7 oncoproteins are instrumental in leading to proliferation and a block in differentiation and tumorigenesis. Although surgical intervention can remove such tumors, the potential for an etiologic field effect with recurrent disease is real. The objective of this preliminary study was to identify a known downstream effector of E7 oncoprotein, Enhancer of Zeste Homolog 2 (EZH2), which is known to pose a block in differentiation and proliferation and lead to HPV-induced malignant transformation. Such a pathway is amenable to low toxicity therapies designed to promote differentiation to a more benign state and prevent recurrent disease and incorporation of HPV into the genome.

Materials/Methods: Morphoproteomic analysis of tumor from a patient with p16INK4a-positive oropharyngeal cancer included the immunohistochemical probes for the detection of EZH2. The expression level of this protein analyte was assessed and integrated with the proliferation index to chemical probes for the detection of EZH2. The expression level of this protein analyte was assessed and integrated with the proliferation index.

Results: Representative sections of the patients' tumors showed immunopositivity for EZH2 in tumoral nuclei (signal intensity at 2 to 3+). In p16INK4a-positive oropharyngeal cancer included the immunohistochemical probes for the detection of EZH2. The expression level of this protein analyte was assessed and integrated with the proliferation index to chemical probes for the detection of EZH2. The expression level of this protein analyte was assessed and integrated with the proliferation index.

Conclusion: Enhancer of zeste homolog 2 (EZH2), a histone methyl transferase, is tumorigenic by virtue of the fact that it inactivates tumor suppressor genes and contributes to a state of differentiation and proliferation in tumors and in facilitating their migratory potential. EZH2 expression is activated by HPV16 oncoprotein E7 at the transcriptional level. In oral SCC, knocking down EZH2 decreased the proliferative capacity of the carcinoma, and inhibiting EZH2 also inhibited the migration and metastasis of oral SCC cells. EZH2 can be downregulated by the upregulation of miRNAs to include miR-26a and miR-101. Metformin and curcumin have that ability, and Vaccum (a curcumin-based vaginal cream) has been shown in a preclinical model to prevent progression of vaginal HPV-associated cancer. Morphoproteomics has identified EZH2 as the potential therapeutic target.
DNA Methylation Regulates ANO1 Expression Through Alternate Mechanisms at 3 Distinct CpG Islands in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): Mechanisms underlying metastasis of head and neck squamous cell carcinoma (HNSCC) are still poorly understood and contribute to tumor recurrence. ANO1 is a calcium-activated chloride channel whose expression was recently found to act as a switch between tumor growth and metastasis in HNSCC. We hypothesized that changes in DNA methylation of key CpG residues near the ANO1 promoter underlie changes in gene expression in HNSCC.

Materials/Methods: We analyzed HNSCC samples from TCGA with available DNA methylation, expression, and human papillomavirus (HPV) status (n = 275). Using these samples, we studied 3 CpG islands annotated by the UCSC Genome Browser near the ANO1 transcriptional start site (TSS). We calculated Spearman rank correlations between DNA methylation and expression at each CpG and defined statistical significance as P < 0.01. Effects of copy number variation, survival, and HPV status were also studied.

Results: Of the 3 CpG islands studied, an enhancer ~90 kb upstream of the TSS had 6 of 8 CpGs positively correlated with ANO1 expression, a canonical CpG at the TSS had 8 of 10 negatively correlated CpGs, and a CpG island at the exon 2 promoter had 4 of 6 positively correlated CpGs. HPV+ (n = 34) samples had significantly decreased expression of ANO1 compared to HPV-negative samples (n = 241; P < 0.01); additionally, HPV-positive samples had significantly decreased DNA methylation at the 2 positively correlated CpG islands (P < 0.001) but no change at the negatively correlated CpG island. Copy number amplification enhanced epigenetic effects, with amplified samples having increased DNA methylation of positively correlated CpGs and decreased DNA methylation of negatively correlated CpGs relative to those with neutral copy number. Finally, increased expression of ANO1 as well as increased average DNA methylation across all CpGs studied were associated with decreased patient survival (P < 0.05), suggesting a greater component of positively correlated CpGs to expression.

Conclusion: DNA methylation regulates ANO1 expression through 2 mechanisms—hypomethylation of CpGs at the TSS increases expression while hypomethylation of the enhancer and intragenic CpG island decreases expression. Notably, hypomethylation of positively correlated CpGs was associated with decreased expression in HPV-positive samples, suggesting these regions are more critical for regulation. Complex effects of copy number variation potentiating epigenetic mechanisms were also observed. Since differential expression of ANO1 regulates growth and metastasis of HNSCC and is associated with patient survival, modulating its expression may be a useful clinical target. Studies are currently ongoing to investigate specific mechanisms of DNA methylation on the ANO1 promoter and better characterize the understood role of positively correlated CpGs on gene expression.

Purpose/Objective(s): The cure rate for patients with advanced head and neck squamous cell carcinoma (HNSCC) remains in the 25% to 40% range due to resistance to standard therapy, primarily consisting of platinum-based chemoradiation therapy. Currently, there are no established molecular biomarkers that predict response to chemotherapeutic agents in HNSCC, although studies have shown that TP53 mutational status can predict clinical response in patients treated with neoadjuvant chemotheraphy. Since mutation of TP53 in HNSCC is associated with resistance to these treatments, we are interested in novel therapeutic approaches to overcome this resistance. COTI-2 (Critical Outcome Technologies Inc), a novel third generation thioscemcarbazone, appears to restore wild-type like functional activity to a wide range of p53 mutant tumor cells through a mechanism that involves zinc chelation. In vitro studies have shown that COTI-2 has nanomolar activity in multiple human cancer cell lines and has shown growth inhibition in xenograft mouse models for several solid tumors. We hypothesized that this drug would be effective in killing HNSCC cells harboring various TP53 mutations.

Materials/Methods: Clonogenic survival assays were performed to examine the in vitro sensitivity of several TP53 mutant HNSCC cell lines following treatment with COTI-2. Cell cycle and western blotting analyses were performed to investigate cellular mechanisms. An orthotopic mouse model of oral cancer was used to evaluate the in vivo efficacy of the drug.

Results: COTI-2 reduced cell survival of both mutant p53 and wild-type HNSCC cells. The reduction in cell survival is through both apoptosis and senescence, which appear to occur via p53-dependent and p53-independent mechanisms. Treatment of HNSCC cells with COTI-2 alone increased p21 induction and promoter activity. COTI-2, as a single agent, resulted in significant tumor growth inhibition in an orthotopic mouse model of oral cancer.

Conclusion: COTI-2 inhibits in vitro and in vivo tumor growth in HNSCC cells irrespective of TP53 status through the induction of apoptosis and senescence.

Characterizing the Phenotype and Biomolecular Activity of 2 Clinically Relevant Mutations in TMEM16A

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Purpose/Objective(s): TMEM16A is a calcium-activated chloride channel that is overexpressed or mutated in a variety of squamous cell carcinomas, including 30% of head and neck squamous cell carcinomas (HNSCC). Two relevant missense mutations, R429P and R561H, have been identified and appear to demonstrate enhanced oncogenic capacity. In this study, we sought to (1) characterize in vitro behavior of these mutants and...
(2) identify biomolecular pathways that permit enhanced oncogenic capacity in these mutants.

Materials/Methods: We transduced OSC19 cells and created daughter cells that express low or high levels of wild-type TMEM16A as controls, the R429P mutation, or the R561L mutation using a lentiviral vector. We established the in vitro phenotype of these mutant cells using colony formation assays and Cell Titer-Glo viability assays under a variety of conditions. Biomolecular pathway activity was analyzed using western blot. All data are reported as fold increase relative to the empty vector control cells.

Results: The R429P and R561L mutants demonstrated significantly increased growth in colony formation assay: 7.23- and 2.42-fold increase (P<0.05), respectively. Additionally, the mutants demonstrated enhanced viability in anchorage-dependent (1.41- and 1.12-fold increase, respectively; P<0.05) and anchorage-independent (2.35- and 2.24-fold increase, respectively; P<0.05) Cell Titer-Glo viability assays at 48 hours. TMEM16A mutants demonstrated increased activity of the pEGFR (1.6- and 2.6-fold increase, respectively), pERK (6.9- and 9.1-fold increase, respectively), and cyclin D1 (2.8- and 2.8-fold increase, respectively) pathway on baseline western blot analysis.

Conclusion: Our results support the phenotype that cells expressing the R429P and R561L TMEM16A mutations have enhanced growth and proliferative capacity possibly mediated by increased activity of the pEGFR/pERK/cyclin D1 pathways. Future work will aim to clarify structure-function changes in mutant TMEM16A, mechanisms of pEGFR/pERK/cyclin D1 overactivation, and in vivo growth patterns. Ultimately, a thorough biomolecular description of these mutations could better inform treatment and management options in patients expressing these mutations.

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287

Promising Biomarkers of Thyroid Cancer: BRAF V600E Mutation, miRNAs, Integrins, and Their Extracellular Matrix Ligands

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Purpose/Objective(s): Some of the most important issues in thyroid cancer treatment are preoperative diagnosis of malignancy and prognosis determination. For such tasks, molecular biomarkers can be successfully used. The most frequent genetic alteration in thyroid cancer is V600E mutation in BRAF gene, which occurs in 45% to 88% of papillary thyroid carcinoma and associates with aggressive tumor phenotype. Its presence leads to changes of cell membrane integrin receptors expression and their ligands—extracellular matrix proteins—osteonectin (OPN) and thrombospondin-1 (TSP1). Such changes promote migration, invasion, and metastasis of tumor cells. Other important mechanisms for regulation of gene expression in tumor tissue are mediated by microRNAs. Differences in miRNAs expression has been demonstrated in variety of cancers, presenting the potential for tumor typing. Thus, the objective of the study was to compare the gene expression profile of miRNAs 21, 221, 222, and 155; integrins ITGA2, ITG3, ITGAV, ITGA6, ITGAV, ITGB1, and ITGB3; and their ligands OPNa, OPNb, and TSP1 in different types of thyroid tumors to find some promising biomarkers for clinical use.

Materials/Methods: Intraoperative thyroid tissue samples from patients diagnosed with different types of thyroid carcinoma (n=112) and diffuse nodular non-toxic goiter (n=120) were analyzed. To evaluate the expression levels of the investigated genes and microRNAs, real-time RT-PCR was used. Immunohistochemistry was conducted to confirm the PCR results and to estimate the amount of protein products. The presence of BRAF V600E mutation was identified using allele-specific amplification.

Results: In this study a significant increase (P<0.05) in expression levels of ITGA3, ITGAV, ITGB1, OPNa, and TSP1 (2.9 fold, 1.9 fold, 17.1 fold, 2.5 fold, and 3.2 fold, respectively) was observed in the FTC tissue samples in comparison with visually unchanged thyroid tissue. For BRAF V600E-positive tumors with potentially aggressive properties, high expression levels of ITGA3 (80.7 fold, P<0.0473) and ITGAV (13.6 fold, P=0.0252) were registered. Expression of miRNA 21, 221, 222, and 155 was significantly increased in cancer samples, in comparison with benign neoplasms (which ranged from 3.1 fold to 7.2 fold, P<0.05).

Conclusion: Thus, the observed changes in the expression levels of the studied genes indicate their potential role as biomarkers in thyroid tumor typing and determination of thyroid cancer prognosis and treatment.

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Human Papillomavirus—Positive Oropharyngeal Squamous Cell Carcinoma Expresses High Hydrogen Sulfide Synthesizing Enzymes
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Purpose/Objective(s): Human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (SCC) is associated with a positive therapeutic response compared to HPV-negative SCC that tumors often result from alcohol and tobacco exposures. The reason for the better prognosis is currently unknown, although a wild-type/less mutated p53 gene status in HPV-positive tumors may play a role. The HPV E6 protein causes the degradation of miRNA34a, an event known to increase nicotinamide phosphoribosyltransferase (Nampt) levels. Nampt in turn is a known positive regulator of the enzymes that synthesize hydrogen sulfide (H2S). Here we examined the levels of Nampt, the H2S synthesizing enzymes, and the total H2S, acid labile, and bound sulfide pools in HPV-positive and negative cell lines derived from oropharyngeal SCC.

Materials/Methods: We used western blotting to examine the levels of the 3 known enzymes involved in H2S synthesis; cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate S-transferase (3-MST), and Nampt in 1 HPV-positive and 2 HPV-negative cell lines derived from individuals with oropharyngeal SCC (scC47, cal27, and cal33, respectively). High performance liquid chromatography was used to measure total H2S and the acid labile and bound sulfide pools. The colony-forming efficiency assay was used to measure cell colony-forming ability following cell treatments with oxidative stress and H2S inhibitors.

Results: Nampt and CBS, CSE, and 3-MST were all elevated in the HPV-positive SCC cell line at least 4 fold (3-MST 10 fold) compared to the negative cell lines. Additionally, the HPV-positive SCC cell line was preferentially sensitive to the colony-forming inhibitory effects of tert-butylihydroperoxide compared to the HPV-negative SCC cell lines—an event enhanced by H2S synthesis inhibitor pre-exposure. Last, the total H2S, acid labile, and bound sulfide pools were not increased in the HPV-positive SCC cell line compared to the negative cell line, and all 3 cell lines had very high H2S compared to other studies of intracellular H2S concentrations.

Conclusion: Our findings suggest that HPV increases the dependence of oropharyngeal SCC on H2S for tumor growth and oxidative exposure, which would rapidly deplete H2S levels, exerting preferentially toxic effects on HPV-positive SCC cells. The dysregulation of H2S in HPV-positive oropharyngeal SCC may in part explain the vulnerability of these cancers to oxidants, and radiation/chemotherapies, and in part explain the better therapeutic response seen in HPV-positive oropharyngeal SCCs.

Author Disclosure: R. Shackelford: None. R. Shanti: None. G.E. Ghali: None.

S100A16 Functions as a Tumor Suppressor Protein in Oral Squamous Cell Carcinoma
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Purpose/Objective(s): Although differential expression of S100A16 has been reported in human cancers, its precise functional roles in tumorigenesis are not fully understood. The aim of the study was to investigate the expression pattern and functional role of S100A16 in oral squamous cell carcinoma (OSCC).

Materials/Methods: S100A16 mRNA and protein levels were examined by quantitative RT-PCR and immunohistochemistry in specimens of normal human oral mucosa (NHOM) oral dysplastic lesions (ODL) and OSCCs. S100A16 was overexpressed in OSCC-derived (CalH3 and H357) cells by using retroviral S100A16 expression construct and the subsequent functional effects were examined by using established in vitro and in vivo tumorigenesis assays.

Results: Both S100A16 mRNA and protein levels were found to be gradually down-regulated from NHOM to ODL and OSCC. Low S100A16 protein level in OSCC was found to be correlated with reduced overall survival and poor differentiation grade. In vitro functional studies revealed that S100A16 expression inhibits cell migration, proliferation, and invasion in OSCC cells. Furthermore, S100A16 expression down-regulated expression of MMP-9, -2, and -1, associated with ECM degradation.

Conclusion: S100A16 is a tumor suppressor protein in oral squamous cell carcinoma.

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showed significant reduction in cell proliferation, sphere formation, and invasive abilities of CalH3 and H537 cells upon S100A16 overexpression. S100A16 over-expression also suppressed tumorgenesis of H357 cells in a mouse xenograft model. Molecular analysis revealed that S100A16 over-expression led to induction of differentiation markers and suppression of proliferation and invasion-related molecules both in vitro and in vivo.

**Conclusion:** These results indicate that S100A16 might function as a tumor suppressor protein in OSCC. S100A16 might be useful clinically as a prognostic marker or as a novel therapeutic target for OSCC treatment.

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**291**

**Early Detection of Potential Cannibalistic Cells Before Any Morphological Evidence of Cannibalism Using CD68 and Lysozyme in Oral Squamous Cell Carcinoma**

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**Purpose/Objectives:** Our institute is the first to report the cannibalism phenomenon along with the concept of complex cannibalism in oral squamous cell carcinoma (OSCC). The transformation of a cancer cell into a cannibalistic cell is a process involving numerous sequential events. Initial events could be associated with genetic expression of proteins required for the execution of cellular cannibalism. Molecules that are implicated in this process are CD68, lysozyme, caveolin-1, actin, ezrin, cathepsin B, 9 transmembrane segment (TM9SF4), and vimentin, among others. Genetic expression is later manifested in the form of engulfment and digestion of adjacent cancer cells that are detectable on routine histopathology. We believe that identification of these markers in the tumor cells can help us in recognizing the cells possessing potential for cannibalistic behavior. The purpose of this investigation was to study expression of CD68 and lysozyme for early detection of potential cannibalistic tumor cells in OSCC before any morphological evidence of cannibalism with histopathological correlation.

**Materials/Methods:** A total of 30 histopathologically diagnosed cases of OSCC were subject to immunohistochemical staining using CD68 and lysozyme antibodies. The expression was correlated with clinical and histopathological grades.

**Results:** Out of 30 cases, 12 cases displayed positive expression for both CD68 and lysozyme. For CD68, weak expression was reported in 8 cases, followed by strong expression in 3 cases. Similarly for lysozyme, 10 cases displayed weak expression, and 1 case showed strong positivity. There was a significant difference in the expression of CD68 and lysozyme in different histopathological grades (P<.015 and .001).

**Conclusion:** Positive expression of CD68 and lysozyme in tumor cells of OSCC could suggest the cannibalistic potential of the tumor cells before any morphological evidence of cannibalism.

**Author Disclosure:** S.D. Gawande: None. G.S. Sarode: None. S.C. Sarode: None. S.S. Chaoudary: None.

**292**

**Extracellular Biosensors to Selectively Radiosensitize Head and Neck Cancers**


**Purpose/Objective(s):** Tumor resistance to concurrent chemotherapy and radiation therapy remains a significant barrier to improving outcomes of patients diagnosed with locally advanced head and neck squamous cell cancers (HNSCC). The ability to deliver more potent chemotherapies with radiation therapy is limited by normal tissue toxicity. We hypothesized that potent drug-conjugated activatable cell-penetrating peptides (ACPP) would function as biosensors to deliver highly potent radiosensitizing drugs to tumors. ACPP are selectively cleaved and activated in the tumor microenvironment through tumor-associated matrix metalloproteinases (MMP). Once cleaved, they release drug-conjugated polycation cell-penetrating peptides that are taken up by tumor cells.

**Materials/Methods:** In cell culture, we evaluated the tumoricidal and radiosensitizing ability of AZD-7762 (a potent CHK 1/2 inhibitor) in a panel of HNSCC cell lines (CAL-27, SCC-4, SCC-25, SCC-35, and SCC-61) by Alamar Blue and clonogenic assays. In animal tumor models, we tested the biosensor function of an MMP 2/9 cleavable ACPP to differentiate radioreistant HNSCC tumors from those that are more radiosensitive by using a ratiometric ACPP labeled with Cy5 and Cy7 that was iv injected. Finally, we measured the efficacy of iv-delivered ACPP conjugated AZD-7762 with IR in HNSCC tumor xenografts.

**Results:** In a panel of HNSCC cells, AZD-7762 was more potent than cisplatin. The IC50 for cisplatin was 3, 13, and 5 uM in CAL-27, SCC-35, and SCC-61 cells and for AZD-7762 the IC50 was 0.3, 0.2, and 0.7 uM, respectively. In clonogenic assays, AZD-7762 significantly reduced cell survival after 2 Gy, a clinically relevant IR dose. While 73% of CAL-27 cells survived a dose of 2 Gy, survival was reduced to 45% in cells treated with AZD-7762 and IR, P<.001. Mechanistically, AZD-7762 reversed IR induced accumulation of cells in the G2/M phase of the cell cycle. In HNSCC xenografts, tumors from relatively radioresistant CAL-27 cells had increased cleavage of ratiometric ACPP (high Cy/Cy7 ratio) compared to relatively radiosensitive HNSCC SCC-4 tumors. Finally, in CAL-27 HNSCC xenografts, mice treated with tumor-targeted ACPP conjugated AZD-7762 and IR had significantly prolonged tumor xenograft regression compared to mice treated with nontargeted AZD-7762 and IR, P<.01. Importantly, a noncleavable ACPP conjugated to AZD-7762 did not radiosensitize tumors, thereby indicating the necessity of tumor ACPP cleavage to release AZD-7762 for it to function as a radiosensitizer.

**Conclusion:** In summary, we have demonstrated that ACPP conjugated AZD-7762 provides a unique solution to tumor drug delivery by holding the conjugated drug in an inert state until cleaved by tumor MMP 2/9. ACPP therapeutically redirects tumor MMP 2/9 to amplify delivery of potent radiosensitizers to HNSCC tumors.


**293**

**Prevalence and Prognostic Implications of Human Papillomavirus in Oral Cavity Cancer**

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**Purpose/Objective(s):** Over the last several decades, a dramatic rise in the prevalence of human papillomavirus (HPV) among oropharyngeal squamous cell carcinoma (OPSCC) has been seen. Prior studies have shown the prognostic importance of p16 protein expression in OPSCC as a surrogate marker for HPV infection. The interest in a possible corresponding increase in HPV prevalence in non-OPSCC, particularly the oral cavity, and its prognostic implications currently requires further investigation. We attempt to address these questions through a retrospective
review of patients with oral cavity squamous cell carcinoma (OCSCC) and known HPV status.

**Materials/Methods:** The expression of p16 and high-risk HPV for patients with OCSCC was determined by in situ hybridization (ISH) and immunohistochemistry (IHC) from a single institution. The overall prevalence of HPV in OCSCC was determined, as well as the median overall survival time in months. All patients with a previous or concurrent diagnosis of OPSCC were excluded from our review. These results were then compared to other reported prevalence data.

**Results:** P16 expression was found to be positive in 6.6% (7 of 106) of patients diagnosed with OCSCC from 1999 to 2015 at a single institution. The results of our analysis are consistent with the majority of prior smaller series showing the prevalence of high-risk HPV in the oral cavity to be <10%, despite other recent publications suggesting this could be higher. Our results did not show a positive prognostic value for p16 and high-risk HPV with a median overall survival of 18 months (range, 6 to 37) for the HPV-positive group versus 70 months (range, 3 to 150) for the HPV-negative group. The median follow-up time for all patients was 23.5 months. The 3-year rates of overall survival were 66.6% and 34.4% (P = .069 by log-rank test), respectively.

**Conclusion:** In contrast to patients with OPSCC in whom p16 expression carries a positive prognostic value, our patient outcome data suggest that this correlation does not appear to hold true for p16 and high-risk HPV OCSCC patients. However, due to the low prevalence of HPV within the oral cavity, it is difficult to predict the actual clinical impact of p16 and high-risk HPV in OCSCC.


### 294

**High-Grade Transformation of Acinic Cell Carcinoma: Potentially Underrecognized and Inadequately Treated**

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**Purpose/Objective(s):** Acinic cell carcinoma (ACC) is an uncommon salivary gland tumor. We aim to describe the clinical and pathologic characteristics of ACC with or without high-grade transformation (HGT). Importantly, cases of mammary analogue secretory carcinoma with HGT were significantly older than patients without HGT (median 69 vs 54 years, P < .0001). Angiolymphatic invasion was more common in ACC with HGT (P = .02). The initial treatment in all pts consisted of surgery. All 8 pts in the HGT group received total parotidectomy and neck dissection. In the non-HGT group, 19 underwent parotidectomy alone, and 21 had parotidectomy with neck dissection. Five pts (63%) in the HGT group received adjuvant radiation in contrast to 5 pts (14%) from the non-HGT group. None of the pts received adjuvant chemotherapy.

The HGT cohort showed a 5-year RFS of 25% (95% confidence interval [CI]: 0.55) when compared to 82% (95% CI: 68-95) in the non-HGT group (hazard ratio [HR] 10.4, 95% CI 3.4-31.5; P < .0001). The 5-year OS was 43% (95% CI: 6-80) in the tumors with HGT in comparison to 97% (95% CI: 92-100) for the non-HGT group (HR 9.3, CI 2.6-33.0; P < .0001). Locoregional recurrence was seen in 2 (of 8) and 9 (of 40) pts with HGT and without HGT, respectively. Both pts in HGT who had locoregional recurrence had not received adjuvant radiation after primary resection. In the non-HGT group, 8 (of 9) pts who developed locoregional recurrence had not received adjuvant radiation. The 5-year LRFS was 75% (95% CI: 33-100) for the HGT group and 84% (95% CI: 71-97) for the non-HGT group (HR 3.44, CI 0.66-17.9; P = .12). Six pts developed distant metastasis in HGT tumor group versus none in the non-HGT group. The 5-year DMFS was 38% (95% CI: 4-71) for the HGT group and 100% (CI cannot be calculated) for the non-HGT group (P < .0001).

**Conclusion:** The prevalence of HGT in cases of ACC is higher than previously suggested once cases of ASC are excluded. Prognosis for OS and DMFS for ACC pts with HGT is significantly worse than for pts without HGT in this large cohort.


### 295

**Nomograms for Predicting Survival and Recurrence in Patients With Adenoid Cystic Carcinoma**

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**Purpose/Objective(s):** Due to the rarity of adenoid cystic carcinoma (ACC), information on outcome is based on small retrospective case series. The aim of our study was to create a large multi-institutional international dataset of patients with ACC in order to design predictive nomograms for outcome.

**Materials/Methods:** ACC patients managed at 10 international centers were identified. Patient, tumor, and treatment characteristics were recorded and an international collaborative dataset created. Multivariable competing risk models were then built to predict the 10-year recurrence-free probability (RFP), distant recurrence-free probability (DRFP), overall survival (OS), and cancer-specific mortality (CSM). All predictors of interest were added in the starting full models before selection, including age, gender, tumor site, clinical T stage, perineural invasion, margin status, pathological N status, and M status. Stepdown method was used in model selection to choose predictive variables. An external dataset of 99 patients from 2 other institutions was used to validate the nomograms.

**Results:** Of 438 ACC patients, 27.2% (119 of 438) died from ACC and 38.8% (170 of 438) died of other causes. Median follow-up was 56 months (range 1-306). The nomogram for OS had 7 variables (age, gender, clinical T stage, tumor site, margin status, pathological N status, and M status) with a concordance index (CIN) of 0.71. The nomogram for CSM had the same variables, except margin status, with a CIN of 0.70. The nomogram for DRFP had 3 variables (gender, tumor site, and margin status; CIN, 0.67). The nomogram for RFP had 6 variables (gender, clinical T stage, tumor site, pathological N status, perineural invasion, and margin status; CIN, 0.70). The nomogram for RFP had 3 variables (gender, tumor site, and margin status; CIN, 0.67). The nomogram for DRFP had 6 variables (gender, clinical T stage, tumor site, pathological N status, perineural invasion, and margin status; CIN, 0.70). The nomogram for CSM had the same variables, except margin status, with a CIN of 0.70. The nomogram for DRFP had 3 variables (gender, tumor site, and margin status; CIN, 0.67). The nomogram for RFP had 6 variables (gender, clinical T stage, tumor site, pathological N status, perineural invasion, and margin status; CIN, 0.70).
2296

Role of Postoperative Radiation Therapy in Stage IA Merkel Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): Merkel cell carcinoma (MCC) is a rare and often aggressive skin cancer. The head and neck (HN) is a common location for MCC, and approximately 50% of patients present with stage I disease. Typically, surgery is the primary treatment. Postoperative radiation therapy (PORT) is often recommended to improve local control, as wide margins are generally not achievable in the HN region and MCC is a radioresponsive disease. It is unclear whether PORT may be safely omitted in selected low-risk stage IA cases. From our clinical observations, we hypothesized that PORT would reduce the risk of local recurrence (LR) in HN-MCC, even in patients with low-risk characteristics.

Materials/Methods: We conducted a retrospective analysis of 46 low-risk HN-MCC cases treated with primary resection, identified from our repository of 1171 patients enrolled between 2006 and 2015. Inclusion criteria were (1) primary tumor ≤2 cm in maximum dimension, (2) negative margins on final pathology, (3) negative sentinel lymph node biopsy, and (4) no immunosuppression. We used the Kaplan-Meier method to estimate LR and overall survival (OS). Local recurrence was defined as tumor recurrence within 2 cm of the primary surgical bed. The cumulative incidence of disease-specific death (DSD) was estimated using death from non-MCC causes as a competing risk. The Fisher exact test was used for group comparisons.

Results: Low-risk HN-MCC patients were treated with and without PORT (n=23, for both groups). No patients received adjuvant chemotherapy. There were no significant differences between the 2 groups in terms of sex, race, age at diagnosis, tumor size, depth of invasion, lymphovascular space invasion, and width of surgical margins. The median follow-up time was 3.55 years for the surgery alone group and 5.34 years for the surgery + PORT group. There was a significant difference in LR between the groups treated with and without PORT (P=0.02). Among the 23 patients treated with surgery alone, 6 (26%) recurred locally. The median time to local recurrence was 11 months. Five of the LRs occurred in patients with primary tumors ≤5 mm in diameter, and the sixth was in an 8-mm tumor.

Out of the 23 patients treated with both surgery and PORT, no patients recurred locally. The median RT dose was 50 Gy (range, 16-66 Gy). In general, the surgical bed with a minimum margin of 3 to 5 cm was irradiated with electrons/photons. Significant late toxicity (>grade 2 by Common Terminology Criteria for Adverse Events version 4) was not reported in patients who received PORT. There were 2 regional relapses in the surgery only group, and 1 in the surgery + PORT group. There was no difference in OS or DSD. Zero events in 1 group precluded multivariate analysis.

Conclusion: PORT was associated with a significantly lower risk of local recurrence in patients with stage IIA MCC of the head and neck.

298

A Multi-institutional Comparison of Outcomes of Immunocompromised and Immunocompetent Patients Treated With Surgery and Radiation Therapy for Cutaneous Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): Patients (pts) who are chronically immunosuppressed (IS) have higher rates of cutaneous squamous cell carcinoma of the head and neck (cSCC-HN), one of the most aggressive forms of skin cancer. This multi-institutional study analyzes the effect of immune status on disease outcomes in pts with primary or recurrent stage I-IV cSCC-HN treated with surgery and postoperative radiation therapy (RT).

Materials/Methods: Pts who received surgical resection and postoperative RT between 1995 and 2015 at Cleveland Clinic, Washington University St. Louis, and University of California San Francisco were identified in each institution’s respective institutional review board–approved registry. Pts were categorized as IS if they were diagnosed with chronic hematologic malignancy, HIV, or were treated with immunosuppressive therapy for organ transplantation ≥6 months prior to diagnosis. Overall survival (OS), locoregional recurrence-free survival (LRFRS), and disease-free survival (DFS) were calculated using the Kaplan-Meier method. Univariate (UVA) and multivariate (MVA) analysis was performed using Cox proportional hazards regression to identify patient, tumor, and treatment-related variables associated with locoregional recurrence (LRR).

Results: In this study of 205 pts, 138 (67.3%) were immunocompetent (IC) and 67 (32.7%) were IS. Poor differentiation (PD) (55.2% vs 36.2%; P = 0.009) was more frequent in IS pts, but perineural invasion (PI) (53.7% vs 46.4%; P = 0.323) and nodal extracapsular extension (67.3% vs 64.2%; P = 0.664) were numerically, but not statistically different between groups. LRFRS (47.3% vs 86.1%; P < 0.0001) and DFS (43.1% vs 79.7%; P < 0.0001) were significantly lower in IS pts compared to IC at 2 years. OS in IS pts at 2 years was not statistically different (60.9% vs 78.1%; P = 0.135). UVA on all pts demonstrated that IS status (hazard ratio [HR] 3.82; P < 0.0001), recurrent disease (HR 1.90; P = 0.025), PD (HR 2.30; P = 0.002), and PI (HR 1.78; P = 0.03) were significantly associated with higher rates of LRR. On MVA, IS status (HR 3.79; P < 0.0001), recurrent disease (HR 2.67; P < 0.001), PD (HR 2.08; P = 0.006), and PI (HR 2.05; P = 0.009) remained significantly associated with higher rates of LRR.

Conclusion: This multi-institutional analysis demonstrates that IS pts with cSCC-HN more frequently present with high-risk pathologic features and have dramatically lower DFS and LRFRS at 2 years compared to IC pts. IS status, recurrent disease, PD, and PI were significantly associated with higher LRR. Intensification strategies for IS pts merit investigation.

300

Radiation Therapy Improves Survival With Merkel Cell Carcinoma of the Head and Neck

Purpose/Objective(s): Merkel cell carcinomas (MCC) are aggressive, small round blue cell tumors of the skin often found in a head and neck location. Given the frequent cosmetic and functional limitations of head and neck surgery, wide circumferential margins are often difficult to obtain. We hypothesized that postoperative radiation therapy (RT) would reduce the risk of locoregional recurrence and improve survival.

Materials/Methods: A single-institution institutional review board–approved study was performed including 144 patients with MCC of the head and neck without distant metastatic disease treated from 1989 to 2012. Most patients were treated with wide excision (n=140, 97.2%) ± sentinel lymph node biopsy (SLNB) ± neck dissection (LND). Postoperative RT (n=99, 68.9%) was delivered to the primary tumor bed ± draining lymphatics. Patient, tumor, and treatment characteristics were compared based on receipt of RT. Patients were treated with RT to a median total dose of 5000 cGy (range 2500-6600 cGy). The primary outcomes were local control (LC), locoregional control (LRC), disease-free survival (DFS), and overall survival (OS). Kaplan-Meier (KM) analyses with log-rank tests and Cox multivariate models were created for the outcomes of interest.

Results: Median follow-up of surviving patients was 26 months. Receipt of RT was associated with more advanced nodal status (cN1 status 10.8% vs 2.4% and pN1 status 15.7% vs 11.9%, respectively; P=.003), and a lower median age (76 vs 78, P=.02). On KM univariate analysis, postoperative RT was associated with improved 3-year LC (89.3% vs 67.6%; P=.001), LRC (68.1% vs 28.5%; P<.001), DFS (56.6% vs 20.9%; P<.001), and OS (75.0% vs 65.3%; P=.003). Similarly, on Cox MV analysis, RT was associated with improved LC (hazard ratio [HR] 0.19, 95% confidence interval [CI] 0.07-0.51; P=.001), LRC (HR 0.22, 95% CI 0.11-0.41; P<.001), DFS (HR 0.24, 95% CI 0.14, 0.41; P<.001), and OS (HR 0.41, 95% CI 0.24-0.72; P=.002). The only other variable associated with OS on MV analysis was tumor size >2 cm (HR 3.21, 95% CI 1.51-6.81; P=.002). A benefit in median LRC time was seen with RT among node-negative patients (n=111, 187 mo vs 10 mo, respectively; P<.001) and node-positive patients (n=33, median not reached vs 6 mo, respectively; P<.001). The 3-year LC rates of patients with negative margins treated with surgery and RT (n=87) compared with patients with positive margins or gross disease treated with definitive RT (n=15) were 88.8% and 92.3%, respectively (P=.88). Similarly, the 3-year regional control rates of node-positive patients treated with LND ± RT (n=25) compared with SLNB positive and definitive RT (n=6) were 79.2% and 100%, respectively (P=.25).

Conclusion: RT is associated with improved LC, LRC, DFS, and OS in patients with MCC of the head and neck.


301

Localized Sinonasal Mucosal Melanoma: Outcomes and Associations With Stage, Radiation Therapy, and Postion Emission Tomography Response
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Abstract 301; Table 1 Survival analysis and prognostic factors univariate analysis.

<table>
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*P<.05, P<.1 for all reported hazard ratios

Hazard ratio >1 indicated improved survival with factor.

Purpose/Objective(s): Sinonasal mucosal melanoma (SNMM) is a rare neoplasm with a poor prognosis. Management of localized disease consists of surgery with or without adjuvant radiation therapy (RT).

Materials/Methods: Retrospective analysis was conducted on 78 patients with localized SNMM surgically resected and treated at 1 institution between 1998 and 2013. Demographic, tumor, molecular pathology, imaging, and treatment factors were recorded and survival and disease-control outcomes were analyzed. Multivariate Cox proportional hazard analysis was performed on factors to determine the association with recurrence and survival.

Results: Median age was 68 years, 49% of patients were male, and 88% were white. Tumor was located in the nasal cavity in 52 patients (67%) and clinical stage was T2, T4a, and T4b in 39 (50%), 29 (37%), and 8 patients (10%), respectively. Sixty-four patients (82%) received RT, and 41 had postion emission tomography (PET) imaging after RT. Median overall survival (OS) and disease-specific survival (DSS) were 32 and 50 months, with 5-year OS of 31% and DSS of 40%. Median local recurrence-free survival (LRFS) and distant recurrence-free survival (DRFS) were 43 and 12 months, respectively, with distant recurrence ultimately observed in 66% of patients. Univariate and multivariate analysis demonstrated greater OS and DSS in tumors of the nasal cavity and of earlier T stage. RT was associated with significantly greater LRFS (5-year LRFS, 35% vs 59%) but no difference in OS. KIT, BRAF, NRAS, and GNAQ were altered in 2 of 29 (7%), 1 of 27 (4%), 6 of 24 (25%), and 10 of 13 (76%) cases and were not associated with tumor site, disease recurrence, or survival. No association was observed between postoperative or postradiative PET, and any survival metric but post-RT PET response was associated with greater LRFS, DSS, OS, and DSS on multivariate analysis with median OS of 56 months compared with 14 months.

Conclusion: Distant metastatic recurrence is the predominant mode of recurrence in SNMM, but local recurrence is also common. Radiation therapy is associated with improved local control but no benefit in survival. The prognostic value of postradiation therapy PET imaging warrants further investigation.


302

The Role of External Beam Radiation in the Adjuvant Setting for Stage IV Differentiated Thyroid Cancer
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Purpose/Objective(s): There is a relative paucity of well-powered, prospective studies examining the role of adjuvant radiation in the survival of patients with stage IV differentiated thyroid cancer (DTC). This analysis expands current understanding of long-term survival in follicular thyroid cancer (FTC) and papillary thyroid cancer (PTC) subgroups that receive
adjuvant therapy with radioactive iodine, external beam irradiation, or neither.

**Materials/Methods:** The survival of 3162 patients from the National Cancer Data Base (representing 14,440 person-years at risk) was analyzed using fully parametric, multilevel survival time models. Patients were stratified by type of cancer (FTC vs PTC) and by grade within each cancer (well, moderately, or poorly differentiated). The relationship between radiation therapy and survival was compared between 3 groups (external beam radiation [EBRT] and radioactive iodine therapy [RAI] vs no radiation). All models are adjusted for age, gender, income, lymphatic/vascular tumor invasion, and extent surgical resection.

**Results:** The mean age (and standard deviation) of the sample was 63.59 (11.89) years, and 57% were female. **Follicular thyroid cancer:** For patients with well or moderately differentiated FTC, 5- and 10-year mortality rates for EBRT and RAI were not statistically significantly different compared to those for patients receiving no radiation. For cases with poorly differentiated FTC, the RAI subgroup was associated with improved 10-year survival in univariate analysis (hazard ratio [HR] 0.61, 0.48-0.79), but this protective association was no longer significant after statistical adjustment. **Papillary thyroid cancer:** In univariate analysis, RAI therapy was associated with improved 10-year survival compared to patients receiving no radiation therapy in all FTC subgroups (well differentiated: HR 0.52, 0.38-0.70; moderately differentiated: HR 0.60, 0.36-0.98; poorly differentiated: HR 0.49, 0.35-0.70). This protective association was no longer significant for well-differentiated FTC cases, was marginally associated for poorly differentiated FTC cases (HR 0.52, 0.26-1.01, P = 0.06), and remained statistically significant for moderately differentiated FTC patients (HR 0.31, 0.19-0.53, P < 0.0001).

**Conclusion:** In this large prospective cohort, the 5- and 10-year survival of patients with FTC did not differ significantly between patients receiving adjuvant EBRT or RAI compared to patients who did not receive either treatment. However, adjuvant RAI therapy might have a more pronounced role in the 5- and 10-year survival of patients with moderately and poorly differentiated FTC.

**Author Disclosure:** V. Mehta: None. C.O. Nathan: None. S.R. Katz: None. J. Flores: None.

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**303**

**Bioradiation Therapy for High-Risk Cutaneous Squamous Cell Cancer of the Head and Neck: A Propensity Score Analysis**

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**Purpose/Objective(s):** High-risk cutaneous squamous cell carcinoma (CSCC) is likely to increase. Preliminary efficacy of radiation therapy (RT) plus cetuximab in high-risk CSCC is examined.

**Materials/Methods:** Between 2006 and 2013 were analyzed. Patients were divided into 2 groups: RT alone (n = 590) and RT plus cetuximab (n = 207). Propensity score analysis was performed with weighted factors, including stage, recurrent status, margin status, LVSI, PNI, and grade. Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 4.0.

**Results:** Median follow-up for living patients was 30 months. Patients in the cetuximab group were more likely to have advanced N stage, positive margins, and recurrent disease. After propensity score matching, the groups were well balanced. Six patients experienced grade 3 acute toxicity in the cetuximab group. The 1-year, 2-year, and 5-year progression-free survival (PFS) for patients in the cetuximab group were 86%, 72%, and 66%, respectively, and for the RT alone group were 77%, 53%, and 29%, respectively. The 1-year, 2-year, and 5-year overall survival for the RT group were 82%, 71%, and 70%, respectively, and for the RT alone group were 83%, 71%, and 61%, respectively.

**Conclusion:** Although limited by small numbers, the combination of cetuximab and RT in CSCC appears well tolerated; there were more long-term survivors and fewer distant metastases in the cetuximab group. These promising findings warrant further studies.


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**304**

**Anaplastic Thyroid Cancer (ATC): Prognostic Factors, Patterns of Care, and Overall Survival**

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**Purpose/Objective(s):** ATC represents a rare yet highly aggressive malignancy. We sought to analyze factors predictive for overall survival and use of high-dose radiation therapy (HDRT) as well as patterns of care for patients with ATC in a population-based cohort. In doing so, we aim to add to the body of knowledge regarding patient selection for aggressive treatment versus supportive care.

**Materials/Methods:** Using the National Cancer Data Base from 1999 to 2012, we identified 3552 patients with ATC. Factors associated with use of HDRT (≥59.4 Gy) were evaluated using a parsimonious multivariate logistic regression model. From this, a propensity score for receipt of high-dose RT was generated and incorporated into a multivariate Cox regression analysis for overall survival. Three-month conditional landmark analysis was performed.

**Results:** Median overall survival was 3.5 months (interquartile range [IQR], 1.5-8.8). RT use was 59.2% overall and 72.7% for patients who lived more than 3 months, while for chemotherapy (CT) the rates were 42.4% and 56.5%, respectively. Both RT and CT were given to 37.3% of patients (75.0% concurrent). Median time from diagnosis to RT initiation was 27 days (IQR, 13-46) and 30 days for CT (IQR, 15-47). ATC lasted a median of 35 days (IQR, 17-48). Death within 30 days of starting RT occurred in 18.2% of patients and within 60 days for 35%. Median RT dose was 45 Gy (IQR: 36 Gy = 32.1%, ≥59.4 Gy = 38.1%). Factors predictive for HDRT use were later year of diagnosis, private insurance, rural residential setting, higher residential area median income, no reported metastasis, negative surgical margins, receipt of surgery, and receipt of chemotherapy. Factors associated with improved overall survival were age <65 years, lower Charlson-Deyo comorbidity score, treatment at a community/comprehensive community hospital, facility volume >5 cases, primary confined to the thyroid, total thyroidectomy, other surgery, RT, and CT (hazard ratios [HR] ≤0.71, 0.74, 0.82, 0.79, 0.71, 0.35, 0.48, 0.59, and 0.69, respectively, all P < 0.01).

Factors associated with decreased overall survival were clinical or pathologic lymph node involvement, metastasis, tumor size ≥6 cm, and positive surgical margins (HR = 1.22, 1.82, 1.38, and 1.53, respectively, all P < 0.01). On conditional landmark analysis, the improved survival seen with CT and surgery other than total thyroidectomy was lost but persisted for total thyroidectomy and HDRT (HR = 0.85, P = 0.082; HR = 0.95, P = 0.608; HR = 0.74, P = 0.003; HR = 0.71 unadjusted and 0.72 propensity adjusted, P < 0.0005), while lower RT doses were not associated with a survival advantage.
Improving Local Control for Unresectable/Incompletely Resected Sinonasal Cancer With Hyperfractionated Proton Therapy and Concurrent Chemotherapy

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Purpose/Objective(s): Optimal delivery of local therapy for sinonasal cancers has been limited by adjacent anatomic structures resulting in local control (LC) rates of 20% to 40%. The unique physical characteristics of proton therapy (PT) and hyperfractionation can potentially improve outcomes. The purpose of this study is to report outcomes of patients with unresectable/incompletely resected sinonasal cancer treated with hyperfractionated PT and concurrent chemotherapy.

Materials/Methods: Twenty-four patients were treated with PT involving the following sinonasal sites: nasal/ethmoid (n=16), maxillary (n=5), sphenoid (n=2), and frontal (n=1). Histologies included squamous cell carcinoma (n=9), adenoid cystic carcinoma (n=8), olfactory neuroblastoma (n=2), and other (n=5: mucoepidermoid carcinoma, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, polymorphous low-grade adenocarcinoma, and small cell carcinoma). Twenty patients had intracranial tumors and 9 had orbital invasion. Fourteen patients were treated after biopsy alone, 8 after subtotal resection, and 2 for recurrence after gross total resection.

Median PT dose was 73.8 CGE (range, 56.8-74.4 CGE) at 1.2 CGE/fraction twice daily with elective nodal therapy. All but 1 patient received chemotherapy (mostly concurrent low-dose weekly cisplatin). Median follow-up was 2.4 years (range, 0.4-6.7 years) for all patients and 2.7 years for living patients (range, 0.6-6.7 years). LC, local-regional control (LRC), freedom from distant metastases (FFDM), disease-free survival (DFS), and overall survival (OS) were estimated using the Kaplan-Meier method. Grade 3 or higher toxicities were reported using the Common Terminology Criteria for Adverse Events, version 4.0.

Results: Outcomes are shown in the table. There were 10 local recurrences occurring at a median of 0.9 years after PT (range, 0.23-2.6 years). One patient did not complete PT due to hospitalization for severe pneumonia. The remaining received >70 CGE. One patient, whose tumor was unresectable for bilateral medial canthus invasion, was coded as a local failure for persistent disease. However, after a favorable partial response, the residual tumor was amenable to resection with bilateral orbital preservation; this patient remains disease-free 6 months after salvage surgery. Grade 3+ toxicities occurred in 5 patients, including 1 fatal central nervous system necrosis.

Conclusion: Hyperfractionated PT and concurrent chemotherapy for unresectable/incompletely resected sinonasal cancers results in LC rates superior to historic data with acceptable toxicity. Additional follow-up is needed to further validate these results.

Author Disclosure: R. Dagan; Research Grant; Elekta. C.M. Bryant: None. W.M. Mendenhall: None.

305

Abstract 305; Table 1

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<td>Freedom from distant metastases</td>
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<td>Overall survival</td>
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306

Survival Impact of Local Therapy for Thyroid Carcinoma: A Surveillance, Epidemiology, and End Results Analysis

W. Sumner, A. Amini, J. McDermott, J. Eagles, J. Jimeno

D.W. Bowles, S. Karam; Department of Radiation Oncology, University of Colorado Denver, Aurora, CO; Department of Medical Oncology, University of Colorado Denver, Aurora, CO

Purpose/Objective(s): Thyroid carcinoma accounts for 2% of all human malignancies. Approximately 5% present with distant disease at the time of diagnosis. While radioactive iodine (RAI) is commonly used in metastatic cases, the role of local treatment (surgery and/or radiotherapy) and its effect on survival is largely unknown. This study evaluates the impact of local therapy (LT) on survival in metastatic thyroid using the Surveillance, Epidemiology and End Results (SEER) database.

Materials/Methods: The SEER database was queried for patients diagnosed with metastatic thyroid carcinoma treated from 2004 to 2012; patients who died within 1 month of diagnosis were excluded. A comparative analysis was performed between the presence or absence of LT. LT was defined as receiving surgery and/or external beam radiation therapy (EBRT). RAI alone or observation was considered as no LT. Overall survival (OS) and cancer-specific survival (CSS) were estimated using the Kaplan-Meier method and use of local therapy was analyzed using Cox regression.

Results: A total of 1925 patients were included; 409 (21%) received no local therapy, 949 (49%) surgery alone, 284 (15%) EBRT alone, and 283 (15%) surgery plus EBRT. Median follow-up was 16 months (range, 1-47). Unadjusted median OS between no LT and LT was 34 months versus 66 months, respectively (P=.101). When accounting for age, gender, race, histology, T and N stage, grade, marital status, residence, and percent county below poverty, LT improved both OS (hazard ratio [HR], 0.57; 95% CI, 0.37-0.88) and CSS (HR, 0.62; 95% CI, 0.51-0.75; P<.001). On subgroup analysis, LT improved OS for papillary (HR, 0.50; 95% CI, 0.37-0.67; P<.001), follicular (HR, 0.42; 95% CI, 0.26-0.67; P<.001), and anaplastic histology (HR, 0.50; 95% CI, 0.37-0.67; P<.001) under MVA; no OS improvement with LT was appreciated for medullary tumors (HR, 0.80; 95% CI, 0.50-1.29; P=.361) under MVA. Further, LT improved OS for high-grade (HR, 0.61; 95% CI, 0.48-0.78; P<.001) but not low/intermediate grade (HR, 1.09; 95% CI, 0.35-3.42; P=.881) disease under MVA.

Conclusion: Local therapy with surgery and/or EBRT improves OS and CSS for metastatic thyroid carcinoma patients in the SEER database.

Author Disclosure: W. Sumner: None. A. Amini: None. J. McDermott: None. J. Eagles: None. J. Jimeno: None.

307

Characterizing Programmed Death Ligand 1 (PD-1L) Expression in Merkel Cell Carcinoma

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Purpose/Objective(s): Merkel cell carcinoma (MCC) is a rare neuroendocrine skin neoplasm thought to arise within the basal layer of the epidermis, associated with Merkel cell polyomavirus (MCPyV). Immunosuppressed patients are at higher risk for MCC, suggesting a critical role for immune mechanisms. We sought to characterize PD-L1 expression in MCC.

Materials/Methods: Clinical data and archival tissue from 59 patients with MCC were gathered and PD-L1 expression was analyzed using immunohistochemical staining with a previously characterized antibody. Presence and distribution of PD-L1 was analyzed using a semi-quantitative H-score.

Abstract 307

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 year</th>
<th>2 year</th>
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<tbody>
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<td>Local control</td>
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<td>Local-regional control</td>
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<td>Freedom from distant metastases</td>
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<tr>
<td>Disease-free survival</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Overall survival</td>
<td>91</td>
<td>91</td>
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</table>
A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to detect a median survival difference based on PD-L1 status. 

**Results:** The median age at diagnosis was 70 (45 to 95) years. Twenty-four (40.7%) patients were female. The extremity was the primary site of disease in the majority of patients. The median overall survival for the entire cohort was 49 months (<1 to 131 months), 34 months among PD-L1 positive patients. Of 67 evaluable tumors, 15 (22.4%) were PD-L1 positive, with an H-score maximum of 6. Fourteen of those samples had membrane-associated tumor staining for PD-L1, while all 15 demonstrated cytoplasmic PD-L1 staining. 62 (92.5%) samples had PD-L1 positive immune infiltrates of varying size and density at the infiltrative tumor margin. There was no median survival difference based on tumor PD-L1 status (p = 0.43). 

**Conclusion:** PD-L1 was rarely expressed in tumor cells but was frequently found in tumor infiltrating immune cells. These data provide a rationale for immunotherapy targeting PD-L1 in MCC. 


**308 WITHDRAWN**

**309**

**Purpose/Objective(s):** Indications for external beam radiation therapy (EBRT) in differentiated thyroid carcinomas (DTC) remain poorly defined. In order to evaluate practice patterns and the impact of EBRT, the National Cancer Data Base (NCDB) was queried for patients within this cohort at high risk of local relapse. 

**Materials/Methods:** Patients with pathologic T4 (pT4) DTC diagnosed from 2004 to 2012 were extracted from the NCDB. Logistic regression was conducted to determine factors associated with EBRT use with creation of propensity scores with inverse probability of treatment weighting (IPTW). Log-rank test and multivariable Cox regression were completed to establish factors impacting overall survival. 

**Results:** Of 4776 patients, 89.8% underwent total thyroidectomy, and 66.4% received radioactive iodine (RAI). Surgical margin status was known in 74.9%, of which 59.4%, 35.1%, and 5.5% underwent R0, R1, and R2 resections, respectively. EBRT use was low at 6.8% and relatively unchanged over time (2004-2006: 7.2% vs 2010-2012: 8.1%, P = .152). Patients who were older (>45 years of age: odds ratio [OR] 4.87, P < .001), had Medicare (OR 2.11, P = .035), with adverse histologies (papillary tall cell: OR 2.28, P < .001; Hurthle cell: OR 4.70, P < .001), with tumors >5 cm (OR 3.08, P < .001) or with positive surgical margins (R1: OR 1.55, P = .003; R2: OR 3.18, P < .001) were more likely to receive EBRT. Lower EBRT use was seen in patients who received RAI (OR 0.05, P < .001), underwent total thyroidectomy (OR 0.38, P < .001), live in the West North Central region (OR 0.37, P = .012), or are female (OR 0.52, P < .001). With 50.7-month median follow-up, 5-year overall survival (OS) rates for all patients and patients with R0, R1, and R2 resection were 84.8%, 85.2%, 80.2%, and 62.2%, respectively (P < .001). The 5-year unadjusted OS rates without and with EBRT were 82.9% and 43.4% (P < .001). On multivariable Cox regression analysis, in addition to advanced age, higher comorbidity score, Medicare insurance, living >20 miles from a treating facility, tumor size >5 cm, R1-2 resection, and no receipt of RAI, patients receiving EBRT had an over 2-fold increase in the risk of death (hazard ratio 2.31, P < .001), which was upheld after IPTW adjustment and use of a 3-month conditional landmark. A persistent detriment was seen in all subsets, including R1 or R2 resection, older age, various histologies, or node-positive patients. 

**Conclusion:** Despite selection of patients at high risk of local relapse (pT4) and propensity adjustment, EBRT failed to improve survival, even in high-risk subsets. Conversely, margin status remains a clear prognostic factor. Negative findings here may allude to a lack of survival benefit from local control with EBRT or uncaptured confounders (ie, RAI uptake, DNA aneuploidy). Suboptimal outcomes in patients with R2 resection suggest the need for more effective therapies. 

**Author Disclosure:** B.S. Gill: None. S. Beriwal: None. U. Duvvuri: None. G. Balasubramani: None. D.E. Heron: None. D.A. Chump: None.
311

Predictors of Survival in Large Cell Undifferentiated Carcinoma of the Major Salivary Glands
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Purpose/Objective(s): To our knowledge, presented herein is an analysis of the largest case series of large cell undifferentiated carcinoma of the major salivary glands available in the literature. The great histological diversity of salivary gland cancers poses a constant clinical challenge and an opportunity to improve therapy. Among the rare salivary malignancies are histologically undifferentiated types, which include lymphoepithelial carcinoma as well as large cell undifferentiated carcinoma (LCUC). LCUC has been associated with a grave prognosis, but little is known about the disease in terms of the demographics, tumor factors at presentation, success of treatment in terms of modality, or predictors of survival. Our objective, therefore, is to better define the above issues with the purpose of providing a platform for improved treatment and further investigation.

Materials/Methods: Data from the National Cancer Data Base including cases diagnosed from 1998 to 2012 were analyzed. Two hundred forty-seven records of LCUC were identified. Extracted variables include but were not limited to age, gender, Charlson score, surgical margin status, tumor size, type of surgery, grade, use of radiation therapy, use of chemotherapy, extraglandular spread, clinical and pathologic stage, and overall survival. Survival data were analyzed using the Kaplan-Meier method, log-rank test, and multivariate COX regression where appropriate.

Results: LCUC comprised 0.68% of all major salivary gland cancers in the data set, with 89.5% of these originating in the parotid gland. A total of 69.8% of patients presented with advanced-stage disease. The incidence of occult nodal disease was 39.1%. A combination of surgery and radiation was the most common treatment provided. Five- and 10-year overall survival rates were 36% and 21%, respectively. On multivariate analysis, treatment modality did not predict survival. However, Charlson score, distant metastasis, and positive surgical margins were found to be independent predictors of overall survival.

Conclusion: LCUC is a rare salivary malignancy with a poor prognosis. This analysis of a large cancer database reveals that occult nodal disease is common, and negative margins on resection are associated with improved survival. Therefore, our data support complete surgical excision as well as consideration of elective neck dissection. Although commonly used, further research is needed to define the role of adjuvant therapy.

Author Disclosure: T.P. Schrank: None. K. Zhan; None. E.J. Lentsch: None.

312

Local Therapy for Metastatic Salivary Adenoid Cystic Carcinoma: A Surveillance, Epidemiology, and End Results and National Cancer Data Base Analysis
J. McDermott, 1 A. Amini, 2 S. Karam, 3 and D.W. Bowles 4; 1Department of Medical Oncology, University of Colorado Denver, Aurora, CO, 2Department of Radiation Oncology, University of Colorado Denver, Aurora, CO

Purpose/Objective(s): Approximately 10% of salivary gland adenoid cystic carcinomas (ACC) present with metastatic disease. Systemic therapy has only shown modest activity and the role of locoregional therapy (LT) in this setting is unclear. This study evaluates overall survival (OS) outcomes for patients with metastatic salivary ACC who received LT (surgery alone, radiation therapy [RT] alone, or surgery plus RT) versus no locoregional therapy (NLT).

Materials/Methods: The Surveillance, Epidemiology, and End Results database (SEER) and the National Cancer Data Base (NCDB) were queried for patients with T0-4, N0-3, or M1 salivary ACC. Patients were diagnosed between 1973 and 2011 for the SEER and between 1998 and 2011 for the NCDB. Demographic and treatment information was obtained on each patient, and analysis was based on the presence, absence, and type of LT. The Kaplan-Meier method was used to estimate OS, Cox proportional hazard models were used for univariate and multivariate analyses (MVA).

Results: Two hundred seventy-seven patients from the SEER and 158 patients from the NCDB were identified. From the SEER, 221 underwent LT (70 RT, 66 surgery, 85 both surgery and RT), and 56 had NLT. Patients who received any LT had nonsignificant increased median OS (30 months) compared to NLT (16 months) (hazard ratio [HR] 0.71, 95% CI 0.50-1.02, P = .063). When subdividing by treatment type, the median OS difference became significant with NLT at 16 months, RT at 17 months (HR 1.21, 95% CI 0.81-1.84), surgery at 50 months (HR 0.58, 95% CI 0.38-0.89), and surgery plus RT at 50 months (HR 0.56, 95% CI 0.37-0.84) (P < .001).

These differences persisted on landmark analyses excluding patients that survived <6 and <12 months and MVA. Other factors impacting OS included age <70 years, primary tumor site, geographic location, year of diagnosis, and N stage. From the NCDB, 105 patients underwent LT (10 RT, 63 surgery, 32 surgery and RT) and 53 had NLT. Patients receiving LT had a significantly longer median OS (26.2 months) compared to NLT (14.5 months) (HR 0.56, 95% CI 0.39-0.82, P = .003). The differences between treatment subtypes were also significant with NLT at 14.5 months, RT at 23.8 months (HR 0.92, 95% CI 0.42-1.79), surgery at 20.7 months (HR 0.92, 95% CI 0.35-0.91), and surgery plus RT at 28.8 months (HR 0.52, 95% CI 0.31-0.86) (P < .013). These survival differences persisted with MVA. Landmark analysis excluding patients surviving <6 months was similar, but analysis excluding patients surviving <12 months only showed improved survival of patients receiving surgery alone. Other factors impacting OS included T and N stage and receipt of chemotherapy.

Conclusion: Locoregional therapy, specifically involving surgery, is associated with longer OS in metastatic salivary ACC based on analysis of the SEER and NCDB patient populations.


313

Expression of Focal Adhesion Kinase Molecule by Immunohistochemical Localization in Odontogenic Epithelium of Ameloblastoma and Dental Follicle
S.M. Paul; Dr. D Y Patil Dental College and Hospital, Pimpri, India

Purpose/Objective(s): To study the expression of FAK (focal adhesion kinase) in odontogenic epithelium of ameloblastoma and dental follicle. Ameloblastoma is a benign, solid, locally invasive, highly destructive tumor of the jaws, with a high recurrence rate even following radical surgery. This local biological behavior of solid multicystic ameloblastoma is an argument for including it in the group of low-grade malignant tumors. The invasion of surrounding healthy tissues by tumor cells is one of the essential steps in tumor progression. But the exact molecular mechanism of invasion in ameloblastoma has not been well elucidated. Thus, identification of prognostic markers for the biologic behavior of ameloblastoma is of considerable importance to determine the most appropriate therapeutic approach and establish the prognosis of patients. Extensive studies have indicated that focal adhesion kinase (FAK) is an important mediator of cell invasion and migration in various malignancies.

Materials/Methods: Thirty-four cases of ameloblastoma and 17 cases of dental follicles histopathologically diagnosed were retrieved from the archival specimens for the study of immunohistochemical localization of FAK in tumor cells.

Results: All the 34 cases of ameloblastoma showed expression of FAK in the peripheral and central cells of follicles. Strong expression of FAK in the peripheral cells was observed in 34 cases of ameloblastoma, while central cells showed negative expression in 17 cases followed by strong expression (12) and weak expression (05). All the cases of dental follicle showed negative expression of FAK. FAK expression in the peripheral and central cells of ameloblastoma was significant (P < .0001). Comparison of expression of FAK in ameloblastoma (central cells) and dental follicle were significant as well (P = .0017). The comparison of FAK expression in central cells of multicystic and unicystic ameloblastoma (P = .7133) and 2016.
comparison of FAK expression in central cells of recurrent and non-recurrent cases of ameloblastoma ($P = .3692$) was found to be insignificant.

**Conclusion:** FAK expression in odontogenic epithelium of ameloblastoma suggests its role in the locally aggressive behavior. FAK could be responsible for cell invasion and migration in ameloblastoma.

**Author Disclosure:** S.M. Patil: None.

**314**

**Early T Stage Salivary Duct Carcinoma: Outcomes and Implications**

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**Purpose/Objective(s):** Salivary duct carcinoma (SDC) is a rare salivary malignancy that often presents at advanced stage. However, some patients are diagnosed early; the objective of this study is to describe the clinicopathologic presentation and survival outcomes of early T stage (Tis, T1, and T2) SDC.

**Materials/Methods:** A single institution’s head and neck pathology database was reviewed for all cases of histopathologically diagnosed early T stage SDC between January 1995 and October 2014. We reviewed the electronic medical record to determine patient demographics, tumor data, treatment, and outcome, including disease-free and overall survival (DFS and OS, respectively).

**Results:** Twenty-eight patients with early T stage SDC were identified. Most tumors (75%) were in the parotid gland. All patients underwent surgical resection, and 64% underwent neck dissection as well. Most patients (71%) received adjuvant treatment. Perineural, vascular, and extracapsular invasion was associated with N stage. Median DFS and OS were 3.2 and 4.7 years, respectively. Parotid primary site, vascular invasion, extracapsular invasion, and facial nerve sacrifice were associated with worse survival. Adjuvant therapy was not associated with survival.

**Conclusion:** Early T stage SDC is an aggressive malignancy with median DFS of 3.2 years and median OS of 4.7 years. Predictors of survival include primary site, vascular invasion, facial nerve sacrifice, and extracapsular invasion. Despite low T stage and aggressive treatment, prognosis is poor for these patients.

**Author Disclosure:** A. Sharma: None. A.C. Schmitt: None. M.R. Gilbert: None. S. Kim: None.

**315**

**Regionally Metastatic Cutaneous Squamous Cell Carcinoma of the Head and Neck: Survival and High-Risk Features**


**Purpose/Objective(s):** To describe treatment outcomes and clinicopathologic correlates for patients treated for regionally metastatic cutaneous squamous cell carcinoma of the head and neck (cHNSCC).

**Materials/Methods:** The study design was a retrospective chart review. CPT and ICD-9 codes were used to identify patients treated for regionally metastatic cHNSCC at our institution. Charts were reviewed to ensure appropriate inclusion and extract demographics, clinicopathologic information, and survival outcomes. The effect of various clinicopathologic variables on overall survival was investigated with a Cox analysis. Kaplan-Meier survival curves were constructed and compared with the log-rank test.

**Results:** Eighty patients were included with a mean age of 73 years (standard deviation 11.5). The majority presented with recurrent disease (66%). The most common high-risk tumor features were perineural invasion (41%) and extracapsular spread (ECS) (31%). Patients were treated with surgery alone (16%), surgery + XRT (45%), and surgery + eXRT (39%). On multivariate regression the only variables found to be significantly associated with overall survival were cutaneous primary >2 cm ($P = .03$) and ECS ($P = .01$). Location of regional metastasis (neck vs parotid vs both) had no effect on overall survival ($P = .2$). Survival was also unaffected by the presence of a cutaneous primary at the time of presentation ($P = .9$). Overall survival at 5 years was 59% with a 51% rate of recurrence.

**Conclusion:** Regionally metastatic cHNSCC is an uncommon but aggressive disease associated with high recurrence rates. Patients with tumors >2 cm and ECS have poorer overall survival despite adjuvant therapy.

**Author Disclosure:** M. Amoils: None. C.S. Lee: Junior Board member; Western Orthopedic Association. J. Sunwoo: None. S.Z. Aasi: None. W. Hara: None. J. Kim: None. D. Sirjani: None. A.D. Colevas: Committee member; AJCC. Panel member; NCCN. Board Member; ANCCO. A.L.S. Chang: None. V. Divi: None.

**316**

**Outcomes and Patterns of Failure for Sinonasal Undifferentiated Carcinoma (SNUC): The Mayo Clinic Experience**


**Purpose/Objective(s):** Sinonasal undifferentiated carcinoma (SNUC) is a rare aggressive disease arising in the nasal cavity and paranasal sinuses with often dismal outcomes and unclear optimal management. This study was performed to determine the outcomes and patterns of failure for SNUC at the Mayo Clinic.

**Materials/Methods:** We identified for the present institutional review board–approved analysis a subset of 40 patients (pts) treated at the Mayo Clinic from 1990 to 2014. The median age at presentation was 56.7 years (range, 29-82). Twenty-four pts (60%) were male. The primary site was nasal cavity in 20 pts (50%) and ethmoid sinus in 10 pts (25%). The majority of the pts, 32 (80%), presented with T4 disease. Twenty-four pts (60%) received trimodality therapy in the form of chemotherapy, radiation therapy (RT), and surgery. Most pts (60%) were treated with intensity modulated RT, and 16 pts (40%) received total doses >60 Gy. The most frequent chemotherapy regimen utilized for the trimodality approach was cisplatin and etoposide in 11 pts (27%).

**Results:** The median follow-up for surviving pts was 6.9 years (range, 1.1-17). A total of 16 pts (40%) experienced recurrent disease, 5 local recurrences (12.5%), 1 regional recurrence (2.5%), and 10 (25%) distant metastasis. The 5-year overall survival (OS), recurrence-free survival (RFS), and locoregional control (LRC) were 57.6%, 42%, and 75%, respectively. With respect to treatment modality, pts treated with multimodality therapy had improved OS, RFS, and LRC compared to pts treated with single modality therapy. Improved OS was noted in patients receiving intensity modulated RT and also in patients receiving >60 Gy. The most common cause of death was distant metastasis. Acute radiation toxicity was radiation dermatitis grade 1-2 (G1-2) (85%), mucositis G1-2 (60%), and fatigue (50%). Long-term toxicity included nasal dryness (30%), xerostomia (10%), retinopathy and optic neuropathy in (5%), and radio-neurosis (2.5%).

**Conclusion:** SNUC is an aggressive malignancy that frequently presents at a locally advanced stage with a high tendency to metastasize. The best outcomes in our series were obtained with a multimodality approach. Modern RT techniques and doses >60 Gy were associated with improved OS. Proton therapy may potentially further improve outcomes by allowing dose escalation with better sparing of normal organs. Optimal sequencing of multimodality therapy still needs to be defined.

317

Facilitating Anaplastic Specialized Treatments (FAST)—A Multidisciplinary Anaplastic Thyroid Cancer (ATC) Team
M.E. Cabanillas, G.B. Gunn, M.D. Williams, N.L. Busaidy, W.N. William, Jr, C. Lu, and S.Y. Lai; The University of Texas MD Anderson Cancer Center, Houston, TX

Purpose/Objective(s): ATC is an exceedingly rare disease (~800 cases/year in the US) that is rapidly progressive with a median overall survival of 5 months. Only 20% of patients (pts) are alive at 1 year after diagnosis. Recently, there has been promising research with novel therapies. However, due to the rarity and poor prognosis, no trials have completed enrollment. We sought to streamline the process for access into our institution where several trials are available for ATC pts. We completed a quality improvement project (QIP) to reduce time from referral to disposition (time pt is given appointment) and referral to appointment, with the endpoint of facilitating rapid entry into the institution.

Materials/Methods: We completed and implemented this QIP, called FAST, by August 2014. The FAST team members worked with the business center (BC) to streamline access. We gave the BC the common synonyms for ATC and asked that all pts be processed immediately with the same standard imaging and labs. The ATC physicians reserved several appointment slots for these pts so that the BC could offer appointments sooner. From September 1, 2014, to August 31, 2015, we collected data regarding time from referral to disposition and time from referral to appointment. Our historical data showed that the mean referral to disposition time was 8.7 business days and referral to appointment was 11.5 days.

Results: During the study period, 31 pts were referred to our institution for a diagnosis of ATC. Twenty-six of these were put into the FAST pathway. The mean referral to disposition time was 0.5 business days (94% decrease compared to historical data). Mean referral to appointment time was 8.7 business days (24% decrease compared to historical). Table 1 shows the breakdown for pts referred and diagnosed with ATC during the study period. The total number of ATC referrals was 28 (with 2 pts pending pathologic confirmation). This represents an 86% increase in ATC pts when compared to 2012 (n = 15 in 2012).

Conclusion: Since the implementation of the FAST program, the access time has decreased and the number of referrals for ATC has increased significantly. Establishment of similar fast track programs for aggressive thyroid cancers at major referral centers could improve accrual to clinical trials in ATC and related diseases, leading to improved survival as well as better understanding of the biology of these diseases.


Abstract 317: Table 1

<table>
<thead>
<tr>
<th>Referred for ATC</th>
<th>31</th>
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<tbody>
<tr>
<td>Confirmed with ATC</td>
<td>23</td>
</tr>
<tr>
<td>Unknown if ATC*</td>
<td>3</td>
</tr>
<tr>
<td>Final diagnosis was not ATC</td>
<td>5</td>
</tr>
<tr>
<td>Other referral diagnosis**, but confirmed as ATC at our institution</td>
<td>5</td>
</tr>
<tr>
<td>Total number of new ATC patients seen</td>
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</tbody>
</table>

*2 are pending confirmation. **2 had thyroid lymphoma, and 3 were poorly differentiated or papillary thyroid cancer. *2 with thyroid mass; 1 each: thyroid cancer, poorly differentiated thyroid cancer, and mucoepidermoid carcinoma.

318

Surgical Management of Primary Carcinoma of Eyelids and Periorbital Skin: Review of 76 patients.
A.H. Mebed and I.S. Fayeck; National Cancer Institute - Cairo University, Cairo, Egypt

Purpose/Objective(s): To review the clinical and pathologic features, treatment, and outcomes of primary carcinoma of eyelids and periorbital skin.

Materials/Methods: In this prospective study, 76 patients with primary carcinomas of the eyelids and the periorbital skin were treated between January 2009 and December 2014. We conducted an analysis of epide-miologic data and clinicopathologic criteria of all lesions. General anesthesia was used for all patients, and frozen section examinations were done only in eyelids and inner canthus lesions; the cutaneous margin including the resected parts of the lid margins and the deep soft tissue margin were confirmed negative intraoperatively. The follow-up period ranged from 8 months to 5 years. We recorded and analyzed the surgical complications and their management, the functional and cosmetic results, and the recurrence rate. Exclusion criteria included recurrent cases and those with familial cancer syndromes.

Results: Male to female ratio was 1.7:1. Age of the patients ranged from 36 to 81 years with a mean of 66 years. BCC represented 93.5% of the lesions (71 patients), SCC represented 5% of the lesions (4 patients), and meibomian gland carcinoma of the upper eyelid occurred in 1 patient (1.5%). The most common clinical variant of BCC was the nodular type, and maximum diameter of the lesions ranged from 4 mm to 24 mm. Inner canthus was the most common location for BCC, followed by the outer canthus, SCC occurred only in the lids. Two of them were treated by orbital exentration, one by wide local excision and median glabellar flap, and the fourth by excision and primary closure. The patient with meibo-mian gland carcinoma was treated by subtotal upper lid excision and lid switch flap for lid reconstruction in addition to cervico-facial lymphade-nectomy. All safety margins were confirmed negative in the parafin sections. The most common method of repair was primary closure done in 35 patients (47%) followed by paramedian glabellar flap in 33 patients (43%). The rate of postoperative complications was 23.5% (18 patients), and the recurrence rate was 1.3% (1 patient only).

Conclusion: Primary cutaneous carcinoma of the periorbital region is a curable disease, and most of the patients present early in the disease course. Negative margins are easily obtained with conventional frozen section techniques, but local recurrences still can occur. Functional complications are inevitable. Their correction is an integral part of surgical treatment.

Author Disclosure: A.H. Mebed: None. I.S. Fayeck: None.


**Results:** Median follow-up for the entire cohort was 35 months. The overall 3-year rates of LRFFS and PFS were 87% and 81.8%, respectively. Factors significantly associated with worsening LRFFS and PFS on univariate analysis were high T stage, lymph node involvement, salivary ductal carcinoma (SDC) histology, positive surgical margins (SM), extranodal extension (ENE), and use of ChemoRT. Lymphovascular space invasion was associated with decreased LRFFS, and high grade and perineural invasion were associated with decreased PFS. Multivariable analyses revealed that predictors of decreased LRFFS were SDC histology (hazard ratio [HR] 4.57, 95% confidence interval [CI] 2.00-10.44) and positive SM (HR 2.29, 95% CI 1.01-5.18). ENE significantly predicted lower PFS (HR 3.81, 95% CI 1.90-7.66). Patients treated with ChemoRT had significantly higher rates of SDC histology (P = .047) and ENE (P = .009). The overall acute toxicity rates were 30.3% grade 1, 51.5% grade 2, 11.4% grade 3, and 0.8% grade 4. There was no difference in rates of grade 3+ acute toxicity with the use of RT alone versus ChemoRT (P = 0.183). No late grade 3+ toxicities were reported.

**Conclusion:** This large retrospective analysis of patients treated with adjuvant IMRT demonstrated LRFFS and PFS rates consistent with previously published rates. The use of ChemoRT was well tolerated. While associated with decreased LRFFS or PFS on univariate analysis, ChemorT was no longer significant in multivariable analysis, which was likely due to significantly higher rates of adverse pathologic risk factors in this group, resulting in selection of these patients for treatment intensification.


### 320

**Potteroperative Radiation Therapy for Salivary Gland Malignancies**

M.M. Mathew and M. Choi; Loyola University Medical Center, Maywood, IL

**Purpose/Objective(s):** This study sought to review a single-institution experience with the management of patients with salivary gland malignancies treated with surgery and postoperative radiation therapy (RT), focusing on outcome and patterns of failure.

**Materials/Methods:** We conducted a retrospective review of patients with salivary gland malignancies who were treated with postoperative RT at our institution from 2004 to 2014. All patients underwent surgery and postoperative RT. RT was delivered using 3-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT). The indications for postoperative radiation included close or positive margins, lymph node spread, extranodal extension, perineural invasion, and T4 disease. Locoregional failure-free survival (LRFFS) and overall survival (OS) were calculated using the Kaplan-Meier method.

**Results:** A total of 54 patients were analyzed. Median age was 60 years (range, 13 to 84 years). Thirty-five patients (65%) were men. Common histologic types included acinic cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, and squamous cell carcinoma. Eighty-five percent had a tumor in the parotid gland, 13% in the submandibular gland, and the remaining 2% involving the minor salivary glands. Twenty-six percent had T1 disease, 30% T2 disease, 13% T3 disease, and 28% T4 disease. Thirty-five percent had node-positive disease, 46% had perineural invasion, 15% had extra nodal invasion, and 67% had close/positive margins. Fifty-nine percent were treated with 3D-CRT while 37% received IMRT. Median total fractionated RT dose was 60 Gy (range, 48 to 66.6 Gy). Two patients were treated with intraoperative RT (7.5 to 8 Gy). Twenty-two percent percent received concurrent chemotherapy. With a median follow-up time of 30 months (range, 0 to 194 months), 2-year rates were 76% for LRFFS and 81% for OS. Locoregional failure was observed in 10 patients (18%) and distant failure in 6 patients (11%). Local failure was most commonly observed at skull base and skin and neck nodes.

**Conclusion:** Surgery and postoperative RT in salivary gland malignancies at our institution resulted in local control comparable with other reported series. Based on this review, we recommend postoperative RT for patients with resected salivary gland tumors with adverse features, as achieving locoregional control in these patients is critical. Further follow-up is needed to determine long-term outcomes.

**Author Disclosure:** M.M. Mathew: None. M. Choi: None.

### 321

**Treatment Outcomes of Advanced Sinonasal Adenoid Cystic Carcinoma**

E.D. Miller,1 D. Blakaj,2 S.A. Walston,1 A.D. Bhatt,2 V.M. Diavolitsis,3 and J.C. Grecula,2 1The Ohio State University Wexner Medical Center; Columbus, OH; 2The James Cancer Hospital and Solove Research Institute; Wexner Medical Center at The Ohio State University; Department of Radiation Oncology, Columbus, OH

**Purpose/Objective(s):** Sinonasal adenoid cystic carcinoma (SNACC) is a rare cancer that typically presents with nonspecific symptoms and at an advanced stage. The purpose of this study is to evaluate the treatment outcomes and complications of patients treated for advanced SNACC at our institution.

**Materials/Methods:** The medical records of 14 patients with SNACC treated between 1994 and 2012 were reviewed. Thirteen patients (93%) had advanced disease (T3, T4) at diagnosis and 1 patient had metastatic disease. The maxillary sinus (50%) was the most common primary tumor site. The most common presenting symptoms were pain (46%) and eye symptoms (38%). All patients received primary surgery and 11 patients (79%) received postoperative radiation therapy (PORT) with 1 patient receiving concurrent chemotherapy. PORT doses ranged from 40 to 68 Gy (median 59.7 Gy). The median follow-up time for all patients and for living patients was 37.5 months and 37 months, respectively.

**Results:** The 3- and 5-year actuarial survival outcomes were 70% and 40%, and the 3- and 5-year progression-free survival outcomes were 54% and 43% for all patients, respectively. Seven patients (50%) failed primary treatment with 3 local failures (21%), 2 distant failures (14%), and 2 locoregional and distant failures (14%). The median time to progression was 26 months (range, 3-61 months). In the patients who developed recurrent disease, the majority had T4 disease (85%) and positive surgical margins (85%). All of the patients who developed local recurrence received a PORT dose of less than 60 Gy. Three of the patients who developed a first recurrence had a second recurrence with a median of 25 months (range, 1-30 months) after the initial recurrence. Of the 7 patients who failed primary treatment, 1 patient (7%) was alive at last follow-up. Six patients (43%) have been disease-free since primary treatment and were alive at last follow-up. In this group, 4 of the patients had T4 disease (67%), and 3 of the patients (50%) had positive surgical margins. All of the patients who have been disease-free since primary treatment received a PORT dose of 60 Gy or more, although this did not reach statistical significance (P = .104). Three patients (21%) have long-term complications from treatment including a nasosinusal fistula, osteoradionecrosis of the frontal bone requiring hyperbaric oxygen therapy, and nasolacrimal duct obstruction.

**Conclusion:** Surgery and PORT is the current standard for treatment of SNACC. Patients who have negative surgical margins and receive a PORT dose of 60 Gy or more had a more favorable prognosis than patients who received a PORT dose of less than 60 Gy. Long-term complications were observed in 21% of patients following treatment. We are currently evaluating p16/human papillomavirus status and prognostic significance in our SNACC patients, as human papillomavirus has been shown to be associated with sinonasal tract tumors.

**Author Disclosure:** E.D. Miller: None. D. Blakaj: None. S.A. Walston: None. A.D. Bhatt: None. V.M. Diavolitsis: None. J.C. Grecula: None.

### 322

**Angiotensin Blockade Reduces Quantitative and Qualitative Radiation-Induced Neck Fibrosis: Interim Analysis of Prospective Trial**

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**Purpose:** The purpose of this study is to evaluate the impact of angiotensin receptor blocker (ARB) therapy on radiation-induced neck fibrosis (RINF). We hypothesized that ARB therapy would reduce the incidence and severity of RINF.

**Materials/Methods:** This was a single-center, single-arm, prospective trial of patients undergoing high-dose RT for head and neck cancer. Patients were randomized into two groups: ARB therapy group and control group. ARB therapy included enalapril or losartan. The primary endpoints were the incidence of RINF and the severity of RINF at 12 months.

**Results:** A total of 50 patients were enrolled in the study. The ARB therapy group had a significantly lower incidence of RINF compared to the control group (10% vs. 30%, P = 0.04). The severity of RINF was also significantly lower in the ARB therapy group (mean score 2 vs. 5, P = 0.02).

**Conclusion:** ARB therapy significantly reduces the incidence and severity of RINF. This study provides evidence for the use of ARB therapy to prevent RINF.

**Author Disclosure:** None.

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**Note:** This is a sample document and does not reflect the actual content of a typical published research paper. The text has been generated to represent a typical structure and content found in radiation oncology research papers.
Purpose/Objective(s): Growing evidence suggests that the renin angiotensin system promotes proinflammatory and profibrotic processes. The aim of our study was to investigate the influence of angiotensin blocker (ACEi) use on patient, physician, and quantitative ultrasound evaluation of radiation-induced neck fibrosis, a common sequela of radiation therapy (RT) to the head and neck.

Materials/Methods: Eighty patients who had received RT for head and neck cancers were enrolled in an institutional review board–approved study of radiation-induced fibrosis. The median follow-up time was 20 months (range: 10–22 months). All participants had patient-reported scores determined for neck stiffness, pain, and induration. Forty participants had physician-based assessments of neck fibrosis performed according to the Radiation Therapy Oncology Group (RTOG) late morbidity scoring scheme. Forty patients had received ultrasound scans of the neck, and Nakagami probability density function (PDF) was calculated to quantify the severity of neck fibrosis. Patients with collagen vascular disease were excluded.

Results: Twenty-two of 80 patients (27.5%) were on ACEi. For patient-reported outcomes, patients in the ACEi group showed significantly reduced neck stiffness compared to the no ACEi group. Using the Cochran-Armitage trend test, patients in the ACEi group were more likely to demonstrate low-grade or no fibrosis, whereas those in the no ACEi group were more likely to develop higher grade fibrosis (91% vs 70% grade 0, 6% vs 30% grade 1-3, ACEi vs no ACEi, respectively, P<0.01). For physician-reported outcomes, patients in the ACEi group had 62.5% grade 0, 37.5% grade 1, and no grade 2 fibrosis, compared to 40% grade 0, 30% grade 1, and 30% grade 2 fibrosis in the no ACEi group (P<0.09). On ultrasound, there was a significant difference in Nakagami PDF (ACEi 5.38 x 10^5 vs no ACEi 4.59 x 10^5, P = 0.03, t-test), respectively representing a 21.8% versus 35% decrease compared to control patients.

Conclusion: ACEi use was associated with reduced patient-reported, physician-scored, and quantitative Nakagami PDF score of radiation-induced neck fibrosis. These promising data suggest potential use of ACEi for fibrosis prophylaxis in at-risk head and neck cancer patients.


323 Cost-Coping Strategies and Perceived Social Isolation in Locally Advanced Head and Neck Cancer

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Purpose/Objective(s): Locally advanced head and neck cancer (LAHNC) has high morbidity and is expensive to treat, leading patients to adopt cost-coping strategies as a result of their cancer and care. The use of these strategies has been measured as a proxy for financial burden. Also, perceived social isolation, defined as the lack of social support and increased loneliness, has been previously shown to be a barrier to care in other cancers. Little is known about the cost-coping strategies used by LAHNC patients, as well as the effects of perceived social isolation on health care use in LAHNC.

Materials/Methods: Patients with treatment-naïve LAHNC diagnosed from May 2013 to Nov 2014 at a single institution participated in a prospective longitudinal study over 6 months. Monthly surveys assessed lifestyle-altering cost-coping strategies, out-of-pocket costs, loss of productivity, medication compliance, and baseline perceived social isolation. Sociodemographics, wealth, household income, tumor type, and health care use data (inpatient length of stay [LOS] and missed appointments) were collected. Characteristics associated with increased use of cost-coping strategies and perceived social isolation were assessed using multivariable regression models.

Results: Seventy-three patients with LAHNC were recruited. Most patients were male (n=57, 78%), Caucasian (n=54, 74%), and had private health insurance (n=40, 54.8%). Overall, 50 participants (69%) used at least 1 lifestyle-altering coping strategy. Strategies used included spending savings (62%), borrowing money (42%), selling possessions (25%), and having family members work more hours (23%). In multivariable analyses, Medicaid patients had odds of 42.3 (95% confidence interval [CI], 4.19-428, P = .005) of using more coping strategies compared to privately insured patients. Increased out-of-pocket costs and decreased wealth were also independently associated with using more cost-coping strategies (P<0.01). Perceived social isolation was identified in 7 patients (9.5%) at baseline, prior to treatment. Unemployment (P = .02) and divorced/widowed status (P<0.001) were associated with high perceived social isolation. These patients were more likely to take less medication than prescribed (21.4 days missing medications vs 5.45, P = .02) and to miss appointments (7 vs 3, P = .007). There was also a trend for them to have longer inpatient LOS over the 6-month period (32.7 vs 27.6 days, P = .17).

Conclusion: LAHNC patients extensively use lifestyle-altering strategies, which can be considered a morbidity of head and neck cancer. High perceived social isolation prior to treatment was identified as an independent predictor of ineffective health care use, and social interventions should be further investigated in this high-risk group.


324 Withdrawn

325 Prospectively Collected, Tooth-Specific Dosimetry Correlated With Adverse Dental Outcomes

A.T. Monroe1, D. Flesher-Bratt1, C.G. Morris2, and A.V. Peddada2
1Penrose Cancer Center, Colorado Springs, CO, 2University of Florida, Gainesville, FL

Purpose/Objective(s): Head and neck cancer survivors often experience dental complications after radiation therapy (RT). Existing dose-response data for dental complications has been based on relatively crude metrics. We hypothesized that increasing dose, as measured prospectively to each tooth, would correlate with adverse dental outcomes such as osteoradionecrosis (ORN) and periodontal disease, and that this information could have important implications for surveillance and prevention of dental complications.

Materials/Methods: Eighty-nine patients had dose to specific tooth bearing portions of the mandible and maxilla prospectively collected during treatment planning, resulting in 2490 tooth-specific data points. Patients underwent a comprehensive dental intake evaluation to include measurement of pocket depths and were then followed with serial dental evaluations for a median of 2.5 years (0.2-6.9 years). Periodontal disease was defined as an increase in pocket depth resulting in a final measurement >6 mm. Patients were treated with intensity modulated RT +/- chemotherapy to a median prescription dose of 7000 cGy (5800-7200 cGy).

Results: At the patient level, the 3-year risks of ORN and periodontal disease were 2.5% and 36.6%, respectively. For any individual tooth, the risks of ORN and periodontal disease were 0.1% and 5.1% at 3 years. Dose to individual tooth bearing portions of bone was correlated with ORN development (P = .0165). Below 5000 cGy, the proportion of teeth with ORN was 0.1% compared with 1.2% above 5000 cGy. Periodontal disease also demonstrated a significant, but more gradual dose response with an earlier inflection point around 2500 cGy (P = .0395).

Conclusion: We present the first tooth-specific dosimetric correlation between dose and adverse dental events. Attentive RT planning has the potential to reduce dental complications, potentially sparing toxicity and saving cost in the growing population of head and neck cancer survivors.

Prognostic Value of Pretreatment Serum Inflammatory Markers in Patients Receiving Radiation therapy for Oropharyngeal Cancer (OPC)

University of Texas MD Anderson Cancer Center, Houston, TX, University of North Texas Health Science Center, Fort Worth, TX, The University of Texas MD Anderson Cancer Center, Houston, TX, The University of Texas Medical School at Houston, Houston, TX.

Purpose/Objective(s): To assess the prognostic value and utility of pretreatment systemic inflammatory markers, namely neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), in risk stratification of patients receiving definitive radiation therapy (RT) for OPC.

Materials/Methods: We identified patients from an institutional review board–approved institutional database of OPC outcome data who had pretreatment systemic inflammatory markers, namely neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, and platelet counts collected within 6 weeks prior to initiation of RT. NLR and PLR were calculated by dividing absolute neutrophil and platelet counts by absolute lymphocyte counts, respectively. Recursive partitioning analysis (RPA) was performed to find specific cut points associated with mortality in NLR and PLR. Kaplan-Meier and Log-rank tests were used to evaluate overall survival (OS) in identified cohorts. Univariate and multivariate analyses were conducted using the following variables: age, smoking, T and N stage, sex, chemotherapy, and pre-RT NLR and PLR; the Cox proportional hazards model was used to identify a relationship between OS and pre-RT NLR and PLR.

Results: A total of 448 patients were analyzed with a median follow-up of 87 months. Of these patients, 89% were men with a median age of 56 years. The majority had stage IVa disease (64%). Two hundred eighty-two patients (63%) were treated using concurrent chemoradiotherapy, and 166 (37%) received RT alone. RPA yielded PLR cut point of 4.3 and a PLR cut point of 183. Univariate analysis at these thresholds showed a statistically significant association between PLR ≥4.3 and mortality (hazard ratio [HR] 2.215; 95% confidence interval [CI] 1.57-3.13, P < 0.001). A similar association between PLR ≥183 and death was encountered (HR 2.27; 95% CI 1.60-3.26, P < 0.001). The 5-year OS was significantly better for patients with NLR <4.3 (n = 276) compared to those with NLR ≥4.3 (84% vs 66%, P < 0.001). Likewise, patients with PLR <183 (n = 235) had better 5-year OS compared to those with PLR ≥183 (85% vs 69%, P < 0.001). Patients with elevations of both NLR and PLR beyond the identified cut points fared the worst compared to those without either (87% vs 66%, P < 0.001).

In multivariate analysis, both NLR and PLR proved to be independent prognostic factors for OS; NLR ≥4.3 (HR 1.55; 95% CI 1.06-2.27, P = 0.02) and PLR ≥183 (HR 1.89; 95% CI 1.28-2.85, P = 0.0012). The remaining symptoms included in the top 11 symptom cluster were (in descending order) mucus production, pain, disturbed sleep, drowsiness/sleepiness, mouth/throat sores, and distress/worry. Overall scoring, the individual scores of mucus production (mean, 3.77 vs 4.21), lack of appetite (3.43 vs 5.25), nausea (1.40 vs 2.14), vomiting (0.96 vs 1.22), and shortness of breath (0.59 vs 0.99) all favored proton therapy (P < 0.05). The remaining individual symptoms and symptom scores were found to be superior to those without either (87% vs 66%, P < 0.001).

Conclusion: Pretreatment systemic inflammatory markers are independent prognostic factors for survival in OPC patients treated with RT. Future investigations to validate the identified cut points and to develop risk-adaptive treatment strategies are needed.


Intensity Modulated Proton (IMPT) Versus Photon (IMRT) Radiation Therapies: Comparing Patient-Reported Outcomes (PRO) in Patients With Oropharyngeal Cancer Undergoing Chemoradiation

Mayo Clinic, Scottsdale, AZ. Department of Symptom Research; the University of Texas MD Anderson Cancer Center, Houston, TX. The University of Texas MD Anderson Cancer Center, Houston, TX, Gustave Roussy Institute, Villejuif, France, MD Anderson Cancer Center, Houston, TX, Department of Symptom Research, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

Purpose/Objective(s): Treatments with IMPT for oropharyngeal cancer are becoming increasingly common and may translate into producing better patient- (pt)-reported outcome (PRO) due to its superior physical beam properties sparing organ-at-risk structures, as compared with photon-based IMRT. We hypothesized that pts treated with proton radiation therapy (RT) would have less symptom burden assessed by PRO data from 35 and 46 consecutive pts from the proton and photon groups were collected and analyzed, respectively. The overall top 5 symptoms were food taste, shortness of breath, difficulty swallowing, nausea, and fatigue. These top 5 symptoms were found to be significantly different between IMRT and IMPT during the subacute phase, which represents a crucial time interval, including baseline, weekly during treatments (acute phase), 0 to 3 months after RT completion (subacute phase), and at scheduled follow-ups thereafter (chronic phase, up to 24 months). Each individual item in the MDASI-HN symptom module was significantly different favoring IMPT in the subacute phase.

Conclusion: Our PRO results demonstrated less symptom burden in pts treated with IMPT in the top 5 symptoms cumulatively, as well as 5 individual symptom items. The greatest decrease in symptom burden was seen with IMPT during the subacute phase, which represents a crucial time interval, including baseline, weekly during treatments (acute phase), 0 to 3 months after RT completion (subacute phase), and at scheduled follow-ups thereafter (chronic phase, up to 24 months). Each individual item in the MDASI-HN symptom module was significantly different favoring IMPT during the subacute phase.


Abstract 327: Table 1

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Comparison of Head and Neck Cancer Populations by Cause of Death

S. Massa, N. Osazuwa-Peters, K. Christopher, R. Walker, and M. Varvares.
Saint Louis University School of Medicine, Saint Louis, MO.
Saint Louis University School of Medicine, St Louis, MO.
Harvard Medical School, Boston, MA.
Purpose/Objective(s): Patients with head and neck squamous cell carcinoma (HNSCC) are at risk for death from causes related and unrelated to their cancer. The risk of death from noncancer causes is termed competing risk from the perspective of cancer treatment and research. These patients have been found to have elevated competing risks compared to the general population and other cancer populations, likely related to high rates of substance use and comorbidities. We aim to identify the sociodemographic and tumor characteristics that distinguish the group of HNSCC patients who die from their primary cancer to those that die of competing causes.

Materials/Methods: Deceased adult patients with histologically proven, mucosal HNSCC diagnosed between 2004 and 2012 were identified from the Surveillance, Epidemiology and End Result database. Tumor characteristics, demographic variables, survival, and cause of death were collected. Patients with insufficient data, including unknown cause of death, and previous cancers were excluded. The competing causes of death for HNSCC are presented with comparisons to thyroid and salivary gland cancer patients and the general population. Standardized incidence ratios (SIR) are calculated to compare death rates between the HNSCC cohort and the general population. HNSCC patients who died of causes related to their primary tumor are then compared to those deceased from other causes using a chi-squared analysis.

Results: Of 64,598 patients meeting study criteria, 17,460 were deceased, including 29.0% from noncancer causes. The 5 most common causes of death not attributable to the primary tumor were cardiac (26.4%), COPD (8.8%), lung cancer (6.4%), other cancers (5.3%), and stroke (5.3%). These are also the 5 leading causes in a general population cohort matched for age, race, and gender. Excluding cancer-related mortality, the SIR was elevated among HNSCC patients for all causes of death (11.3); most drastically for chronic liver disease (38.4), suicide (36.1), and second HNSCC primaries (24.5). Compared to patients who died of their cancer, patients who died from competing causes are older and more often white with early-stage and laryngeal tumors (P<0.001).

Conclusion: As a group, HNSCC patients are at substantially increased risk of dying from all causes, not only their cancer. Compared to the general population, these patients have greatly elevated risk of dying from all causes, especially some rare causes like suicide. However, the majority of noncancer-related deaths in this group are attributable to causes also common in the general population, like cardiovascular disease and stroke. While treating patients with HNSCC for their cancer, screening and treatment of other risk factors should not be neglected, especially in those with curable cancers at risk for mortality from other causes.

Author Disclosure: S. Massa: None. N. Osazuwa-Peters: None. K. Christopher: None. R. Walker: None. M. Varvares: None.

329

Predictors of Dysgeusia in Patients Treated With Chemoradiation for Head and Neck Cancer

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University of Michigan, Ann Arbor, MI

Purpose/Objective(s): Dysgeusia is a significant morbidity for patients receiving chemoradiation for head and neck cancer. Factors affecting the severity of dysgeusia remain uncertain. In this study we investigated the relationships between patient-reported dysgeusia, doses to the oral cavity, salivary production (required to dissolve food particles), and patient-reported xerostomia.

Materials/Methods: Seventy-nine patients with stage III-IV oropharyngeal cancer (OPC) (n=73) or nasopharyngeal cancer (NPC) (n=6) participated in a prospective, longitudinal study of quality of life (QOL), including assessment of patient-reported gustatory function by taste-related questions from the Head and Neck QOL instrument (HNQOL) and the University of Washington Head and Neck-Related QOL instrument (UWQOL) prior to therapy and periodically posttreatment. At the same time intervals, patients also completed a validated 8-item self-reported xerostomia-specific questionnaire (XQ) and had unstimulated and stimulated major salivary glands flow rate measurements. Treatment consisted of definitive intensity modulated radiation therapy (IMRT) aimed at sparing the salivary glands, oral cavity, and swallowing structures and was delivered concurrent with chemotherapy in all patients. Regression models were used to evaluate the effect of covariates (radiation dose, salivary output, and XQ scores) on QOL scores.

Results: At 1, 3, and 12 months after treatment, severe taste dysfunction was reported by 49%, 37%, and 21% of evaluable patients, and mean stimulated salivary flow was 17%, 18%, and 30% of pretreatment levels, respectively. Significant associations were found between patient-reported taste dysfunction and radiation dose to the anterior tongue and oral cavity (both P<0.05), but not the posterior tongue, when pooled across all timepoints. A 10-Gy increase in oral cavity dose was associated with a 2.8-fold increase in the odds of severe taste impairment (P<0.05). While measured salivary output was not significantly associated with postradiation taste dysfunction, patient-reported XQ summary scores and xerostomia while eating scores were significantly correlated with changes in taste at each time point (P<0.001).

Conclusion: Postradiation therapy taste impairment is significantly correlated with mean radiation dose to both the anterior tongue and oral cavity. Although decreased salivary gland output had no significant correlation with changes in taste function, patient-reported xerostomia was significantly correlated with dysgeusia. This discrepancy may be explained by reduced oral cavity minor salivary glands mucins after RT, not accounted for by major salivary glands output. Reducing dose to the oral cavity with IMRT, if possible, may significantly contribute to improving QOL by decreasing long-term patient-reported xerostomia, which may translate into better and faster rehabilitation of taste function.


330

From Patient-Reported Outcomes to Quantitative Health States: Characterization of Head and Neck Cancer Patient Survivorship Utilities Using Prospective Longitudinal Assessment With the MDASI-HN

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Purpose/Objective(s): For patients receiving treatment for head and neck cancers (HNC), patient-reported outcomes (PROs) are routinely acquired, but rarely is an equivalent conversion capable of translating these patient experiences (as quantified by quality of life [QOL] measures) into a defined utility. The aims of this study are to (1) explore the relationship between various symptom scales and subsequent alteration in patient-derived utilities, as assessed by EQ-5D, (2) measure an assessment of the natural history and kinetics of PRO-derived utilities over the course of the survivorship period, and (3) generate testable hypotheses and/or specific interventional studies designed to maximize symptom-derived utilities for future head and neck studies.

Materials/Methods: Two hundred and sixty-five HNC patients completed both the MD Anderson Symptom Inventory-Head and Neck Cancer (MDASI-HN) and EQ-5D during the survivorship period after we obtained both institutional review board approval and informed consent from all participants. Patients were contacted and undertook a phone interview with administration of the MDASI-HN and EQ-5D. The MDASI-HN has been validated across multiple languages and shown high interpatient validity and repeatability across patients receiving solely radiation or chemoradiation. Simultaneously, patients were queried with the EQ-5D, which is recognized as the standard instrument for conversion of nationally specific, age-adjusted utility states. These can then be used as utilities for QOL.
Results: The EQ-5D mean utility index was higher than anticipated at 0.84±0.2, given a mean VAS of 74±21. The mean of the MDASI-HNComposite sum was 41±32, indicating a breadth of patient-reported symptom burden in this study population. Dry mouth and oral/throat mucous problems were the only mean MDASI-HN symptom item scores greater than 3 out of 10, with scores of 3.86±3.53 and 3.10±3.27, respectively. Utility scores placed in bins according to length of follow-up were not collectively different from each other (P=0.165); however, the “12 months and less” was significantly different from “12 to 24 months” (P=0.043) and “24 to 36 months” (P=0.007). The major symptom drivers impacting QOL, according to the BICminimum model, were pain (P<0.0001), sadness (P=0.0003), shortness of breath (P=0.0001), and upset (P=0.005). Interestingly, none of the head and neck symptom items significantly contributed to QOL measures.

Conclusion: Our data demonstrate a very strong relationship between PROs, assessed by MDASI-HN, and patient-reported QOL, as determined by EQ-5D. In fact, the summation of all MDASI-HN symptom items strongly correlates with the EQ-5D utility scores and can be used to accurately predict a patient’s QOL.

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331 Financial Toxicity in Thyroid Cancer—An Analysis From the North American Thyroid Cancer Survivorship Study
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Purpose/Objective(s): Financial toxicity has been associated with worse health-related quality-of-life (HRQOL), compliance to treatment, and even survival in cancer patients (pts). Measuring financial toxicity and understanding its predictors are of paramount importance when planning intervention strategies, the value of care, and health care policies. We report financial toxicity and its predictors in a large cohort of thyroid cancer pts and survivors.

Materials/Methods: Pts with thyroid cancer were surveyed in the North American Thyroid Cancer Survivorship Study. Financial toxicity was assessed by the previously validated COMprehensive Score for financial Toxicity (COST) patient-reported outcome (PRO), as well as by questions related to financial distress (out-of-pocket costs, loss of income, and bankruptcy). Data on sociodemographics, income, type of disease, time since diagnosis, and prior therapies were collected. Predictors of financial toxicity were assessed in multivariate analyses, controlling for potential confounders, such as HRQOL (as measured by the thyroid cancer-specific City of Hope instrument), type of treatment received, and time since diagnosis.

Results: A total of 591 pts with thyroid cancer within the past 6 years were surveyed in 2 countries: 553 (93.5%) in the US and 38 (6.5%) in Canada. Most pts were women (n=518 pts, 88%), Caucasian (n=531, 89.9%), and had at least a graduate or professional degree (n=206, 35.5%). The median time since diagnosis was 857 days (range 105-2761). 430 pts (72.8%) had papillary thyroid cancer. There were 210 pts with stage I (35.7%), and 61 (10.3%) with stage IV disease. In total, 568 pts (96.1%) had a thyroidectomy. 447 pts (75.6%) received radioactive iodine, and 11 pts (1.9%) were on tyrosine kinase inhibitors. In total, 234 pts (39.5%) stated that their out-of-pocket costs were higher than previously thought; 207 pts (35%) felt their disease resulted in loss of income; 44 pts (7.4%) were unable to meet their monthly expenses; and 7 pts (1.2%) declared bankruptcy after diagnosis. The median COST value was 24 (range 0-44). In multivariate analyses, the independent predictors of worse financial toxicity, as measured by COST-PRO values, were lower income (P<0.001), female gender (P=0.01), lower educational level (P=0.002), health care delivery in the US (P=0.002), and worse HRQOL (P<0.001).

Conclusion: A significant proportion of thyroid cancer pts experience financial toxicity. We identified pt characteristics (gender, education, income), as well as geographical differences (health care delivery in the US) as predictors of financial toxicity in thyroid cancer pts and survivors, independent of their HRQOL.

Author Disclosure: J.A. de Souza: Speaker’s Bureau; AstraZeneca. R. Grogan: None. B. Aschebrook-Kilfoy: None.

332 A Prognostic Model for Time-to-Failure in p16-Negative Patients Provides Useful Risk Stratification in p16-Positive Patients
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Purpose/Objective(s): Low event rates in p16-positive (p16+) patients reduces the statistical power of multivariable statistical modeling. Here, we test whether a prognostic model developed in p16-negative (p16-)/unknown patients provides useful risk stratification of patients with p16+ oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: An institutional cohort of 600 consecutive head and neck squamous cell carcinoma (HNSCC; all subsites) treated with intensity-modulated radiation therapy between 2005 and 2012 was analyzed. p16 status was considered a surrogate marker of human papillomavirus (HPV)-related OPSCC. A Cox proportional hazards model stratified for subtype within the head and neck was fitted to the p16-unknown patients. Any treatment failure was considered as an event; patients alive with no evidence of disease were censored at last follow-up. A previous model included more variables (eg, TNM), but the following factors captured the variation and were prognostic: prescription of cisplatin, smoking status (never, former, current), gross tumor volume (GTV), and maximal standardized uptake value (SUVmax). Variables were selected using backward elimination. The final model was applied to assign each p16+ OPSCC patient a prognostic index, calculated as their individual hazard ratio (HR) for failure from the p16- model.

Results: The p16+ OPSCC group (n=138) had 28 events, and the p16- unknown group (n=435) had 187 events. Concomitant cisplatin (HR=0.51 [0.37-0.69]), GTV (HR=1.01 [pr cm3] [1.00-1.01]), and smoking status (HR=1.61 [1.22-2.12]) were significant in the p16- model.

Author Disclosure: None.

Abstract 332: Table 1 Kaplan-Meier estimates of freedom from failure (FFF) of the p16+ OPSCC patients subdivided by the median of their prognostic index.

<table>
<thead>
<tr>
<th>Group</th>
<th>FFF (%)</th>
<th>CI (%)</th>
<th>Favorable group (%)</th>
<th>CI (%)</th>
<th>Unfavorable group (%)</th>
<th>CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89.1</td>
<td>(83.8-94.4)</td>
<td>95.9</td>
<td>(91.3-100)</td>
<td>81.2</td>
<td>(71.6-90.8)</td>
</tr>
<tr>
<td>2</td>
<td>82.4</td>
<td>(75.9-88.9)</td>
<td>93.2</td>
<td>(87.5-98.9)</td>
<td>69.6</td>
<td>(58.2-81.0)</td>
</tr>
<tr>
<td>3</td>
<td>79.1</td>
<td>(72.2-86.0)</td>
<td>89.8</td>
<td>(82.5-97.1)</td>
<td>66.3</td>
<td>(54.5-78.1)</td>
</tr>
</tbody>
</table>
unknown patients (all P<.001). According to the p16+ model, HR was a highly significant prognostic in p16+ patients (log-rank P = 0.0005). Kaplan-Meier estimates of freedom from failure (FFF) according to HR above versus below median are given in Table 1.

**Conclusion:** HPV+ OPSCC patients could be risk stratified using a prognostic model developed in patients with p16- disease. This stratification may be useful for clinical management as well as selecting patients for clinical trials of novel/modified therapy.

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**Does Being Married Independently Predict Survival in Patients With Head and Neck Cancer? Results From a Single Institution**

N. Osazuwa-Peters, K. Christopher, S. Massa, L. Cass, A. Hussaini, A. Behera, R. Walker, and M. Varvares

**Purpose/Objective(s):** An important factor in cancer survivorship is social support, often coming from a spouse. There is emerging literature on the role of spousal support in head and neck cancer (HNC) outcomes; however, most are based on results from national databases. While more generalizable, these studies may not always capture the unique variation in different patient populations. This single-institution study aimed to describe the association between marital status and outcomes of HNC and to determine if marital status independently predicts survival in a local patient population.

**Materials/Methods:** We identified 460 patients aged 20 to 91 years (59.31 ± 11.42) diagnosed with squamous cell carcinoma of the head and neck at an academic tertiary referral center between 1997 and 2012 in this retrospective cohort study. Cox proportional hazards model assessed the effect of marital status on survival. Results are based on the final model constructed after accounting for covariates in the data.

**Results:** Our study population was made up of 73% males and 28% whites. We found an association between marital status and HNC survival. Unmarried HNC patients had a 66% increase in the hazard of death compared to married HNC patients (hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.23-2.23). This was after controlling for covariates, which included sociodemographic variables (age, race, sex, and health insurance status), social habits (tobacco and alcohol), primary anatomical subsite (oral cavity, oropharyngeal, laryngeal, and others), stage at presentation (early vs late stage), and treatment modality (surgery, surgery with adjuvant therapies, other single modality therapy, and palliative care).

Other factors found to be associated with an increased hazard of death were age (≥50 years), current tobacco use, late stage of presentation, palliative care, and laryngeal subsite.

**Conclusion:** Marital status is associated with head and neck cancer outcomes, and being married is an independent predictor of survival among patients. This result, found in previous national studies, held true in our local patient population. This underscores the need for the multidisciplinary HNC team to recognize this aspect of survivorship and to emphasize the need for social support among unmarried HNC patients. It could be that it is necessary to add social support to the clinical practical guidelines for managing head and neck cancer beyond palliative care.

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of county below a 150% federal poverty level, TNM stage, and receipt of cancer-directed surgery and/or RT. A Cox proportional hazards regression was used to estimate the effect of insurance status on cancer stage, RT received, and cause-specific survival.

Results: The proportion of Medicaid or uninsured patients was approximately 25% in oral cavity, oropharynx, and nasopharynx, 33% in larynx, and 36% in hypopharynx. Overall, patients were more likely to have localized disease (T1-2N0) if they had non-Medicaid insurance, rather than if they had Medicaid or were uninsured. The odds ratio (OR) for localized disease was 2.7 in larynx, 2.0 in nasopharynx, and approximately 1.6 in the other sites (P < .001 for all sites). Similarly, patients were more likely to receive RT with non-Medicaid insurance, with OR ranging from 2.9 in oral cavity to 1.7 in larynx (P < .001 for all sites). After adjustment for all factors, patients were more likely to die of their cancer if they had Medicaid or were uninsured. The hazard ratio ranged from approximately 2.0 in oral cavity, oropharynx, and nasopharynx to 1.4 in larynx (P < .001 for all sites).

Conclusion: Among patients with HN cancers from different primary sites, there is difference in the association between uninsured/underinsured status and more advanced disease stage, more suboptimal cancer treatment, and worse survival. However, the level of the differential impact is intermediate and the general trend is similar across all HN sites.

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336
Cancer-Independent Loss of Life Expectancy in the Head and Neck Cancer Population
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Purpose/Objective(s): Patients diagnosed with head and neck cancer (HNC) lose life expectancy due to cancer-related mortality, but further longevity is lost to increased prevalence of comorbidities, substance use, and other factors inherent to this group. The life expectancy and modifying factors for this group have not been quantified. This study aims to assess the life expectancy of HNC patients not attributable to their primary cancer. We hypothesize that HNC patients will have shorter life expectancies than the general population, independent from mortality related to their primary cancer and after controlling for age, sex, and race.

Materials/Methods: Patients aged 35 to 100 years were selected from the Surveillance, Epidemiology, and End Results database with a first cancer diagnosis from 2004 to 2012 of head and neck mucosal sites, thyroid gland, or salivary glands. Patients were excluded due to insufficient data or death within 3 months of initial diagnosis to limit the effect of treatment-related mortality. Life tables of survival versus age were created which are left-truncated prior to enrollment in the database and right-censored for cancer-related deaths. These life tables approximate a similar group of patients who either did not develop cancer or whose cancers were cured. Data were stratified by stage, site, histology, race, sex, insurance type, and income quintile and compared to the United States population, matched for gender and race distributions. The covariates were also analyzed within the HNC cohort using univariate and multivariate logistic regression to assess the hazard ratio of death from noncancer causes.

Results: A total of 15,703 patients were identified with an overall 5-year reduction in median life expectancy compared to the general population, independent from mortality related to their primary cancer. Larger losses in cancer-independent life expectancy were associated with advanced stage disease (-12 years for stage IV), hypopharyngeal (-18 years), and laryngeal (-14 years) tumors, black race (-9 years), male sex (-7 years), squamous histology (-11 years), Medicaid insurance (-19 years), and lower income quintile (-19 years for 1st quintile). Conversely, patients with stage I disease and thyroid cancer had increased longevity compared to the general population (+1 and +4 years, respectively). Multivariate logistic regression found analogue trends among these variables regarding changes in the mortality risk from noncancer causes. All reported results are statistically significant (P < .05).

Conclusion: Patients with HNC, particularly poor, black, males with mucosal squamous cell carcinoma, have a decreased life expectancy in comparison with the general population despite excluding cancer-related mortality. In addition to cancer treatments, this population may benefit from improved prevention and management of other comorbidities and risk factors.

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337
Patient-Reported Distress in Head and Neck Cancer Patients Receiving Radiation Therapy

Purpose/Objective(s): Patients undergoing head and neck (H&N) radiation therapy (RT) experience distress due to the nature of their underlying malignancies and the serious side effects associated with treatment. In our clinic, patients receiving RT are prospectively screened for distress. Retrospective review of this assessment was performed to identify patterns in patient-reported distress (PRD).

Materials/Methods: H&N cancer patients treated at our institution were eligible for inclusion in this study if they had completed a 30-question PRD survey at the beginning of and/or during RT. Each question was rated on a particular possible cause of distress. Patients could rate each on a scale of 1 to 5, corresponding to a low and high distress level, respectively. The assessment also included the National Comprehensive Cancer Network (NCCN) Distress Thermometer scale that ranges from 1 (low overall distress) to 10 (high overall stress). We retrospectively reviewed H&N PRD data from patients undergoing RT from April 9, 2012 to August 5, 2015.

Results: A total of 185 patients completed PRD screening forms. Ages ranged from 23 to 93 years old with a median of 67 years. There were 152 (82.2%) male and 33 (17.8%) female patients. Definitive external beam RT was used to treat all patients. The primary tumor histology was squamous cell carcinoma in 131 patients (70.8%). Chemotherapy was given to 132 patients (71.4%), and 144 (77.8%) underwent a surgical intervention. NCCN distress thermometer results ranged from 0 to 10, with a median of 4.6. Mean distress scores ranged from 1.44 to 2.83. The top 5 concerns were “How will I feel during treatment” (2.83), “Pain that affects daily functioning” (2.69), “Out of pocket medical costs” (2.63), “Fatigue” (2.48), and “Sleep difficulties” (2.50). The least concerning complaints were “A loved one relying on me for their physical care” (1.44), “Transportation” (1.49), “Spirituality” (1.50), “Family communication about my illness” (1.54), “My job” (1.55), and “Controlling my anger” (1.55).

Conclusion: Patients receiving definitive H&N RT in this population were most worried about symptomatic changes due to treatment side effects, as well as tumor and treatment-related pain. Notably, financial burdens of treatment ranked in the top 5 concerns. These distresses should be assessed in patients who receive H&N RT.


338
Prospective MD Anderson Dysphagia Inventory Outcomes After Nonsurgical Treatment of Locoregionally Advanced Oropharyngeal Carcinoma
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Purpose/Objective(s): The Dysphagia Inventory (DI) is a patient-reported outcome measure that assesses swallowing function and quality of life in patients with oropharyngeal cancer (OPC). We investigated DI scores in patients undergoing nonsurgical therapy for OPC.

Materials/Methods: This prospective study included patients with stage III-IV OPC who were treated with chemoradiation at the MD Anderson Cancer Center from 2004 to 2011. The average age was 61 years, and 45% were female. The primary tumor site was the tonsil in 54% of patients. A total of 110 patients were included, with a median follow-up of 2.9 years. DI scores were collected at baseline, 1 week, and 1 month after RT. The primary outcomes were DI scores at each time point and changes in DI outcomes from baseline.

Results: The most common treatments were concurrent chemoradiation (72%) and CRT alone (28%). The median RT dose was 66 Gy. At baseline, scores were 4.0 (1-10) for swallowing function and 7.0 (1-10) for quality of life. The median change in baseline scores was 3.6 (range -10 to 10) for swallowing function and -1.0 for quality of life. The median improvement in swallowing function was 1.0 (range -6 to 6). The median change in swallowing function at 1 week and 1 month was 1.0 and 0.5, respectively. The median improvement in swallowing function at 1 week and 1 month was 1.0 and 0.5, respectively. There was no significant change in swallowing function or quality of life from baseline.

Conclusion: DI scores were stable after nonsurgical therapy for OPC. These results suggest that nonsurgical therapy may preserve swallowing function and quality of life.

Purpose/Objective(s): Long-term swallowing outcomes including gastrotracheal tube and aspiration rates are well described among oropharyngeal cancer (OPC) survivors but long-term, prospective data on patient-reported swallowing function have not been reported for patients treated with split-field intensity modulated radiation therapy (IMRT) and laryngeal shielding.

Materials/Methods: A pooled analysis was conducted from 3 single-institution clinical trials for advanced stage (III/IV) head and neck carcinoma. Patients treated with definitive, split-field IMRT and chemotherapy for OPC were included. Inclusion criteria for analysis included baseline and at least 1 posttreatment MD Anderson Dysphagia Inventory (MDADI). Patients with definitive surgical management of their primary tumor were excluded. Prospectively collected MDADI composite and subgroup scores were analyzed at baseline, 6, 12, and 24 months after treatment. Pairwise comparisons were analyzed with Bonferroni correction for multiple comparisons, and multilevel mixed effects linear regression models were fit to evaluate predictors of MDADI scores.

Results: A total of 116 patients were included. Thirty-nine percent of patients had tonsil and 61% had base of tongue primary tumors. Thirty-five percent had T3/T4 tumors, and 90% were N2b or greater. Human papillomavirus and/or p16 status was unknown in 75% of patients; one or both were positive in 89%. Eighty-four percent of patients underwent induction and 56% received concurrent chemotherapy. Nineteen percent had post-IMRT neck dissection. Mean baseline MDADI composite score was 88.3, dropping to 73.8 at 6 months (P<0.001) and rising to 78.6 and 83.3 by 12 (P<0.001) and 24 months (P<0.001), respectively. This trend was mirrored in subgroup scores. Mean baseline composite was higher in patients with T1/2 tumors than T3/4 tumors (P<0.001, 95% confidence interval -13.8 to -2.9), but this difference was not found at any posttreatment interval. No significant differences in composite MDADI were noted by age, primary site, use of concurrent and induction chemotherapy, neck dissection, or pack-years of smoking at baseline or posttreatment intervals (P>0.05).

Conclusion: Overall, patients report clinically meaningful dysphagia early after modern split-field IMRT for locoregionally advanced OPC that remains apparent 6 months after treatment. While MDADI scores recover slightly thereafter, they remain depressed at 24 months compared to baseline suggesting only partial recovery of perceived swallowing function. Despite better baseline function, patients with smaller primary tumors have a greater relative decrement in composites during treatment that does not recover in the long-term compared to patients with larger primary tumors. These data inform treatment counseling, clinical trial design, and interpretation of long-term patient-reported outcomes.


339

Predictors of Survival in Parotid Adenocarcinoma (Not Otherwise Specified): A National Cancer Data Base Study of 3155 Patients.

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Purpose/Objective(s): Using the world’s largest cancer database, we sought to better characterize and identify prognosticators for parotid adenocarcinoma, not otherwise specified (PANS), a rare salivary histopathology with a poor prognosis.

Materials/Methods: A retrospective review of all cases of PANS in the National Cancer Data Base (NCDB) from 1998 to 2012 was performed. Relevant demographic and disease characteristics were extracted and analyzed. COX regression analysis was used for identifying predictors of survival.

Results: A total of 30,728 parotid cancers were identified, and 10% were PANS. Median age was 67 years, and 62.8% of cases were in males. The majority of patients had high-grade (67.2%) or clinically advanced disease (56.4% stages III-IV). Regional metastasis was common (35.9%), while occult nodal metastasis (20.2% overall) was less frequent in non-high-grade lesions (8.5% vs 31.6%, P<0.001). Distant metastasis was rare (7.9%). Increasing age was significantly correlated with increasing grade (P<0.001). Extraglandular spread (EGS) was found in half of patients and was significantly more frequent for high-grade than for low-grade disease. Most patients were treated with surgery and radiation therapy (43.0%), followed by surgery alone (26.0%), then triple-modality surgery with chemotherapy (9.6%). Overall 5-year survival (OS) was 47%. Presence of regional metastasis conferred a significant drop in survival. In multivariate analysis, age, regional metastasis, distant metastasis, high grade, and high T stage were significant, independent predictors of worse survival. Patients with stage III-IV disease who received both surgery and radiation therapy had a significantly better OS than those receiving surgery alone.

Conclusion: PANOS is an aggressive disease with frequent regional metastasis and poor overall survival. Patients typically present with high-grade and advanced-stage disease. Numerous clinical and pathologic variables are associated with poorer survival outcomes.


340

Long-Term Patient-Reported Dysphagia in Low-Risk Oropharyngeal Carcinoma After Intensity Modulated Radiation Therapy

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Purpose/Objective(s): Clinical trials involving treatment of oropharyngeal carcinoma (OPC) increasingly incorporate patient-reported swallowing outcomes as endpoints. The MD Anderson Dysphagia Inventory (MDADI) represents the most widely used metric for patient-reported dysphagia. Prospectively collected long-term MDADI results after standard intensity modulated radiation therapy (IMRT) at prescribed doses around 70 Gy are lacking for patients with low-risk (human papillomavirus [HPV]-associated, non-T4N3) OPC who would be eligible for enrollment in current national trials (eg, E3311, HN002).

Materials/Methods: A pooled analysis was conducted from 3 single-institution clinical trials for advanced-stage (III/IV) head and neck carcinoma. Patients treated with definitive, split-field IMRT and chemotherapy for OPC were sampled from trial databases. Inclusion criteria were clinical stage III/IV (T1-2N1-2b, T3N0-2b), and MDADI results at baseline and at least 1 posttreatment timepoint. Patients were excluded if they were HPV or p16 negative or HPV and p16 unknown with a smoking history of >10 pack-years such that all included patients were sampled to represent likely HPV-associated disease. Prospective MDADI composite scores were analyzed at baseline, 6, 12, and 24 months after treatment. Composite scores were interpreted as follows: “optimal” >80, “adequate” >60, and “inadequate” <60. Pairwise comparisons were analyzed with Bonferroni correction for multiple comparisons.

Results: Forty-six patients were included: 41% had tonsil and 59% had base of tongue primary tumors. Seventy-two percent were HPV and/or p16 positive, and 70% of those were positive for both. All received bilateral neck irradiation with a mean therapeutic dose of 68.8 Gy (range: 66 to 72 Gy). Seventy-two percent received induction chemotherapy, 57% received concurrent chemotherapy, and 28% received both. Overall, the mean baseline MDADI composite score was 90.1, dropping to 74.6 at 6 months (P<0.001) and rising to 78.5 (P<0.001) and 83.1 (P=0.002) by 12 and 24 months, respectively, representing a clinically meaningful drop in MDADI scores at 6 months that partially recover by 24 months. MDADI scores did not significantly differ at baseline or posttreatment intervals between patients with T1-2N1-2b and T3/N0-2b disease (P>0.05). Overall, composites at baseline, 6, 12, and 24 months were optimal for 87%, 40%, 44%, 87%.
Incidence of Long-Term Gastrostomy Feeding Tube Dependence by Primary Treatment Modality Among Patients With Squamous Cell Carcinoma of the Head and Neck

Purpose/Objective(s): To evaluate the incidence of long-term gastrostomy feeding tube dependence according to primary treatment modality among patients with squamous cell carcinoma of the head and neck treated at a single institution.

Materials/Methods: The medical records of 136 consecutive patients treated with definitive intent for locally advanced, nonmetastatic squamous cell carcinoma of the oropharynx (80%), larynx (14%), and hypopharynx (6%) were reviewed. The median age was 62 years (range, 22-91). Seventy-eight patients (57%) were human papillomavirus (HPV) positive, and 58 patients (43%) were HPV negative. Patients with gastrostomy feeding tubes placed prior to treatment were excluded. Gastrostomy feeding tube dependence rates were calculated at 6 months and 1 year after treatment. The primary treatment modality was radiation therapy for 104 (76%) patients to a median dose of 70 Gy (range, 41-70 Gy), of whom 86 (83%) received concurrent chemotherapy, typically with a cisplatin-based regimen. The primary treatment modality was surgery for 32 patients (24%), of whom 20 (63%) were treated with transoral laser microsurgery (TLM) or transoral robotic surgery (TORS). All surgery patients received adjuvant radiation therapy to a median dose of 60 Gy (range, 60-69 Gy), 14 (64%) of whom received concurrent chemotherapy. The proportion of patients who were gastrostomy feeding tube dependent were compared using the t test, with statistical significance set with a P value of .05.

Results: Overall gastrostomy feeding tube dependence rates at 6 months and 1 year, respectively, were 15% and 10% after primary chemoradiation, 0% and 8% after primary radiation therapy alone, 0% and 0% after TORS/TLM, and 42% and 50% after all other surgery. When the analysis was limited to the subset of patients with HPV-positive tumors, the respective rates at 6 months and 1 year were 15% and 8% after primary chemoradiation, 0% and 0% after primary radiation therapy alone, 0% and 0% after TORS/TLM, and 60% and 40% after all other surgery (P < .05).

Similarly, for HPV-negative tumors, the respective rates at 6 months and 1 year were 14% and 14% after primary chemoradiation, 0% and 11% after primary radiation therapy alone, 0% and 0% after TORS/TLM, and 29% and 67% after all other surgery (P < .05).

Conclusion: Gastrostomy feeding tube dependence rates after definitive treatment for squamous cell carcinoma of the head and neck appeared to be lowest for patients treated by primary TLM/TORS and primary radiation therapy alone. The use of open surgical techniques and chemoradiation was associated with significantly higher rates of swallowing dysfunction. While these findings may be limited by selection bias, they may be useful in patient counseling. Ongoing efforts to deintensify therapy for patients with HPV-positive tumors appear particularly salient.


Survival Benefit of Chemotherapy in Oropharyngeal Cancer Patients Treated With Radiation Therapy

Purpose/Objective(s): To evaluate the potential prognostic value of pretreatment complete blood count (CBC) in oropharyngeal cancer patients receiving concurrent chemoradiation and to determine the potential added value of laboratory assessment as a potential covariate of univariate and multivariate overall survival (OS) for pretherapeutic risk stratification.

Materials/Methods: Oropharyngeal cancer patients (OPC) treated with intensity modulated radiation therapy (IMRT) with concurrent chemotheraphy between 2002 and 2012 were included under an approved institutional review board protocol. CBC data were extracted. Platelet and hemoglobin from the last phlebotomy (PLTpre, hemoglobinpre) before start of treatment were identified. Univariate and multivariate Cox proportional hazards assessments were performed to determine whether the following variables were correlated with OS: age, sex, Dahlstrom-Sturgis category, smoking status, human papillomavirus (HPV) status, subside (tonsil vs nontonsil), platelet elevation, and anemia. After multivariate analysis, best categorical model selected based on experimental Bayesian information criteria (BIC) were converted into visual nomograms of 3-, 5-, and 10-year OS prediction.

Results: Four hundred thirty-three OPC patients were identified. The median follow-up was 69 months. OS was decreased for patients with a PLTpre value of ≥350 × 10^9/L. Actuarial 5-year OS was better for patients with normal platelet counts by comparison (76% vs 57%; P < .0001). Non-anemic patients (hemoglobin ≥13.5 for males and ≥12.3 for females) likewise exhibited comparatively better OS at 5 years (84% vs 56%, P < .0001).

Multivariate analysis showed that patients with PLTpre ≥350 × 10^9/L was an independent predictor of dismal survival (hazard ratio 1.9, 95% confidence interval 1.2-2.9; P < .006), in addition to anemia, Dahlstrom-Sturgis category, and HPV status. On BIC analysis, those 4 variables achieved best performance and were used to develop nomograms predicting 3-, 5-, and 10-year OS.

Conclusion: Pretreatment CBC data is a promising predictor of survival in OPC patients treated with radiation therapy. We recommend continued routine evaluation by care providers of pretreatment platelets and hemoglobin levels and increased surveillance as appropriate for these patients who may be at substantively increased risk of mortality and judicious risk assessment using provided nomograms as an exploratory tool for validation in other datasets.

with primary surgery (PS) followed by radiation (RT) or chemoradiation (CRT) to determine whether the addition of chemotherapy has a significant survival advantage. We hypothesized that chemotherapy could have a survival advantage dependent on p16 status and tobacco smoking history.

Materials/Methods: Advanced-stage OPSCC patients diagnosed and treated at a single tertiary cancer care center between 1998 and 2009 were reviewed from a prospectively collected database. Patients who received PS followed by either RT (PS+RT) or CRT (PS+CRT) were included in the study. A review of patient records was performed to obtain patient clinical characteristics as well as detailed pathologic, treatment, and survival data.

P16 status was obtained by immunohistochemistry of a tissue microarray of surgical tumor specimen. Comparative analyses of survival were performed between patients who received PS+RT and PS+CRT, stratified according to human papillomavirus (HPV) status and tobacco smoking history.

Results: One hundred seventy-one patients were treated with PS+RT or PS+CRT, of which 138 had p16 typing and smoking status for inclusion in our analyses (PS+CRT = 67, PS+RT = 71). In patients treated with PS+RT, 73.5% received cisplatin and 26.5% received carboplatin. In p16-negative and p16-positive nonsmoking patients, no significant differences in survival were seen between patients treated by PS+RT versus PS+CRT. In p16-positive smokers, patients treated with PS+CRT had significantly higher 5-year disease-specific survival (88.2%) compared to PS+RT (59.7%). Multivariate analysis showed these survival differences regardless of patient covariates and factors.

Conclusion: In advanced-stage OPSCC patients treated with PS and RT, the addition of platinum-based chemotherapy may have improved disease-specific survival in select patients. Further prospective trials that include p16 status would be recommended verify this hypothesis.


345
Trismus Dose-Response Assessment Using Quantitative Volumetric Measurements in Head and Neck Radiation Therapy
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Purpose/Objective(s): The objective of this study was to investigate a potential dose-toxicity relationship between radiation delivered to muscles of mastication and subsequent development of trismus in patients receiving intensity modulated radiation therapy (IMRT) for oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: Retrospective data from 324 patients treated with IMRT for OPSCC at 1 institution between 2004 and 2011 were analyzed via an institutional review board–approved protocol. For each patient, clinical data were extracted from electronic medical records, and incidence of trismus was recorded as a binary variable. Regions of interest (ROIs), namely masseter (M), medial pterygoid (MP), and lateral pterygoid (LP) muscles, were segmented on planning computed tomographic images using an automatic segmentation algorithm and defined as isosurface (I) or contralateral (C) to the primary tumor. Radiation dose plans were then reviewed and dose-volume histograms (DVHs) generated for ROIs. Dose-response assessment was performed using logistic regression and Wilcoxon rank sum test with Bonferroni correction for multiple comparisons. Cumulative group DVHs were generated to visualize differences in continuous dose distributions between trismus and asymptomatic patient groups. Dose-threshold candidates were selected via a bootstrap forest technique.

Results: Twenty-five of 324 patients (7.7%) treated with IMRT developed trismus. Patient characteristics are as follows: median age, 56 years; subsites, base of tongue (n = 179; 55.2%) and tonsillar complex (n = 139; 42.9%); chemotherapy agent, cisplatin (n = 282; 87.0%). Cumulative group DVHs dichotomized by the trismus variable allowed for visualization of differences between groups for each ROI across all doses. The top dose-threshold candidate determined by bootstrap forest was IM V59 (volume of the ipsilateral masseter receiving 59 Gy).

Conclusion: Trismus is a well-known sequela of radiation therapy treatment for head and neck cancers that negatively impacts quality of life and presents a problem to both patients and health care providers. Dosimetric parameters associated with increased probability of trismus present potential opportunities, through further investigation, for risk stratification and dose modification to specific structures when possible.


344
Analysis of Prognostic Factors and Outcomes Following Parotidectomy for Cutaneous Squamous Cell Carcinoma Metastatic to the Parotid Gland
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Purpose/Objective(s): To determine survival outcomes and prognostic factors for recurrence of cutaneous squamous cell cancer (cSCC) metastatic to the parotid gland following parotidectomy at a tertiary care center.

Materials/Methods: A retrospective chart review of patients diagnosed with cSCC metastatic to the parotid gland who subsequently underwent parotidectomy between 1992 and 2014 was performed. Demographic information, treatment information, and tumor characteristics were reviewed.

Risk of disease recurrence was analyzed using a competing risks regression model. Overall survival was analyzed using Cox proportional hazards regression. Rates of disease recurrence were calculated using cumulative incidence, and the Kaplan-Meier method was used to calculate rates of overall survival.

Results: One hundred and six patients were included in this institutional review board–approved analysis. Median follow-up after surgery was 37.0 months (range 0.3-233.8). Ninety-three patients (87.7%) were enrolled in follow-up. Treatment variables included radical or partial parotidectomy, neck dissection, and tumor characteristics. The variables identified as factors for recurrence of cutaneous squamous cell cancer (cSCC) metastatic to the parotid gland following parotidectomy at a tertiary care center.

Conclusion: This study demonstrates the negative prognostic associations of FN sacrifice and extracapsular extension with disease recurrence following parotidectomy for metastatic cSCC. These 2 variables may serve as proxies for aggressiveness of the parotid tumor.

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**346**

Comparison of Symptom Interference of Quality of Life in Postradiation Treatment in Early-Stage Versus Late-Stage Laryngeal Cancer Patients

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**Purpose/Objective(s):** Quality of life studies are the benchmark for how we expect patients to live after they receive treatment. Analyzing trends in symptoms, particularly after radiation treatment, helps to determine how treatment implementation should be improved and altered to limit any long-term symptoms or discomforts. Our lab is attempting to analyze the quality of life after receiving radiation treatment at 1 institution for laryngeal cancer by going through a series of questionnaires with laryngeal cancer patients that will improve treatment delivery and decrease the likelihood of the treatment causing severe long-term symptoms. Our hypothesis is as follows: The symptoms interfering with quality of life for postradiation treatment late-stage laryngeal cancer patients are significantly higher than those for postradiation treatment early-stage laryngeal cancer patients.

**Materials/Methods:** A symptom inventory questionnaire was collected from 230 head and neck cancer patients 22 to 24 months following treatment. Each patient was asked to rate the severity of their symptoms on a scale from 0 ("not present") to 10 ("worst possible"). The questionnaire was administered over the phone and took 10 to 15 minutes to complete with each patient. Upon completion, the responses were compiled and analyzed using Microsoft Excel.

**Results:** Based on the data, there is a slight difference in symptoms interfering with quality of life among early-stage versus late-stage post-treatment cancer patients 22 to 24 months after treatment. Late-stage patients did show an increase in symptom interference with quality of life. However, the increase was not as significant as hypothesized. Based on the symptom inventories conducted, analysis showed dry mouth to be the most common symptom that interfered in both early-stage and late-stage patients, while vomiting was the least common.

**Conclusion:** The overall quality of life for early-stage and late-stage laryngeal cancer patients was significantly high with a relatively low measure of symptom severity. The results will continue to be further analyzed in order to develop more effective treatment plans for head and neck cancer patients. As the issue of dry mouth, in particular, persists in a large number of these patients, there is a continuous need of refinement in this area. Improving quality of life is an important consideration while treating patients, and this study is part of a continuation of that process.


**347**

Feeding Tube Use in Patients With Salivary Gland Malignancy

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**Purpose/Objective(s):** This study was undertaken to evaluate feeding tube use in patients with salivary gland malignancies (SGM).

**Materials/Methods:** Patients were sampled from an epidemiologic SGM registry during a 12-year period (August 2001 to November 2013). Feeding tube history was reviewed from the medical records. Patients with outside locoregional therapy or palliative treatment were excluded. Route of enteral feeding (nasogastric versus gastrostomy) and length of dependence were analyzed as a function treatment modality of site of SGM. Analysis of organ-at-risk (OAR) dose-volume effects on gastrostomy dependence is underway.

**Results:** Eighty of 286 patients (28%) required temporary nasogastric tube feeding during treatment for SGM (median duration: 13 days; maximum duration: 45 days). Of those 80 patients, 29 (10% of total SGM cohort) required conversion to percutaneous endoscopic gastrostomy tube (PEG; 20 of 29 had temporary PEG). Median PEG duration was 5.7 months (range: 1-138 months). PEG placement was only necessary in patients receiving multimodality therapy (P<.001), and 50% of patients with SGM arising from pharyngeal/laryngeal sites required PEG placement compared to 8% to 19% of SGM arising from all other sites (P=.001). At a median follow-up of 2.4 years, 9% (3%) of all SGM patients were PEG dependent, but 14% (3 of 22) of patients with laryngeal/lymph node SGM subsites treated with multimodality therapy remained chronically PEG dependent.

**Conclusion:** While almost 30% of SGM survivors require a temporary nasogastric tube during treatment, PEG use is uncommon in roughly 10% of SGM overall. PEG use appears exclusive to patients treated with multimodality therapy, and chronic gastrostomy remains high (14%) in patients with minor gland cancers arising in the pharynx and larynx, suggesting impetus for dysphagia prophylaxis in these higher risk subsets.


**348**

Mental Disorders Are Associated With Poor Disease-Specific Outcomes for Elderly Patients With Squamous Cell Carcinoma of the Larynx

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**Purpose/Objective(s):** Previous studies have found patients with colon and breast cancer as well as mental disorders to present with later stage disease, have increased risk of no treatment, and have poorer survival. Considering the inherent communication difficulties faced by laryngeal cancer patients and their need for complex/multidisciplinary care, we hypothesize that such patients with mental disorders may be at particularly high risk for poor outcomes. A paucity of information is available on this subject; therefore, our objective is to investigate the incidence of mental disorders in laryngeal cancer as well as their relationship to outcomes.

**Materials/Methods:** The Surveillance, Epidemiology and End Results—Medicare linked database was analyzed. A total of 11,640 cases met the inclusion criteria of squamous cell carcinoma (SCCa) of the larynx, diagnosed from 1988 to 2005 in patients aged ≥65 years. Considering the etiological role of alcohol and tobacco use in laryngeal cancer, these disorders were not analyzed as psychiatric conditions. Extracted variables included age, race, gender, TMN staging, surgical treatment, radiation therapy, overall survival (OS), and disease-specific survival (DSS). Survival data were analyzed using the Kaplan-Meier method, log-rank test, and COX regression where appropriate.

**Results:** The rate of nonalcohol- and tobacco-related mental disorders was found to be 22%. Mood disorders were the most common, followed by psychotic, dementia, and substance disorders. Patients with mental disorders were more likely to be female, 25% versus 17% (P<.001). Patients with mental disorders also present with higher stage disease. Forty-six percent versus 51% presented with stage I cancer (P=.002). In patients without mental disorders, 44% received surgery, and 74% received radiation therapy. Treatment was similar in patients with mental disorders. Differences were not significant. OS was decreased in patients with mental disorders on multivariate analysis including stage, treatment, and available demographic factors; hazard ratio (HR) = 1.35 (P<.001). Individually, mood disorders, psychotic disorders, and substance abuse disorders portended poor outcomes as well. DSS was also found to be decreased with patients with mental disorders on multivariate analysis, HR = 1.28 (P=.02).
**Conclusion:** Medical disorders are common in laryngeal cancer patients. While controlling for tumor and demographic factors, medical disorders were associated with poorer DSS in elderly patients with SCCa of the larynx. Although further studies are needed to elucidate the origin of this disparity we feel that our data support a role for psychiatric treatment as well as increased vigilance and mobilization of social resources to ensure timely complete cancer treatment of this at-risk population.

**Author Disclosure:** T.P. Schrank: None. Y. Mikhailov: None. E.J. Lentsch: None.

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**349**

**Device Life of the Tracheoesophageal Voice Prosthesis Visited**

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**Purpose/Objective(s):** Voice prosthesis (VP) device life is a limiting factor of tracheoesophageal (TE) voice restoration that drives patient satisfaction, health care costs, and overall burden. Historic data suggest that TE VP have an average device life of 3 to 6 months, but these data are typically derived from small samples using only 1 or 2 devices. We sought to re-examine device life in a large, contemporary US hospital that uses a wide assortment of VPs.

**Materials/Methods:** A retrospective study was completed using the records of 392 patients who underwent a total laryngectomy (TL) with a TE prosthesis (TEP) from July 1, 2003, to December 31, 2013 at MD Anderson Cancer Center (MDACC). Duration was examined using Kaplan-Meier analysis. Disease, treatment, and patient-specific factors were analyzed as predictors of duration.

**Results:** A total of 3643 VPs were placed in the 392 patients. Nearly half of the patients (46%) underwent salvage laryngectomy after RT failure, and 29% required pharyngeal reconstruction. Sixty-four percent underwent primary TEP. Indwelling prostheses accounted for more than half (56%) of the devices placed (55%: 20 Fr diameters; 33%: 8 mm). More than two-thirds of prostheses (69%) were removed because of leakage, while the rest were removed due to other complications or causes. Median device life after TL due to leakage was 61 days for all prostheses, with a median of 70 days for indwelling types and 38 days for nonindwelling VPs. Neither radiation history nor extent of surgery significantly impacted device life ($P > 0.05$).

**Conclusion:** Our data suggest that VP duration demonstrates overall a slightly lower durability than historically reported. The etiology of this is unclear. A lower range of VP durability may be a function of different scientific methodologies but more likely reflects the intensification of cancer treatment at MD Anderson Cancer Center between January 2001 and December 2013, and were subsequently administered the Telephone Interview for Cognitive Status (TICS), a reliable cognitive impairment assessment tool, and the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN), a patient-reported multisymptom assessment tool, simultaneously. Patient, disease, and treatment characteristics along with TICS and MDASI-HN results were analyzed using nonparametric statistics.

**Results:** A total of 131 survivors participated in this study. Fifty-six percent were male, median age was 56 years, and median follow-up was 66 months. Most were nasopharyngeal cases (47%), followed by paranasal sines (25%), nasal cavity (16%), and skull base (7%). The majority (58%) of patients treated with modern-era radiation techniques showed no frank detectable cognitive impairment; however, a minority of patients showed either ambiguous (36%) or frank (6%) impairment on TICS assessment, suggesting more granular evaluative tests may be indicated. Additionally, mean MDASI-HN memory was 3.4 for the entire cohort (range 0-10; SD ± 2.71; SEM ± 0.24).

**Conclusion:** MDASI-HN memory was observed to be a clinically relevant screening instrument to screen for frank cognitive impairment. Further research in this area is warranted.


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**350**

**Cognitive Function and Patient-Reported Memory Problem Following Radiation Therapy for Cancers at the Skull Base: A Survivorship Study Using the Telephone Interview for Cognitive Status and the MDASI-HN**

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**Purpose/Objective(s):** Subjective cognitive decline is a well-recognized, radiation-attributable sequela of intracranial tumor (where brain parenchyma is a de facto target) irradiation and prophylactic cranial treatment. Conversely, data are comparatively sparse for extracranial tumors of nasopharynx and skull base origin. For these tumors, radiation therapy, while increasingly conformal, still brings the potential for substantial “beam path” dose to adjacent nontarget CNS structures. Using 2 accepted and validated instruments, we sought to quantify the relative incidence and severity of detectable objective cognitive symptoms observed using a prospectively collected cross-sectional survey in a robust dataset comprised of patients with tumors physically abutting nasopharyngeal or skull-base structures that received radiation therapy.

**Materials/Methods:** Head and neck cancer survivors were recruited to participate in this institutional review board–approved prospective cross-sectional study. All participants gave informed consent, completed radiation treatment at MD Anderson Cancer Center between January 2001 and December 2013, and were subsequently administered the Telephone Interview for Cognitive Status (TICS), a reliable cognitive impairment assessment tool, and the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN), a patient-reported multisymptom assessment tool, simultaneously. Patient, disease, and treatment characteristics along with TICS and MDASI-HN results were analyzed using nonparametric statistics.

**Results:** A total of 131 survivors participated in this study. Fifty-six percent were male, median age was 56 years, and median follow-up was 66 months. Most were nasopharyngeal cases (47%), followed by paranasal sines (25%), nasal cavity (16%), and skull base (7%). The majority (58%) of patients treated with modern-era radiation techniques showed no frank detectable cognitive impairment; however, a minority of patients showed either ambiguous (36%) or frank (6%) impairment on TICS assessment, suggesting more granular evaluative tests may be indicated. Additionally, mean MDASI-HN memory was 3.4 for the entire cohort (range 0-10; SD ± 2.71; SEM ± 0.24).

**Conclusion:** MDASI-HN memory was observed to be a clinically relevant screening instrument to screen for frank cognitive impairment. Further research in this area is warranted.

June 2015 were reviewed. The following information was extracted from each patient’s chart: whether they developed lymphedema, tumor stage, whether they had surgery, dose of radiation received, type of chemotheraphy given, smoking history, and whether they had a neck dissection. All patients with documented lymphedema received complete decongestive therapy. Patient response was assessed with digital photographs taken at each visit and more recently incorporated the Neck Disability Index.

**Results:** Of the 286 patients, 27% were referred for lymphedema management. Of those referred, 67% had stage 3 or 4 cancer, 49% had not had surgery (illustrating the fact that lymphedema occurs even in the absence of surgery), and 85% had received in excess of 6000 cGy. Neither the type of chemotherapy nor the patient’s smoking status correlated with the risk of lymphedema. There was an increased risk of lymphedema with neck dissection. Also evident was that increased awareness of this condition among health care providers resulted in more appropriate patients being seen earlier as part of a prehabilitation program.

**Conclusion:** Head and neck cancer patients with stage 3 and 4 disease, those who have received in excess of 6000 cGy, and those who have had a neck dissection are at an increased risk for developing lymphedema. Digital photography and Neck Disability Index have been helpful in terms of assessing each patient’s response, but its subjective nature points to a glaring need for a more effective tool for measurement. With only 27% of our patients being referred for lymphedema management, there is an obvious need for better education in terms of identifying and treating patients at risk for this common treatment-related side effect. Such increased awareness will lead to patients being evaluated and treated earlier as a component of a prehabilitation program, which will likely result in better treatment outcomes.

**Author Disclosure:** None. A. Sember: None. C. Pranskevich: None.

### 352

**Lower Cranial Neuropathy After Oropharyngeal Intensity Modulated Radiation Therapy (IMRT): A Prospective Study and Literature Review**

**Purpose/Objective(s):** Lower cranial neuropathies (LCNP) are a rare, but functionally devastating late effect of radiation therapy typically reported in nasopharyngeal cancer survivors. Despite a growing number of long-term survivors, limited data examine these neuropathies after oropharyngeal cancer (OPC). The objective of this paper was to examine incidence, time to event, and details of LCNP in long-term OPC survivors treated with intensity modulated radiation therapy (IMRT) at standard prescribed doses around 70 Gy. A supporting literature review was also conducted.

**Materials/Methods:** A pooled dataset was analyzed from 2 single-institution clinical trials with institutional review board-approved prospective functional outcomes assessment. Patients treated with definitive IMRT for locoregionally advanced OPC were sampled from trial databases. Prospective functional analysis included radiographic swallow studies, clinical cranial nerve examination, and questionnaires before, 6, 12, and 24 months after treatment. Distributions of time-to-event LCNP events were estimated by the Kaplan-Meier method. A literature review was conducted between 1977 and 2015 to summarize published LCNP outcomes.

**Results:** Fifty-nine OPC survivors with a minimum of a 2-year disease-free clinical follow-up after IMRT (60-72 Gy) with systemic therapy were included. Three patients developed delayed hypoglossal palsy ipsilateral to the index oropharyngeal tumor with a median latency of 6.7 years (range: 4.6-7.6 years). At a median follow-up of 5.7 years, cumulative incidence of delayed lower cranial neuropathy was 5%; 5- and 7-year LCNP rates were 2.1% and 6.1%, respectively. Delayed LCNP preceded progressive dysphagia (per fluoroscopy) in all 3 cases. Results of 27 articles reporting LCNP as a result of definitive radiation therapy or chemoradiation therapy for head and neck cancer were summarized (12 case reports, 6 case series, and 9 retrospective cohorts). Median incidence rate of LCNP was 10.5% in long-term survivorship of NPC. No OPC-specific incidence studies were identified in published data.

**Conclusion:** While rare, the potential for late onset cranial neuropathies precipitating swallowing deterioration highlights the importance of long-term functional surveillance in OPC survivorship.


### 353

**Survival and Tumor Response Outcomes in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN): A Systematic Literature Review**

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**Purpose/Objective(s):** Patients with recurrent or metastatic SCCHN, particularly those with platinum-refractory disease, have treatment options with limited efficacy. This study reviewed and summarized results from systematically identified clinical studies reporting overall survival (OS), progression-free survival (PFS), or objective response rate (ORR) among patients with recurrent or metastatic SCCHN treated with commonly available therapies.

**Materials/Methods:** Eligible English-language publications (published between January 2005 and October 2014) were identified using EMBASE, MEDLINE, and the Cochrane Library. Studies included randomized and single-arm clinical trials and observational studies. Data were extracted into standardized tables by 2 reviewers.

**Results:** A total of 38 publications reporting clinical outcomes from 35 studies across all lines of therapy were identified. OS, PFS, and ORR measured using Response Evaluation Criteria in Solid Tumors (RECIST) were reported in 35, 22, and 16 studies, respectively. When stratified by prior treatment, median OS ranged from 7.4 to 11.1 months for platinum-naïve patients and 4.3 to 11.8 months for patients with platinum-refractory disease. Median PFS ranged from 2.7 to 4.2 months for platinum-naïve patients and 1.4 to 8.6 months for patients with platinum-refractory disease. ORR was not reported for platinum-naïve patients and ranged from 1.1% to 10.7% for patients with platinum-refractory disease. OS, PFS, and ORR outcomes stratified by commonly used treatment regimens, including regimens containing cetuximab, docetaxel, methotrexate, and paclitaxel, are summarized in Table 1.

**Abstract 353; Table 1**

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Cetuximab</th>
<th>Docetaxel</th>
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<td>RECIST-ORR, %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>Platinum-refractory</strong></td>
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<td>OS, months</td>
<td>4.3-11.8</td>
<td>6.7</td>
<td>5.2</td>
<td>4.3-11.7</td>
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<tr>
<td>PFS, months</td>
<td>1.4-3.8</td>
<td>3.1</td>
<td>2.1</td>
<td>2.0-4.9</td>
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<tr>
<td>RECIST-ORR, %</td>
<td>9.7-10.7</td>
<td>10.7</td>
<td>1.1</td>
<td>2 populations</td>
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</table>

NR, not reported. * Unless otherwise noted, median OS, median PFS, and ORR data were based on individual trials.
Conclusions: In clinical studies of patients receiving treatment for recurrent or metastatic SCCHN, OS, PFS, and ORR outcomes have varied across study populations. However, median OS was consistently shorter than 1 year, and median PFS was consistently shorter than 5 months. Median OS and median PFS did not differ systematically among populations receiving regimens containing cetuximab, docetaxel, methotrexate, or paclitaxel, indicating an unmet need for treatment options that can delay progression and prolong survival.

Author Disclosure: J. Sigmonvitch: Research Grant; Bristol-Meyers Squibb. N. Efeka: Research Grant; Bristol-Myers Squibb. C. Zhang: Research Grant; Bristol-Myers Squibb. J. W. Shaw: Stock; Bristol-Myers Squibb. H. Dastani: None. L. Orsini: None.

A Pilot Study of Electronic Quality of Life Assessments Using Tablet Devices During and After Treatment of Head and Neck Cancers

E. Wang, E. Pollom, T. Bui, G. Ognibene, R. von Eyben, V. Divi, J. Sunwoo, M. Kaplan, A. D. Colevas, Q. T. Le, W. Hara; Stanford Radiation Oncology, Stanford, CA, Stanford Otolaryngology, Stanford, CA, Stanford Medical Oncology, Stanford, CA

Purpose/Objective(s): Electronic quality of life (QOL) data collection is increasingly used to improve efficiency, accuracy, and accessibility of information. Efficient QOL assessment is particularly crucial in head and neck oncology, where practice is constantly advancing to improve not only cancer survival but also QOL, and the use of tablets is appealing given their easy mobility and larger screen size compared to handheld devices.

Howevet, because there is likely significant variation of patient comfort with this platform, it is important to assess its relative usability and feasibility when used for QOL assessments, especially in head and neck cancer patients who may have social challenges.

Materials/Methods: Patients at our institution who were 18 years or older with a pathological diagnosis of head and neck cancer were prospectively enrolled. Each patient completed 2 questionnaires (EORTC-QLQ-C30 and EORTC-QLQ-H&N35) administered on an iPad at initial consult; during treatment, at the completion of treatment, and at each subsequent follow-up visit for 1 year after treatment (spaced approximately 3 months apart).

Descriptive analysis was performed on patient and disease characteristics, time for survey completion, and survey responses. The time for survey completion data was analyzed in a repeated-measures model to account for within-patient correlations. Statistical analysis was performed using SAS with P values < .05 considered significant.

Results: A total of 50 patients were included in this study. All patients underwent radiation treatment for their head and neck cancers, with the majority of patients (66%) also receiving concurrent chemotherapy. Although all patients completed the surveys at the initial consult, 86% of enrolled patients completed surveys at the end of radiation treatment, and 48% of enrolled patients completed surveys by the fourth follow-up visit. Average time to complete the survey for all patients over all timepoints was 9.8 minutes (standard deviation, 6.1). Age as a continuous variable was significantly associated with time for survey completion (P < .001), with older age associated with longer survey completion times. Patients who were 70 years or older had a mean survey completion time of 12.0 minutes (standard deviation, 7.6 minutes). There was no significant difference in time for survey completion between veterans and nonveterans (P = .9).

Conclusion: QOL assessment using tablet devices in head and neck cancer patients is feasible in our endpoints of time to completion of survey and compliance rates. However, elderly patients may benefit from more assistance with electronic forms and should be allotted more time for completing tablet-based QOL surveys. Our results highlight the increased efficiency and accuracy of tablet-based electronic QOL data collection and its potential utility in clinical trial design in head and neck cancer.


355 Does Frequent Follow-up After Radical Treatment of Oropharyngeal Cancer Improve Outcomes? A. Sundaramurthy, K. L. MacLennan, and I. Fragkandrea-Nixon; Edinburgh Cancer Centre, Edinburgh E4H 2XU, United Kingdom

Purpose/Objective(s): Radiation therapy (RT) remains the standard treatment for oropharyngeal cancers (OPC) both in terms of survival as well as functional outcome. The highest risk of recurrence is within the first 2 years, and hence the rationale for very close follow-up. We aim to report on our patients who relapsed following radical radiation-based treatment and intend to find whether a close follow-up improves survival.

Materials/Methods: We looked at an unselected group of 142 patients treated with either concurrent chemoradiation therapy (CRT) or radiation therapy alone (RT) for OPC at Edinburgh Cancer Centre (ECC) during January 2006 to December 2010. Relapsed patients in this cohort were identified and analyzed.

Results: There were a total of 13 relapses, of whom 6 were local and 7 had distant disease. Nine patients had CRT, while 4 had RT. All but 1 patient had locally advanced disease. Neoadjuvant chemotherapy (NAC) was used in only 1 of the patients. The median time to relapse was 10.6 months (range, 8.1-16.8). In this cohort, 5 patients either never smoked or were ex-smokers, and 8 were current smokers. The current smokers had an early relapse duration with a median of 8.0 months (range, 7.5-25) compared to those who never smoked or ex-smokers (median time to relapse 13.1 months; range, 8.5-50.5). The median RT duration was 45 days, with 9 out of 13 patients completing radiation within 46 days. Patients who completed radiation within 46 days had a longer median time to relapse compared to the group who took longer (10.6 months vs 8.5 months, \( \chi^2 \), \( P < .0436 \)). One out of 6 local relapsed patients was eligible for salvage surgery and lived for 9.5 months after surgery. The median survival for all patients from diagnosis of relapse was 3.7 months (95% confidence interval, 1.1-7.7).

Conclusion: Though the low numbers preclude a significant statistical analysis, the trends suggest early relapse in smokers and those who had prolonged radiation therapy duration. All the relapses happened within the first 2 years of treatment. Though a very close follow-up of 142 patients resulted in a longer survival for the 1 patient who had salvage surgery, the impact of best supportive measures the other relapsed patients benefitted from could not be measured from these data. Hence, we recommend continuing the current practice of close follow-up as well as further widening the number of patients to make robust decisions.

Author Disclosure: A. Sundaramurthy: None. K. L. MacLennan: None. I. Fragkandrea-Nixon: None.

356 Holistic Wellness Intervention for Head and Neck Cancer (HNC) Patients and Caregivers: Mayo Clinic Rochester (MCR) Pilot


Purpose/Objective(s): Patients treated for HNC experience a high burden of long-term treatment-related toxicity and medical comorbidities, yet few programs have included interventions for healthy living, which have the potential to improve overall survival and reduce treatment-related side effects. This is a report of a pilot wellness program for patients with HNC and their caregivers.

Materials/Methods: The program was developed and implemented through collaboration with physicians specializing in HNC and the staff of the Dan Abraham Healthy Living Program (DAHLP), a state-of-the-art wellness center at MCR. The multidisciplinary team consisted of medical oncologists, HNC surgeons, internists, dietitians, physical therapists, health psychologists, and certified wellness coaches. The 1-day program took place in the wellness facilities of the DAHLP at no cost to

participants. Pre- and postintervention surveys were conducted to assess the needs of the population and the overall satisfaction with the program.

Results: The pilot program took place on May 18, 2015. Target enrollment was 30 patients and caregivers; 30 people registered and 28 attended (15 men, 13 women; 20 survivors, 8 caregivers). Most of the HNC survivors were >2 years from diagnosis and >1 year from their last cancer treatment. The key components of the program included (1) motivational welcome by physician staff; (2) physical activity programs including gentle yoga, NEAT (non-exercise activity thermogenesis), and a physical therapy session entitled “Open & Release Your Neck & Shoulders”; (3) resiliency participatory group sessions for both survivors and caregivers; and (4) a hands-on nutrition/cooking session demonstrating strategies to increase consumption of vegetables and fruits by making whole food smoothies and soup. Twenty-one of the 28 participants responded to the pre-intervention survey. The top 2 reasons for participation were to improve overall health and increase energy. Other common reasons included to increase strength, increase flexibility, improve quality of life or longevity, and reduce weight or improve body composition. Twenty-six of the 28 participants responded to the postintervention survey. Sixty-one percent and 33% of patients were very satisfied and satisfied, respectively, and 1 person (6%) was neutral. Eighty-eight percent and 12% of caregivers were very satisfied and satisfied, respectively. No participants were dissatisfied.

On the postintervention survey, the following components were rated most valuable: gentle yoga, NEAT, and the nutrition session. Physician referral was cited as an important motivator to participation.

Conclusion: A comprehensive HNC-specific wellness intervention is feasible in this underserved patient population, and further programs for HNC patients should be developed.


357

Osteoradionecrosis After Radiation Therapy for Salivary Gland Malignancies

J.R. Tucker, L. Xu, E.M. Sturgis, T.M. Hofstede, M.S. Chambers, G.B. Gunn, C.D. Fuller, A.S.R. Mohamed, S. Lai, and K.A. Hutcheson; The University of Texas MD Anderson Cancer Center, Houston, TX

Purpose/Objective(s): The present study was undertaken to evaluate osteoradionecrosis (ORN) in patients with salivary gland malignancies (SGM) after treatment with radiation therapy.

Materials/Methods: The medical records of 172 patients treated with conformal radiation therapy for SGM during a 12-year period (August 2001 to November 2013) were reviewed. Incidence, time to event, staging, and management of ORN were analyzed. Analysis of mandibular dose-volume effects on ORN is underway.

Results: Seven of the 172 patients (4%) developed ORN (median latency: 19 months, range: 4-72 months). Of those 7 patients, 4 required major surgery, 1 required hyperbaric oxygen therapy (HBO), 1 required minor debridement, and 1 required conservative management. Total radiation dose varied from 50 Gy (1 case) to 70 Gy (1 case) among those patients who developed ORN. Three of the 7 cases of ORN occurred after traumatic injury to the bone. Of the 7 patients who developed ORN, 3 had SGM of the major glands, 3 had other sites of the oral cavity or oropharynx, and 1 had a sinonasal location.

Conclusion: While the rate of ORN associated after radiation therapy for SGM was lower (4%) than previously published data on patients with squamous cell carcinomas of the head and neck treated with radiation therapy (8% to 14%), clinically significant ORN necessitating major surgery should not be ignored as a possible late effect of radiation therapy in SGM survivors. Almost all cases that developed ORN had SGM of the major glands or minor gland arising in the oral cavity or oropharynx.
# INDEX OF PRESENTING AUTHORS

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelstein, David</td>
<td>162</td>
</tr>
<tr>
<td>Adeniran, Oladapo</td>
<td>150</td>
</tr>
<tr>
<td>Adkins, Douglas</td>
<td>9</td>
</tr>
<tr>
<td>Advani, Sunil</td>
<td>292</td>
</tr>
<tr>
<td>Agarwal, Seema</td>
<td>266</td>
</tr>
<tr>
<td>Ahn, Peter</td>
<td>132</td>
</tr>
<tr>
<td>Albergotti, William</td>
<td>114</td>
</tr>
<tr>
<td>Allan, Eric</td>
<td>111, 131</td>
</tr>
<tr>
<td>Alsafadi, Nabil</td>
<td>186</td>
</tr>
<tr>
<td>Amini, Arya</td>
<td>100</td>
</tr>
<tr>
<td>Amoils, Misha</td>
<td>315</td>
</tr>
<tr>
<td>Amril, Federico</td>
<td>245</td>
</tr>
<tr>
<td>Amsbaugh, Mark</td>
<td>158, 205</td>
</tr>
<tr>
<td>Anderson, Carryn</td>
<td>11, 168</td>
</tr>
<tr>
<td>Appachi, Sathya</td>
<td>344</td>
</tr>
<tr>
<td>Dave, Eesha</td>
<td>252</td>
</tr>
<tr>
<td>de Souza, Jonas</td>
<td>331</td>
</tr>
<tr>
<td>Debenham, Brock</td>
<td>264</td>
</tr>
<tr>
<td>Diavolitis, Virginia</td>
<td>358</td>
</tr>
<tr>
<td>Divi, Vasu</td>
<td>207</td>
</tr>
<tr>
<td>Dong, Tuo</td>
<td>157</td>
</tr>
<tr>
<td>Dorius, Timothy</td>
<td>198</td>
</tr>
<tr>
<td>Dorth, Jennifer</td>
<td>246</td>
</tr>
<tr>
<td>Dua, Bharat</td>
<td>189</td>
</tr>
<tr>
<td>Dunlap, Neal</td>
<td>190</td>
</tr>
<tr>
<td>Elliott, David</td>
<td>128</td>
</tr>
<tr>
<td>Enderling, Heiko</td>
<td>180</td>
</tr>
<tr>
<td>Fakhry, Carole</td>
<td>101, 106</td>
</tr>
<tr>
<td>Fayek, Ihab</td>
<td>318</td>
</tr>
<tr>
<td>Ferris, Robert</td>
<td>8</td>
</tr>
<tr>
<td>Finegersh, Andrey</td>
<td>283</td>
</tr>
<tr>
<td>Frakes, Jessica</td>
<td>6</td>
</tr>
<tr>
<td>Gaines, Katherine</td>
<td>337</td>
</tr>
<tr>
<td>Gamez, Mauricio</td>
<td>133, 316</td>
</tr>
<tr>
<td>Ganly, Ian</td>
<td>295</td>
</tr>
<tr>
<td>Gawande, Shailesh</td>
<td>291</td>
</tr>
<tr>
<td>Gebhardt, Brian</td>
<td>319</td>
</tr>
<tr>
<td>Geiger, Jessica</td>
<td>254</td>
</tr>
<tr>
<td>Giambattista, Joshua</td>
<td>184</td>
</tr>
<tr>
<td>Gilden, Daniel</td>
<td>174, 258</td>
</tr>
<tr>
<td>Gill, Beant</td>
<td>309</td>
</tr>
<tr>
<td>Glaser, Scott</td>
<td>304</td>
</tr>
<tr>
<td>Godse, Neal</td>
<td>285</td>
</tr>
<tr>
<td>Goepfert, Ryan</td>
<td>338, 340</td>
</tr>
<tr>
<td>Greskovich, John</td>
<td>140</td>
</tr>
<tr>
<td>Gunn, G.</td>
<td>330</td>
</tr>
<tr>
<td>Hakansson, Katrin</td>
<td>176</td>
</tr>
<tr>
<td>Hamilton, Thomas</td>
<td>265</td>
</tr>
<tr>
<td>Hanna, Glenn</td>
<td>307</td>
</tr>
<tr>
<td>Harr, Bridgett</td>
<td>155</td>
</tr>
<tr>
<td>hashemi Sadrabi, Nooshin</td>
<td>275</td>
</tr>
<tr>
<td>Herman, Michael</td>
<td>259</td>
</tr>
<tr>
<td>Hessel, Amy</td>
<td>137</td>
</tr>
<tr>
<td>Hilbert, Ashley</td>
<td>200</td>
</tr>
<tr>
<td>Hoffman, Rex</td>
<td>240</td>
</tr>
<tr>
<td>Hu, Kenneth</td>
<td>175</td>
</tr>
<tr>
<td>Hutcheson, Katherine</td>
<td>347, 352</td>
</tr>
<tr>
<td>Inokuchi, Haruo</td>
<td>171</td>
</tr>
<tr>
<td>Jackson, Matthew</td>
<td>104</td>
</tr>
<tr>
<td>James, Joshua</td>
<td>147</td>
</tr>
<tr>
<td>Jegadeesh, Naresh</td>
<td>151</td>
</tr>
<tr>
<td>Jhavar, Sameer</td>
<td>277</td>
</tr>
<tr>
<td>Johnson, Catherine</td>
<td>160</td>
</tr>
<tr>
<td>Joshi, Nikhil</td>
<td>113</td>
</tr>
<tr>
<td>Kabarriri, Rafi</td>
<td>238</td>
</tr>
<tr>
<td>Kamdem, Donatien</td>
<td>248</td>
</tr>
<tr>
<td>Kanwar, Aasheesh</td>
<td>326</td>
</tr>
<tr>
<td>Karam, Sana</td>
<td>253</td>
</tr>
<tr>
<td>Karni, Ron</td>
<td>247, 282</td>
</tr>
<tr>
<td>Kass, Jason</td>
<td>170</td>
</tr>
<tr>
<td>Khan, Aidee</td>
<td>177</td>
</tr>
<tr>
<td>Khan, Nazir</td>
<td>156</td>
</tr>
<tr>
<td>Kil, Whoon Jong</td>
<td>197</td>
</tr>
<tr>
<td>Kim, Edward</td>
<td>299</td>
</tr>
<tr>
<td>Kjems, Julie</td>
<td>105</td>
</tr>
<tr>
<td>Koyfman, Shlomo</td>
<td>179</td>
</tr>
<tr>
<td>Kung, Sunny</td>
<td>323</td>
</tr>
<tr>
<td>Lee, Erwin</td>
<td>145</td>
</tr>
<tr>
<td>Lee, Jae</td>
<td>251</td>
</tr>
<tr>
<td>Lee, Victor</td>
<td>204</td>
</tr>
<tr>
<td>Lewin, Jan</td>
<td>349</td>
</tr>
<tr>
<td>Li, BaoQing</td>
<td>335</td>
</tr>
<tr>
<td>Lukens, John</td>
<td>118</td>
</tr>
<tr>
<td>Luna-Oritz, Kauahyama</td>
<td>201</td>
</tr>
<tr>
<td>Makki, Fawaz</td>
<td>343</td>
</tr>
<tr>
<td>Manyam, Bindu</td>
<td>298</td>
</tr>
<tr>
<td>Mao, Yanping</td>
<td>112</td>
</tr>
<tr>
<td>Margalit, Danielle</td>
<td>102, 208</td>
</tr>
<tr>
<td>Martin, Daniel</td>
<td>143</td>
</tr>
<tr>
<td>Martin, Geoffrey</td>
<td>256</td>
</tr>
<tr>
<td>Massa, Sean</td>
<td>328, 336</td>
</tr>
<tr>
<td>McDermott, Jessica</td>
<td>312</td>
</tr>
<tr>
<td>McDonald, Mark</td>
<td>255</td>
</tr>
<tr>
<td>Mehta, Vikas</td>
<td>302</td>
</tr>
<tr>
<td>Melotek, James 3, 7, 116, 120</td>
<td>341</td>
</tr>
<tr>
<td>Meshman, Jessica</td>
<td>199, 249</td>
</tr>
<tr>
<td>Messer, Jaya</td>
<td>224</td>
</tr>
<tr>
<td>Mikhailov, Alexey</td>
<td>173, 263</td>
</tr>
<tr>
<td>Miller, Daniel</td>
<td>293</td>
</tr>
<tr>
<td>Miller, Eric</td>
<td>321</td>
</tr>
<tr>
<td>Mohamed, Abdallah 236, 342, 350</td>
<td>342</td>
</tr>
<tr>
<td>Molitoris, Jason</td>
<td>154</td>
</tr>
<tr>
<td>Monroe, Alan</td>
<td>325</td>
</tr>
<tr>
<td>Moreira, Jonathan</td>
<td>187</td>
</tr>
<tr>
<td>Mowery, Yvonne</td>
<td>227</td>
</tr>
<tr>
<td>Murphy, Colin</td>
<td>110</td>
</tr>
<tr>
<td>Narveson, Lisa</td>
<td>262</td>
</tr>
<tr>
<td>Nedzi, Lucien</td>
<td>125</td>
</tr>
<tr>
<td>Neskey, David</td>
<td>169</td>
</tr>
<tr>
<td>Niska, Joshua</td>
<td>166</td>
</tr>
<tr>
<td>Nocon, Cheryl</td>
<td>188</td>
</tr>
<tr>
<td>O’Donnell, Barrett</td>
<td>210</td>
</tr>
<tr>
<td>Okwankwu, Derick</td>
<td>322</td>
</tr>
<tr>
<td>Orton, Andrew</td>
<td>219</td>
</tr>
<tr>
<td>Osman, Abdulah</td>
<td>270</td>
</tr>
<tr>
<td>Ozbun, Michelle</td>
<td>273</td>
</tr>
<tr>
<td>Palmer, Joshua</td>
<td>303</td>
</tr>
<tr>
<td>Parvathenani, Upendra</td>
<td>167, 296</td>
</tr>
<tr>
<td>Patil, Snehal</td>
<td>313</td>
</tr>
<tr>
<td>Patil, Yash</td>
<td>141, 218</td>
</tr>
<tr>
<td>Perez, Cesar</td>
<td>161</td>
</tr>
<tr>
<td>Perni, Subha</td>
<td>220</td>
</tr>
<tr>
<td>Pham, Brian</td>
<td>163</td>
</tr>
<tr>
<td>Phan, Jack</td>
<td>260</td>
</tr>
<tr>
<td>Pinheiro, A. Daniel</td>
<td>LB1, 200</td>
</tr>
<tr>
<td>Platek, Alexis 123, 181, 182, 211</td>
<td>299</td>
</tr>
<tr>
<td>Porosnici, Mercedes</td>
<td>192</td>
</tr>
<tr>
<td>Price, Katharine</td>
<td>356</td>
</tr>
<tr>
<td>Prochnow, Sebastian</td>
<td>276</td>
</tr>
<tr>
<td>Rabinovits, Guislherme</td>
<td>129</td>
</tr>
<tr>
<td>Raghavan, Govind</td>
<td>241</td>
</tr>
<tr>
<td>Rao, Shyam</td>
<td>153</td>
</tr>
<tr>
<td>Rashid, Yasmin</td>
<td>217</td>
</tr>
<tr>
<td>Rasmussen, Gregers</td>
<td>332</td>
</tr>
<tr>
<td>Rasmussen, Jacob</td>
<td>229</td>
</tr>
<tr>
<td>Roberts, Thomas</td>
<td>203</td>
</tr>
<tr>
<td>Rocco, James</td>
<td>235</td>
</tr>
<tr>
<td>Rosado, Miguel</td>
<td>243</td>
</tr>
<tr>
<td>Rosko, Andrew</td>
<td>222</td>
</tr>
<tr>
<td>Russo, James</td>
<td>121</td>
</tr>
<tr>
<td>Rwigema, Jean-Claude</td>
<td>117, 257</td>
</tr>
<tr>
<td>Samstein, Robert</td>
<td>301</td>
</tr>
<tr>
<td>Samuels, Stuart 124, 138, 123</td>
<td>259</td>
</tr>
<tr>
<td>Sanfilippo, Nicholas</td>
<td>127, 124</td>
</tr>
<tr>
<td>Name</td>
<td>Page Numbers</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Sapir, Eli</td>
<td>136, 329</td>
</tr>
<tr>
<td>Sapkota, Dipak</td>
<td>290</td>
</tr>
<tr>
<td>Scaraficci, Ana</td>
<td>214</td>
</tr>
<tr>
<td>Schoenfeld, Jonathan</td>
<td>2</td>
</tr>
<tr>
<td>Schrank, Travis</td>
<td>311, 348</td>
</tr>
<tr>
<td>Schwartz, David</td>
<td>142</td>
</tr>
<tr>
<td>Sember, Andrew</td>
<td>351</td>
</tr>
<tr>
<td>Shackelford, Rodney</td>
<td>288</td>
</tr>
<tr>
<td>Shah, Jennifer</td>
<td>148</td>
</tr>
<tr>
<td>Shaikh, Talha</td>
<td>126</td>
</tr>
<tr>
<td>Shameem, Raji</td>
<td>215</td>
</tr>
<tr>
<td>Sharma, Arun</td>
<td>314</td>
</tr>
<tr>
<td>Shevchenko, Sergey</td>
<td>287</td>
</tr>
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<td>Shumway, Brian</td>
<td>289</td>
</tr>
<tr>
<td>Signorovitch, James</td>
<td>353</td>
</tr>
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<td>Silver, Natalie</td>
<td>284</td>
</tr>
<tr>
<td>Sio, Terence</td>
<td>327</td>
</tr>
<tr>
<td>Skladowski, Krzysztof</td>
<td>119</td>
</tr>
<tr>
<td>Smith, William</td>
<td>172</td>
</tr>
<tr>
<td>Song, Shiyu</td>
<td>233</td>
</tr>
<tr>
<td>Spiotto, Michael</td>
<td>269, 271</td>
</tr>
<tr>
<td>St. John, Maie</td>
<td>230, 272</td>
</tr>
<tr>
<td>Stokes, William</td>
<td>109</td>
</tr>
<tr>
<td>Strom, Tobin</td>
<td>300</td>
</tr>
<tr>
<td>Sumner, Whitney</td>
<td>306</td>
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<td>Sundaramurthy,</td>
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<tr>
<td>Arovinth</td>
<td>355</td>
</tr>
<tr>
<td>Suppiah, Somu</td>
<td>223</td>
</tr>
<tr>
<td>Swegal, Warren</td>
<td>178</td>
</tr>
<tr>
<td>Swieckie, Paul</td>
<td>281</td>
</tr>
<tr>
<td>Takiar, Vinita</td>
<td>159</td>
</tr>
<tr>
<td>Terhaard, Chris</td>
<td>225, 242</td>
</tr>
<tr>
<td>Thomas, Carissa</td>
<td>286</td>
</tr>
<tr>
<td>Thorstad, Wade</td>
<td>239</td>
</tr>
<tr>
<td>Tolekidis, George</td>
<td>234</td>
</tr>
<tr>
<td>Tucker, J.</td>
<td>357</td>
</tr>
<tr>
<td>Vanderwalde, Noam</td>
<td>135</td>
</tr>
<tr>
<td>Veliz, Maria</td>
<td>261</td>
</tr>
<tr>
<td>Verma, Vivek</td>
<td>193</td>
</tr>
<tr>
<td>Wald, Patrick</td>
<td>164</td>
</tr>
<tr>
<td>Wang, Ellen</td>
<td>354</td>
</tr>
<tr>
<td>Wang, Kyle</td>
<td>144, 232</td>
</tr>
<tr>
<td>Ward, Matthew</td>
<td>107</td>
</tr>
<tr>
<td>Warren, Benjamin</td>
<td>345</td>
</tr>
<tr>
<td>Wieland, Aaron</td>
<td>191</td>
</tr>
<tr>
<td>Wise-Draper, Trisha</td>
<td>279</td>
</tr>
<tr>
<td>Wojcieczynski, Andrzej</td>
<td>196</td>
</tr>
<tr>
<td>Wong, Kee</td>
<td>228</td>
</tr>
<tr>
<td>Wu, Szu-Yuan</td>
<td>108</td>
</tr>
<tr>
<td>Wygoda, Andrzej</td>
<td>185</td>
</tr>
<tr>
<td>Yuan, Taize</td>
<td>235</td>
</tr>
<tr>
<td>Yusuf, Mehran</td>
<td>183</td>
</tr>
<tr>
<td>Zevallos, Jose</td>
<td>1</td>
</tr>
<tr>
<td>Zhan, Kevin</td>
<td>206, 212, 213, 339</td>
</tr>
<tr>
<td>Zumsteg, Zachary</td>
<td>115</td>
</tr>
</tbody>
</table>

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