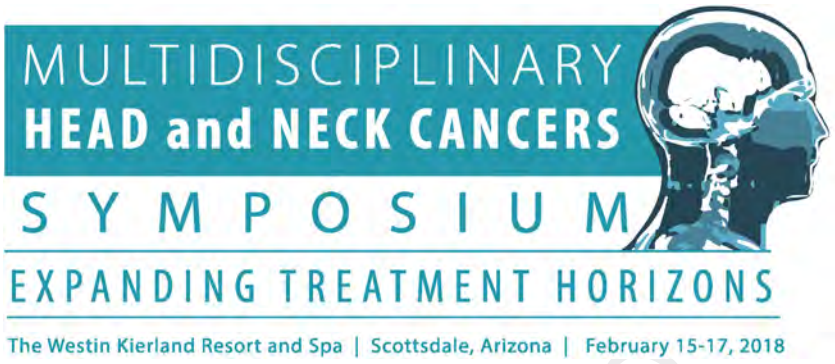

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1

A Randomized, Open-Label, Multicenter, Global Phase 2 Study of Durvalumab (D), Tremelimumab (T), or D Plus T, in Patients With PD-L1 Low/Negative Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: CONDOR

L. Siu,[1] C. Even,[2] R. Mesía,[3] A. Daste,[4] J. Krauss,[5] N.F. Saba,[6] L. Nabell,[7] N.E. Ready,[8] I.Brana Garcia,[9] N. Kotecki,[10] D.P. Zandberg,[11] J. Gilbert,[12] H. Mehanna,[13] A. Jarkowski,[14] G. Melillo,[14] J.M. Armstrong,[14] and J. Fayette[15]; *[1]Princess Margaret Cancer Centre, Toronto, ON, Canada, [2]Institut Gustave Roussy, Villejuif, France, [3]Medical Oncology Department, Catalan Institute of Oncology, University of Barcelona, Barcelona, Spain, [4]Département d'Oncologie Médicale, Hôpital Saint André, Bordeaux, France, [5]Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg, Germany, [6]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, [7]Clinical Studies Unit, University of Alabama at Birmingham, Comprehensive Cancer Center, Birmingham, AL, United States Minor Outlying Islands, [8]Duke University Medical Center, Durham, NC, [9]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [10]Centre Régional de Lutte Contre le Cancer-Centre Oscar Lambret, Lille, France, [11]University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, [12]Dept. of Hematology and Oncology, Henry-Joyce Cancer Clinic, Nashville, TN, [13]Institute of Head and Neck Studies and Education (InHANSE), University of Birmingham, Birmingham, United Kingdom, [14]AstraZeneca, Gaithersburg, MD, [15]Clinical Oncology, Cancer Center "Centre Léon Bérard," University of Lyon, Lyon, France*

Purpose/Objective(s): Head and neck squamous cell carcinoma (HNSCC) commonly has an inflamed phenotype with T-cell infiltration that may benefit from immunotherapy. Durvalumab, a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80, showed encouraging antitumor activity in many tumor types, including recurrent or metastatic (R/M) HNSCC in a phase 1/2 study (NCT01693562). Combining anti-PD-L1 and anti-CTLA-4 Abs showed enhanced preclinical antitumor activity over either agent alone, indicating that the 2 pathways are not redundant (Stewart et al. J Immunol. 2013). The combination of Durvalumab (D) and Tremelimumab (T) (D+T) showed promising efficacy in lung cancer patients (pts), including those with PD-L1 low/negative tumors. (Antonia et al. Lancet Oncol. 2016). Thus, the CONDOR study (NCT02319044) was designed to evaluate D+T in PD-L1 low/negative R/M HNSCC pts. Here we report, for the first time, data for D+T in HNSCC.

Materials/Methods: Eligible pts had measurable PD-L1 low/negative (defined as PD-L1 staining in <25% tumor cells) R/M HNSCC (oral cavity, oropharynx, hypopharynx, larynx) following progression of 1 prior platinum-based regimen in the R/M setting. Pts were stratified by human papillomavirus (HPV) and smoking status and randomized 1:1:2 to D monotherapy (10 mg/kg, IV Q2W), T monotherapy (10 mg/kg IV Q4W), or D+T ([20 mg/kg D Q4W + 1 mg/kg T q4w] ×4 " 10 mg/kg D Q2W) for up to 12 months (mos). The primary endpoint was overall response rate (ORR) of D+T by blinded independent review committee using RECIST v1.1. Secondary endpoints included duration of response and overall survival (OS).

Results: Data cutoff was 31 March 2017, approximately 12 mos after last pt entry. A total of 267 pts were randomized to D (n=67), T (n=67), or D+T (n=133); median follow-up was 5.8 mos. Most pts had metastatic disease (64%) versus recurrent disease (36%) and 28.1% of pts were HPV positive. Most pts had prior cetuximab therapy and prior radiation therapy. Treatment-related adverse events (trAEs) of any grade were seen in 57.9% D+T arm, 63.1% D arm, and 55.4% T arm. Grade 3/4 trAEs occurred in 15.8% D+T arm, 12.3% D arm, and 16.9% T arm. Across all arms, 12 (4.6%) pts discontinued therapy due to a trAE. One death in the D+T arm was associated with trAEs. ORR (all partial responses) was 7.8% for D+T, and 9.2% and 1.6 % for the D and T arms, respectively. Of 17 responses, 10 were ongoing at the cutoff. Median OS for D+T was 7.6 mos, and 6.0 and 5.5 mos for the D and T arms, respectively.

Conclusion: Both D and T monotherapy as well as the combination of D+T had acceptable toxicity in this pretreated, PD-L1 low/negative, R/M HNSCC population, and showed no new safety signals. D and D+T showed antitumor activity in a pt population with few treatment options. Phase 3 trials in first- and second-line HNSCC assessing D+T and D are ongoing with OS endpoints.

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2

Safety Evaluation of Nivolumab Concomitant With Platinum-Based Chemoradiation therapy for Intermediate and High-Risk Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma: RTOG Foundation 3504

M. Gillison,[1] R.L. Ferris,[2] Q. Zhang,[3] A.D. Colevas,[4] L.K. Mell,[5] C. Kirsch,[6] K.L. Moore,[7] M.T. Truong,[8] C.S. Kong,[9] R. Jordan,[10] D.A. Clump II,[11] J. Ohr,[12] K. He,[13] D. Blakaj,[13] J. Deeken,[14] M. Machtay,[15] W.J. Curran Jr,[16] J. Harris,[3] and Q.T. Le[17]; *[1]MD Anderson Cancer Center, Houston, TX, [2]Department of Otolaryngology, Eye & Ear Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, [3]NRG oncology, Philadelphia, PA, [4]Stanford, Palo Alto, CA, [5]UC San Diego, Moores Cancer Center, Department of Radiation Oncology, La Jolla, CA, [6]Northwell Health, New York, NY, [7]University of California, San Diego, La Jolla, CA, [8]Boston Medical Center, Boston, MA, [9]Department of Pathology, Stanford University, Stanford, CA, [10]UCSF, San Francisco, CA,*

[11]Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [12]Department of Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [13]Ohio State University, Columbus, OH, [14]Inova Comprehensive Cancer & Research Institute, Falls Church, VA, [15]Radiation Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH, [16]Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [17]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA

Purpose/Objective(s): Nivolumab (Nivo), which inhibits the programmed death-1 (PD-1) receptor, improved survival for patients (pts) with platinum-refractory recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) compared with standard therapy. A clinical trial was designed to evaluate the safety of adding nivo to four standard radiation therapy (RT) regimens for pts with newly diagnosed intermediate (IR) and high-risk (HR) HNSCC (Table 1). Early safety data for cohort 1 (weekly cisplatin) and accrual for cohort 2 (high-dose cisplatin) are reported.

Materials/Methods: Eligibility includes IR (p16+, oropharynx T1-2N2b-N3/T3-4N0-3, >10 pack-years (pys) or T4N0-N3, T1-3N3 ≤10 pys) and HR HNSCC (oral cavity, larynx, hypopharynx, or p16(-) oropharynx, stage T1-2N2a-N3 or T3-4N0-3). Ten pts are enrolled to obtain 8 evaluable pts in each cohort. The feasibility of adjuvant nivo at 3-12 months post-RT is also evaluated. Primary endpoints are safety and feasibility, with dose-limiting toxicity (DLT) defined as nivo-related: ≥grade 3 adverse event unresolved to ≤grade 1 in ≤28 days; RT delay >2 wks; incomplete RT; or inability to receive ≥70% of prescribed systemic therapy due to nivo-related toxicity. DLT window was from first nivo dose (day -14) to 28 days post RT.

Results: Characteristics of 10 enrolled pts for cohort 1(weekly cisplatin): median age 56, 80% male, 90% caucasian, 40% PS 0, 80% >10 pys, 50% larynx and 50% p16(+) oropharynx cancer, 80% T3-4 and 80% N2-3 disease. Two of 10 pts were unevaluable due to withdrawal of consent. All 8 evaluable pts completed RT. 3 of 8 pts received 10 doses of concurrent nivo: 1 pt received 9 doses, 3 pts are ongoing after 8 doses, and nivo was discontinued due to blurred vision in 1 pt after 8 doses. Seven of 8 pts received >70% of prescribed cisplatin, which was discontinued early in 3 pts due to AEs unrelated to nivo. No DLT was observed. SAEs included anaphylaxis to cisplatin (cis) (n=1), cholecystitis (1), but none attributable to nivo. Grade ≥3 toxicities attributable to nivo included fatigue (n=1), anorexia (1), WBC decrease (2), neutrophil count decrease (1), mucositis (1), lipase (1) elevation. Seven of 8 pts continued on to maintenance nivo. Toxicity data for cohort 2 (high-dose cisplatin), 10 patients accrued, will also be available at the time of the meeting.

Conclusion: Nivo is safe and feasible to administer concurrently with a weekly cisplatin-RT regimen for patients with newly diagnosed IR/HR HNSCC (NCT02764593).

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3

Somatic Frameshift Alterations in Tumor Suppressor Genes May Predict Anti-PD-1/L1 Response in Squamous Cell Carcinoma of the Head and Neck

G.J. Hanna,[1] L.E. Macconaill,[1] P. Lizotte,[1,3] M. Cavanaugh,[1,3] N.G. Chau,[1] J.D. Schoenfeld,[4] J.H. Lorch,[1] R. Uppaluri,[5] and R.I. Haddad[1]; [1]Department of Medical Oncology Dana-Farber Cancer Institute, Boston, MA, [2]Center for Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, MA, [3]Robert and Renee Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute, Boston, MA, [4]Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham & Women's Hospital, Boston, MA, [5]Department of head and Neck Surgical Oncology, Dana-Farber Cancer Institute, Brigham & Women's Hospital, Boston, MA

Purpose: Immune checkpoint inhibitors that block inhibitory PD-1:L1 interactions have efficacy in treating advanced squamous cell carcinoma of the head and neck (SCCHN), but objective response rates are below 20% in unselected patients. Human papillomavirus (HPV) positive tumors and those with ≥1% tumor PD-L1 expression appear to derive greater benefit. To date, PD-1/L1 expression alone is not considered a robust predictor of response. Genomic and immune biomarkers are urgently needed to inform patient selection.

Methods: We present a clinically annotated cohort of 126 SCCHN patients treated with anti-PD-1/L1 therapies at our institution. Prior to treatment, 95 (75%) had targeted next-generation sequencing of tumor specimens. Of these, 42 (44%) underwent multiparametric fluorescence-activated cell sorting to define the tumor immune microenvironment − with the aim of nominating predictors of response.

Results: Clinicopathologic data from 126 patients included all primary sites, with 50 (40%) having virally-mediated disease. Six (5%) complete and 11 (9%) partial responses were observed, with a clinical benefit rate of 39%. There were few grade 3+ immune-related toxicities (12/126, 10%). Those treated with any prior chemotherapy (98, 78%) vs. only surgery and/or radiation had longer overall survival (OS) ($P=0.02$). While smoking status did not impact OS ($P=0.58$), smokers had a higher total mutational burden (TMB) ($p=0.01$). HPV+ patients treated with PD-1/L1 blockade had improved OS (HR 0.58, 95%CI 0.32-1.04, $P=0.02$) and a lower TMB ($P<0.01$). Among responders, NOTCH1 and SMARCA4 were most frequently mutated, and in-frame or frameshift mutations among tumor suppressor genes were common. These alterations occurred at significantly lower frequencies ($P<0.01$) in non-responders and were often missense mutations. Frequent copy-number variations (CNVs) among responders included: single copy-number losses in ATM, CBL and SDHD; low copy amplifications in ETV5, PIK3CA, PRKCI and SOX2. Patients with a higher TMB and greater CD8+ T cell infiltrates (≥ 50% of CD3+ cells) derived a greater benefit from PD-1/L1 blockade ($P<0.01$, 0.01, respectively). Among responders, CD8+ T cells were often activated (CD38/69+) with an effector memory phenotype (CD45RO+ CCR7-). TIM-3 or LAG-3 co-expression with PD-1 was higher on T cells among non-responders ($P=0.03$, 0.02, respectively), suggesting a mechanism for adaptive immune resistance.

Conclusion: Our results suggest that somatic frameshift events in tumor suppressor genes among SCCHN tumors may predict anti-PD-1/L1 response.

Abstract 2; Table 1

Cohort	Cis Eligible	Nivo	Chemotherapy	RT IMRT 70 Gy/7 wk	N enrolled
1	Y	C: 240 mgs q14d X10 A: 480 mgs q28d X7	Weekly Cis (40 mg/m2)	Y	10
2	Y	C : 240-360 mg q21d X6 A : 480 mg q28d X7	High dose Cis (100 mg/m2 q 21d)	Y	10
3	Y	C: 240 mgs q14d X10 A: 480 mgs q28d X7	Cetuximab	Y	9
4	N	C: 240 mgs q14d X10 A: 480 mgs q28d X7	–	Y	3

These genomic alterations or higher TMB may result in a greater neoantigen burden yielding an abundance of activated, effector memory T cells. We also observed improved outcomes in patients receiving chemotherapy prior to PD-1/L1 blockade. Further studies are needed to validate these findings.

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TCGA Data on Head and Neck Squamous Cell Carcinoma Suggest Therapy-Specific Implications of Intratumor Heterogeneity

E.A. Mroz, K. Patel, and J.W. Rocco; *The James Cancer Hospital and Solove Research Institute, Wexner Medical Center at The Ohio State University, Department of Otolaryngology-Head and Neck Surgery, Columbus, OH*

Purpose/Objective(s): To determine whether the relation of intratumor genetic heterogeneity to outcome in head and neck squamous cell carcinoma (HNSCC) differs depending on the therapy received. Three hundred and five initial HNSCC cases from The Cancer Genome Atlas (TCGA) showed a strong relation of high heterogeneity to shorter overall survival (OS) in HNSCC (PLoS Medicine 12: e1001786, 2015), but were insufficient to determine whether the relation to OS depended on therapy type. More complete TCGA data now allow examination of this issue.

Materials/Methods: Clinical and whole-exome sequencing (WES) data on 528 HNSCC cases in TCGA were obtained from the NCI Genome Data Center and the Broad Institute. Clinical data were reviewed to determine if initial therapy included radiation or chemotherapy as primary or adjuvant therapy. Intratumor genetic heterogeneity was assessed by a modification of the MATH measure (Oral Oncology 49: 211, 2013) that improved handling of differing tumor-cell fractions among samples. Cox multiple regression of OS included age, year of diagnosis, smoking history, anatomic subsite, N and T classifications, HPV status, therapy, MATH, and another WES-derived classification. The interaction of MATH with therapy was evaluated to address the project's objective.

Results: Three hundred and ninety-three TCGA HNSCC cases (144 deaths) had sufficient data. The interaction of MATH with therapy was significantly related to OS ($P = .016$). With other clinical variables accounted for, the longest OS was seen for patients with low-MATH tumors who received chemoradiation (baseline for hazard ratio, HR). Intermediate OS was seen for patients with high-MATH tumors receiving chemoradiation (HR, 2.3; 95% CI, 1.1-5.2); patients with low-MATH tumors receiving no adjuvant therapy (HR, 1.7; CI, 0.7-4.2); and patients receiving adjuvant radiation without chemotherapy, with low (HR, 1.6; CI, 0.7-4.1) or high (HR, 1.7; CI, 0.7-4.1) MATH. The shortest OS was for patients with high-MATH tumors not receiving adjuvant therapy (HR = 6.6; CI, 2.8-20).

Conclusion: This first report that the relation of intratumor genetic heterogeneity to OS depends on therapy, although based on retrospective analysis and statistical control of other variables, has provocative implications that deserve prospective study. The results suggest that patients with high intratumor heterogeneity might benefit from radiation even when clinical considerations suggest that adjuvant therapy can be omitted. The results also suggest, however, that such patients might not benefit from the addition of chemotherapy, and thus could be spared the morbidity of complications from combination therapy. Intratumor heterogeneity should be evaluated in controlled trials that compare adjuvant radiation against chemoradiation following surgery for HNSCC.

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5

OPTIMA—A Phase 2 Trial of Induction Chemotherapy Response-Stratified Radiation Therapy Dose and Volume De-escalation for HPV+ Oropharyngeal Cancer: Efficacy, Toxicity, and HPV Subtype Analysis

T. Seiwert,[1] J.M. Melotek,[1] C.C. Foster,[1] E.A. Blair,[1] T.G. Karrison,[1] N. Agrawal,[1] L. Portugal,[1] Z. Gooi,[1] K.M. Stenson,[2] R.J. Brisson,[1] S. Arshad,[1] A. Dekker,[1] S. Kochanny,[1] V. Saloura,[1] M.T. Spiotto,[1] V.M. Villaflor,[3] D.J. Haraf,[1] and E.E. Vokes[1]; *[1]University of Chicago, Chicago, IL, [2]Rush University Medical Center, Chicago, IL, [3]Northwestern University, Chicago, IL*

Purpose/Objective(s): This prospective phase 2 de-escalation study used induction chemotherapy to identify favorable HPV+ oropharyngeal cancer (OPC) patients (pts), including those with high-risk tumors, and applied significantly lower radiation or chemoradiation doses than previously reported. We herein report an updated analysis with p16 IHC and HPV PCR genotyping.

Materials/Methods: Pts with HPV+ OPC were classified as low-risk (≤T3, ≤N2B, ≤10 PYH) or high-risk (T4 or ≥N2C or >10 PYH). Pts received 3 cycles of carboplatin and nab-paclitaxel induction. Low-risk pts with ≥50% response received low-dose radiation therapy (RT) alone to 50 Gy (RT50). Low-risk pts with 30%-50% response OR high-risk pts with ≥50% response received low-dose chemoradiation therapy to 45 Gy (CRT45). All other (=poor response) pts received regular-dose chemoradiation therapy to 75 Gy (CRT75). All pts also received de-escalated RT volumes limited to the first echelon of uninvolved nodes. RT50 was delivered in 2 Gy/fx once daily whereas CRT arms used paclitaxel, 5-FU, hydrea, and 1.5 Gy twice-daily RT every other week. Primary site biopsy and neck dissection were performed only after de-escalated treatment (RT50, CRT45) for pathologic confirmation. The primary endpoint was 2-year PFS. Secondary endpoints included pathologic complete response (pCR) rate and toxicity.

Results: Sixty-two pts were enrolled; p16 IHC was positive in all cases. Confirmatory HPV DNA PCR showed HPV16 in 94.9%, HPV18 in 1.7%, and HPV33 in 3.4%. 28 pts (45.2%) were low-risk and 34 pts (54.8%) were high-risk. 71.4% of low-risk pts received RT50 and 21.4% received CRT45. 70.6% of high-risk pts received CRT45. The pCR rate was 94.7% after RT50 and 89.3% after CRT45. Median follow-up is 1.5 years. The 2-year PFS and OS were both 100% for low-risk pts, and 93.5% and 97.0% for high-risk pts. A single in-field failure occurred in a high-risk pt 11 months after treatment with CRT45 and was surgically salvaged. Acute toxicity was significantly improved including grade ≥3 mucositis (15.8% RT50, 46.4% CRT45, 60.0% CRT75, $P = .033$) and grade ≥3 dermatitis (0% RT50, 21.4% CRT45, 30.0% CRT75, $P = .056$). Long-term PEG-tube dependency was also significantly improved (1-year rate: 0% RT50, 3.5% CRT45, 9.1% CRT75, $P < .0001$).

Conclusion: The use of 50 Gy limited-field RT alone in low-risk HPV+ pts or 45 Gy CRT in high-risk HPV+ pts with favorable response to induction chemotherapy resulted in excellent pCR and survival outcomes with reduced acute and late toxicity rates; long-term follow-up is ongoing.

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Initial Results from a Phase 2 Prospective Trial of De-intensified Chemoradiation therapy for Low-Risk HPV-associated Oropharyngeal Squamous Cell Carcinoma

B.S. Chera,[1] R.J. Amdur,[2] C. Shen,[3] X. Tan,[4] D.N. Hayes,[5] J. Weiss,[6] J. Grilley-Olson,[6] A. Zanation,[6] T. Hackman,[6] J.P. Zevallos,[7] S. Patel,[6] N.C. Sheets,[6] M. Weissler,[6] and W.M. Mendenhall[8]; *[1]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, [2]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [3]University of North Carolina, Chapel Hill, NC, [4]Lineberger Comprehensive Cancer Center, University of North Carolina*

Hospitals, Chapel Hill, NC, [5]UNC School of Medicine, Chapel Hill, NC, [6]University of North Carolina Hospitals, Chapel Hill, NC, [7]Washington University School of Medicine, St. Louis, MO, [8]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL

Purpose/Objective(s): To report initial results from a prospective phase 2 clinical trial of highly de-intensified chemoradiation therapy (CRT) for patients with favorable risk 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 with concurrent weekly intravenous cisplatin 30 mg/m^2 (second choice was cetuximab). Patients received neither induction chemotherapy nor definitive surgery. Patients with T0-T2 N0-1 disease did not receive chemotherapy (i.e. received 60 Gy alone). All patients had a 10- to 12-week posttreatment PET/CT to determine need for planned neck dissection. The primary study endpoint is 2-year progression-free survival (PFS). Secondary endpoint measures include 2-year local control (LC), regional control (RC), distant metastasis free survival (DMFS), and overall survival (OS), and patient reported symptoms (PRO-CTCAE) and quality of life (EORTC QLQ-C30 & H&N35). Data analysis was performed for patients with a minimum of 1 year of follow-up.

Results: One hundred and thirteen patients have enrolled, with 82 having a minimum follow-up of 1 year. Smoking status was as follows: 49% never, 35% $\leq$ 10 pack-years, and 16% $>$ 10 pack-years. Forty-four percent were HPV and p16 positive and 56% were HPV negative/unknown and p16 positive. Posttreatment PET/CT complete response rate was 97% at the primary site and 81% in the neck. Eight patients had planned neck dissection with 1 having pathological residual disease. Twoyear PFS, LC, RC, DMFS, CSS, and OS are the following: 93%, 98%, 99%, 95%, 96%, and 95%. Sixteen patients were treated with RT alone and all remain in cancer control. Mean pre- and 1-year posttreatment EORTC QOL scores were: Global 79/82 (lower worse), Swallowing 8/12 (higher worse), Dry Mouth 15/55 (higher worse), and Sticky Saliva 10/33 (higher worse). Of all patients, 39% patients required a feeding tube (none permanent) for a median of 10.5 weeks (range 3-42 weeks). Mean pre- and 1-year posttreatment PRO-CTCAE (0 to 4 scale, higher worse) scores were: Swallowing 0.5/0.9 and Dry mouth 0.5/1.6. There were no $\geq$ Grade 3 late adverse events.

Conclusion: Initial clinical outcomes with highly de-intensified CRT are excellent in favorable risk OPSCC with evidence of better preservation of quality of life compared to standard therapies (ClinicalTrials.gov, NCT02281955).

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Toxicity, Swallow Function, and Quality of life on MC1273, a Phase 2 Study of Dose De-escalation for Adjuvant Chemoradiation in HPV+ Oropharynx Squamous Cell Carcinoma

K. Price,[1] E.J. Moore,[2] R.L. Foote,[3] S.H. Patel,[4] M.L. Hinni,[5] A.V. Chintakuntlawar,[1] J.J. Garcia,[6] D. Graner,[7] M.A. Neben-Wittich,[3] Y. Garces,[3] C.L. Hallemeier,[3] J.L. Kasperbauer,[8] J.R. Janus,[9] K. Van Abel,[9] D.L. Price,[8] and D.J. Ma[3]; *[1]Division of Medical Oncology, Mayo Clinic, Rochester, MN, [2]Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN, [3]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, [4]Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, [5]Department of Otorhinolaryngology, Mayo Clinic, Phoenix, AZ, [6]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, [7]Department of Neurology, Mayo Clinic, Rochester, MN, [8]Department of Otolaryngology, Mayo Clinic, Rochester, MN, [9]Mayo Clinic, Rochester, MN*

Purpose/Objective(s): Adjuvant therapy for oropharynx squamous cell carcinoma (OPSCC) has rates for acute grade $\geq$3 dysphagia and late grade $\geq$2 toxicities of 37% and 55% (RTOG 0234). The goal of MC1273 is to determine if dose de-escalation to 30-36 Gy after surgery and neck dissection for patients (pts) with HPV+ OPSCC can maintain rates for disease control (primary endpoint) while reducing short and long-term side effects (secondary endpoints).

Materials/Methods: Eligible pts had p16+ OPSCC, $\leq$10 pack-year smoking, and R0 resection. Cohort A ($\geq$T3, $\geq$N2, lymphovascular invasion, or perineural invasion) received 30 Gy in 1.5 Gy BID over 12 days with weekly docetaxel (15 mg/m^2). Pts with +ECE (Cohort B) received the same treatment plus a boost to ECE+ nodal levels to 36 Gy in 1.8 Gy BID using a simultaneous integrated boost technique. Pts received a modified barium swallow impairment profile (MBSImP) at baseline (BL), 1 month (mo) post, and 12 mo post-RT. Pts also had patient-reported QOL assessments consisting of the University of Michigan Xerostomia QOL Scale (XeQOLS), Functional Assessment of Cancer Therapy-HN (FACT-HN), European Quality of Life (Eq)-5D, and EORTC-HN assessed at BL and 1, 3, 12, and 24 mo post−radiation therapy (RT).

Results: Accrual was 9/2013 − 6/2016 (n= 80, A: 37, B: 43). Median follow-up was 24 mo. No pts have died or been lost to follow-up. Grade 1/2/$\geq$3 toxicity rates at BL (post-op, n=78), 1 mo (n=78), 3 mo (n=78), 12 mo (n=71), and 24 mo (n=29) were 60%/12%/3%, 86%/15%/6%, 82%/17%/3%, 72%/1%/0%, and 59%/10%/0%. All grade $\geq$3 toxicity occurred by 3 mo and resolved by 6 mo. One pt had a grade 4 infusion reaction to docetaxel that resolved with treatment. Common late grade 2 toxicities were xerostomia and lymphedema (5%), and dysphagia, fatigue, and dysgeusia (3%). No pts required a feeding tube (PEG) due to RT. Oral swallow study scores worsened from BL to 1 mo post RT (n=76; 1.5±1.9 to 2.0±2.2, P=.0476) but recovered at 1 year post RT (n=61; 1.5±1.9 to 1.5±1.8, P=.68). For pharyngeal swallow, scores were stable from BL to 1 mo post RT (n=76; 5.8±3.9 to 5.8±3.7, P=.9176) and significantly improved by 1 year (n=61; 5.8±3.9 to 4.7±3.6, P=.0194). Evaluable pts for QOL endpoints were 78 (BL), 66 (1 mo), 67 (3 mo), 53 (12 mo), and 25 (24 mo). Only the XeQOLs worsened at 1 and 3 mo post-RT (P<.0001) while the EORTC-HN, FACT-HN, and Eq-5D remained unchanged or improved (table).

Abstract 7; Table 1

QOL tool	BL	1 mo	3 mo	12 mo	24 mo
XeQOLS	69.8±7.9	65.5±8.0	65.8±8.4	70.2±6.4	70.6±4.9
FACT-HN	117.5±17.9	119.7±16.2	124.8±16.1	127.4±17.7	131.8±13.1
Eq-5D	13.6±1.3	14.0±1.4	14.2±1.2	14.5±0.9	14.4±1.2
EORTC-HN	107.1±11.3	105.8±9.0	108.6±8.7	111.3±9.5	112.6±6.1

Conclusion: Adjuvant dose de-escalation to 30-36 Gy resulted in low toxicity, no late grade $\geq$3 toxicity, no decline in swallow function or QOL, and no PEGs.

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Oral Abstract Session

LBA1

Circulating Tumor HPV16 DNA as a Biomarker of Tumor Genomics and Disease Control in HPV-associated Oropharyngeal Squamous Cell Carcinoma

G.P. Gupta,[1] S. Kumar,[1] D. Marron,[1] R.J. Amdur,[2] D.N. Hayes,[1,3] J. Weiss,[4] J. Grilley-Olson,[4] A. Zanation,[4] T. Hackman,[4] J.P. Zevallos,[5] S. Patel,[4] M. Weissler,[4] J.S. Parker,[1] W.M. Mendenhall,[2] and B.S. Chera[6]; *[1]The University of North Carolina, Chapel Hill, NC, [2]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [3]West Cancer Center, University of Tennessee, Memphis,*

TN, [4]University of North Carolina Hospitals, Chapel Hill, NC, [5]Washington University School of Medicine, St. Louis, MO, [6]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC

Purpose/Objective(s): To quantify HPV16 copies in plasma circulating tumor DNA (ctDNA) from patients with favorable risk, HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) during the receipt of de-intensified chemoradiotherapy (CRT) on a prospective phase II clinical trial (NCT02281955).

Materials/Methods: The major inclusion criteria were: 1) T0-T3, N0-N2c, M0, 2) HPV or p16 positive (tumor sample), and 3) minimal/moderate smoking history. De-intensified CRT consisted of 60 Gy intensity modulated radiotherapy with concurrent weekly intravenous cisplatin (30 mg/m^2). Blood specimens were collected at baseline and weekly during CRT for plasma circulating nucleic acid extraction (Qiagen). A Taqman assay targeting the HPV16 E6 gene was developed and implemented on the Bio-Rad QX100 droplet digital PCR (ddPCR) platform. Tumor genomic analyses were performed using a hybrid capture next generation sequencing assay that included probes targeting high-risk HPV strains. A bioinformatics pipeline was developed to quantify normalized HPV counts and to determine the high-risk HPV strain that was most abundantly represented in each sample.

Results: Plasma HPV16 ctDNA was analyzed for 47 patients who completed 6 weeks of de-intensified CRT. Pre-treatment plasma ctDNA quantification by ddPCR stratified patients into three groups: undetectable HPV16 ctDNA (10/47 patients, 21%), low HPV16 ctDNA (12/47 patients, 26%, mean 69 copies/mL, range 29-118 copies/mL), and high HPV16 ctDNA (25/47 patients, 53%, mean 3924 copies/mL, range 257-22,684 copies/mL). Baseline HPV16 ctDNA levels did not correlate with T stage, N stage, or smoking status. Analysis of matched tumor genome sequencing for a subset of 25 patients revealed a strong correlation between tumor HPV copy number and plasma HPV16 ctDNA levels ($p = 0.0037$). Non-HPV16 strains were detected in 27% (3/11) of tumor biopsies with undetectable or low plasma HPV16 ctDNA, compared to 0% (0/14) among patients with high plasma HPV16 DNA ($p = 0.07$). The 1-year actuarial rate of freedom from persistent or recurrent disease after de-intensified CRT was significantly higher in patients with high versus undetectable/low baseline HPV16 ctDNA levels (100% vs. 83%, $p = 0.046$). The majority of patients with high baseline HPV16 ctDNA converted to undetectable by week 6 of CRT (81%), with a subset of "early responders" who cleared HPV16 ctDNA by week 4 (42%).

Conclusion: Plasma HPV16 ctDNA is detectable in the majority of favorable risk HPV-associated OPSCC, and may be a clinically useful biomarker of disease control in the setting of de-intensified CRT. Specifically, undetectable or low HPV16 ctDNA may reflect adverse tumor genomics, including an increased prevalence of non-HPV16 high-risk strains.

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A Phase 2 Trial of Cabozantinib for the Treatment of Radioiodine-Refractory Differentiated Thyroid Carcinoma in the First-Line Setting

M.S. Brose,[1] S. Shenoy,[1] N. Bhat,[1] A.K. Harlacker,[1] R.K. Yurtal,[1] Z.A. Posey,[1] D.M. Torrente,[1] C. Grande,[1] C.M. Squillante,[2] A.B. Troxel,[3] and M. Yarchoan[4]; *[1]University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, [2]MD Anderson Cancer Center at Cooper, Camden, NJ, [3]NYU School of Medicine, New York, NY, [4]Johns Hopkins University, Baltimore, MD*

Purpose/Objective(s): Cabozantinib is a multi-tyrosine kinase inhibitor targeting VEGF receptor kinase, RET, MET, and AXL. We participated in a phase 1 study which suggested activity in the radioiodine (RAI)-refractory patients that had previously been treated with one or more VEGF receptor inhibitors or other therapy. To further understand the activity of this agent in differentiated thyroid cancer, we conducted a single-arm open-label phase 2 study of cabozantinib in patients in the first-line setting with metastatic, RAI-refractory thyroid carcinoma (clinicaltrials.gov: NCT02041260).

Materials/Methods: Patients with metastatic, RAI-refractory, unresectable, or locally-advanced thyroid cancer were administered cabozantinib 60 mg orally QD. Responses were monitored by PET at 4 weeks and CT every 2 months. The primary outcome was response rate (RR) and secondary outcomes included progression-free survival (PFS), time to progression (TTP), duration of response and clinical benefit rate.

Results: Since March 2014, 35 patients were treated on study. Study accrual was completed in August 2017. The median time on study is 19.5 weeks. Median age is 65 years (range 45 to 84); 17 pts (49%) are male. Of these patients 22 (63%) have papillary, 3 (9%) have Hürthle cell, and 10 (29%) patients have poorly differentiated histology. Among the 30 patients who are evaluable for response, partial response (PR) was achieved in 16 (53%) patients with a duration of response of 11 to 174+ weeks. Fourteen (47%) had stable disease (SD) with a duration of response of 8 to 119+ weeks. Median PFS has not been reached. Among the four patients who progressed, the median time to disease progression was 35 weeks. Eighteen patients remain on study. Cabozantinib was well-tolerated with dose interruptions and dose adjustments as needed; the most common treatment-related adverse events included fatigue, weight loss, deep vein thrombosis, pulmonary embolism, hypertension, diarrhea, and mucositis.

Conclusion: This is the first study to document the antitumor activity of cabozantinib in patients with RAI-refractory differentiated thyroid cancer in the first-line setting with an overall response rate of 53% and warrants further investigation in this patient population.

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Multicenter Phase 2 Trial of *C*is/Carboplatin, *nAb*-Paclitaxel, and *Ce**TUX**i*mab (*CACTUX*) as First-Line Therapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

D. Adkins,[1] J. Ley,[2] O. Atiq,[3] C. Rigden,[2] K. Trinkaus,[2] T.M. Wildes,[2] and P. Oppelt[4]; *[1]Washington University in St. Louis, Department of Medical Oncology, St. Louis, MO, [2]Washington University School of Medicine, St. Louis, MO, [3]University of Arkansas for Medical Sciences, Little Rock, AR, [4]Washington University School of Medicine, St. louis, MO*

Purpose/Objective(s): Standard first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC) is 5-FU, cetuximab and platin (EXTREME). The EXTREME regimen resulted in a median progression-free survival (PFS) of 5.6 months, tumor response rate (RR) 36%, and overall survival (OS) 10.1 months. The risk of grade 4 adverse events (AEs) was 31%. More effective and less toxic regimens are needed. In this multicenter phase 2 trial, we hypothesized that substitution of 5-FU in EXTREME with *nab*-paclitaxel would increase the median PFS from 5.6 (historical) to 7.6 months (35% increase, power 0.80, $P = .05$, one-sided test, $N = 70$ patients).

Materials/Methods: Patients with incurable RM-HNSCC were treated with the CACTUX regimen as first-line therapy: *nab*-paclitaxel (100 mg/m^2/week), cetuximab (400 mg/m^2, then 250 mg/m^2/week), and carboplatin (AUC 5, Day 1) or cisplatin (75 mg/m^2, Day 1) in three-week cycles x 6, then maintenance *nab*-paclitaxel (Days 1, 8) and cetuximab (weekly) until disease progression. Tumor response assessments (RECIST 1.1) were

performed every two cycles. Efficacy endpoints included PFS, RR and OS. AEs were graded using CTCAE v3.0.

Results: Thirty-two patients were the subject of this planned interim analysis. Patient/tumor characteristics included a median age of 58 years, HPV-related oropharynx (19 patients), and HPV-unrelated HNSCC (13 patients). The median PFS was 6.3 months (95% CI: 4-9.4), RR of 50% and median OS was 18.4 months. Current status: alive without progression (8 patients), alive with progression (7), and expired (17). Grade 4 AEs occurred in 6 patients (19%). Only seven patients (22%) received PD-1 inhibitor immunotherapy (IT) after progression: median PFS with IT was 2.2 months (range 0.3-9.5).

Conclusion: The CACTUX regimen resulted in a median PFS of 6.3 months and RR of 50%. The median OS of 18.4 months is the highest ever reported with first-line therapy for patients with incurable RM-HNSCC.

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The Negative Impact of Longer Delays to Starting Radiation after Surgery for Head and Neck Cancer Patients in the United States

J.P. Harris,[1] M.M. Chen,[2] R.K. Orosco,[3] D. Sirjani,[3,4] V. Divi,[5] and W. Hara[1]; *[1]Stanford Radiation Oncology, Stanford, CA, [2]Stanford University, Stanford, CA, [3]Stanford Otolaryngology, Stanford, CA, [4]Palo Alto Veterans Affairs Health Care System, Palo Alto, CA, [5]Department of Otolaryngology—Head and Neck Surgery, Stanford University, Stanford, CA*

Purpose/Objective(s): For patients with head and neck cancer, the National Comprehensive Cancer Network recommends keeping the time from surgery to radiation ($T_{S\text{-}RT}$) under 6 weeks when adjuvant therapy is given. However, an associated survival benefit remains controversial. We set out to explore the effect of a delayed $T_{S\text{-}RT}$ for patients in the US.

Materials/Methods: Patients with squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, and larynx treated with definitive surgery followed by adjuvant radiation between 2004-2013 were identified from the National Cancer Database. Overall survival (OS) was compared according to a 6-week $T_{S\text{-}RT}$ cutoff. The effect of ≤42 day, 43-49 day, or ≥50 day $T_{S\text{-}RT}$ was tested using multivariate Cox regressions controlling for socioeconomic variables, comorbidity, clinicopathologic risk factors, type of facility, distance travelled, time from diagnosis to surgery, length of hospital stay, unplanned hospital readmissions, chemotherapy, radiation dose, and use of IMRT. The effect of accelerated fractionation (≥5.2 fractions/week) was tested according to length of $T_{S\text{-}RT}$.

Results: We identified 42,740 patients. Median OS was greater for the 19,859 (46%) patients with a ≤6 week $T_{S\text{-}RT}$ (10.0 years vs 7.7 years, $P < .0001$). Compared to a ≤42 day $T_{S\text{-}RT}$, there was no significant increase in mortality with a 43-49 day $T_{S\text{-}RT}$ (HR 1.03, $P = .19$), although there was for a ≥50 day $T_{S\text{-}RT}$ (HR 1.11, $P < .0001$). Compared to patients who had both surgery and radiation at an academic center, those who transferred care after surgery at an academic hospital (HR 1.12, $P = .0001$), or had all care at a Comprehensive Community Cancer Program (HR 1.06, $P = .01$) or all care at a community center (HR 1.08, $P = .03$) had inferior OS. For patients with a >6 week $T_{S\text{-}RT}$, accelerated fractionation was associated with improved OS (HR 0.92, $P = .02$), and for those with a ≤6 week $T_{S\text{-}RT}$ there was a trend for improved OS (HR 0.93, $P = .08$).

Conclusion: A $T_{S\text{-}RT}$ delayed >7 weeks is associated with worse overall survival. Treatment at academic centers may be associated with improved outcomes, and the benefit to care at specialized centers should continue to be explored. Treating teams should focus on shortening $T_{S\text{-}RT}$, and unavoidable delays may warrant consideration of accelerated fractionation or other dose intensification strategies.

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Panitumumab-IRDye800 as an Optical Agent for Image-Guided Surgery in Patients With Squamous Cell Carcinoma

R.W. Gao,[1] N. Teraphongphom,[2] N.S. van den Berg,[2] S. Hong,[2] B.A. Martin,[3] V. Divi,[2] M.J. Kaplan,[2] R. Ertsey,[2] N.J. Oberhelman,[2] G. Lu,[2] C.S. Kong,[3] A.D. Colevas,[4] and E.L. Rosenthal[2]; *[1]Stanford University School of Medicine, Stanford, CA, [2]Department of Otolaryngology—Head and Neck Surgery, Stanford University, Stanford, CA, [3]Department of Pathology, Stanford University, Stanford, CA, [4]Division of Medical Oncology, Stanford University, Stanford, CA*

Purpose/Objective(s): To determine the safety, sensitivity, and specificity of a fluorescently-labeled, epidermal growth factor receptor (EGFR) antibody for real-time, intraoperative guidance of surgical resections of head and neck cancer.

Materials/Methods: We conducted an open-label, dose escalation clinical trial of panitumumab-IRDye800 in 15 patients with squamous cell carcinoma (SCC) arising from the head and neck. All adult patients with biopsy-confirmed primary or recurrent SCC scheduled to undergo standard-of-care surgery with curative intent were eligible for inclusion. Patients with QT prolongation on pretreatment electrocardiogram (ECG), previous infusion reactions to monoclonal antibodies, or significant liver or cardiovascular disease were excluded. Cohort 1 (n=3) received an intravenous microdose of 0.06 mg/kg 2-5 days prior to surgery. Cohort 2A (n=5) received 0.5/kg, and cohort 2B (n=7) received 1mg/kg. Patients were followed for 30 days after infusion, and adverse events were recorded. Real-time, in vivo imaging was performed intraoperatively with a handheld and a bedside wheeled device. Ex vivo imaging was performed with a close-field fluorescence imaging device during pathological evaluation. Fluorescence locations and intensities were then histologically correlated with tumor location to determine the sensitivity and specificity of study drug targeting.

Results: No dose-limiting toxicities occurred, and only 1 grade 1 adverse event was observed. Intraoperative imaging showed clear demarcation between tumor and normal tissue, and ex vivo imaging findings also correlated well with intraoperative findings. Cohort 1 was not analyzed, as it was primarily to establish safety. The average tumor-to-background ratio (TBR) was 9.96 ± 1.30 for cohort 2A and 8.85 ± 1.26 for cohort 2B. Correlation of fluorescence intensities with tumor location resulted in a sensitivity and specificity of 80.0% and 94.8% for cohort 2A, and 83.7% and 72.1% for cohort 2B. Positive predictive value was 42.7% in cohort 2A and 20.6% in cohort 2B, and negative predictive value was 96.5% and 99.5%, respectively. EGFR expression was also found to be positively correlated with fluorescence intensity.

Conclusion: Preliminary results from this first, in-human trial using panitumumab-IRDye800 suggests that is a highly specific and sensitive optical imaging agent to aid in real-time detection and surgical resection of SCC.

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Multi-institutional Analysis of Next Generation Sequencing of Cell Free Circulating Tumor DNA of Blood Samples from Recurrent and Metastatic Head and Neck Cancer Patients

A. Porter,[1] M. Natsuhara,[2] A.G. Sacco,[3] G. Daniels,[3] S. Patel,[3] M. St.John,[4] R.K. Chin,[5] K. Banks,[6] J. Bykowski,[7] E. Cohen,[3] and D.J. Wong[8]; *[1]UC San Diego, Moores Cancer Center, Department of Hematology/Oncology, San Diego, CA, [2]UC San Diego, San Diego, CA, [3]UC San Diego, Moores Cancer Center, Department of Hematology/Oncology, La Jolla, CA, [4]UCLA David Geffen School of Medicine, Department of Head and Neck Surgery, Los Angeles, CA, [5]UCLA David Geffen School of Medicine, Department of Radiation Oncology, Los Angeles, CA, [6]Guardant Health, Redwood City, CA, [7]UC San Diego, Department of Radiology, San Diego, CA, [8]UCLA David Geffen School of Medicine, Department of Medicine, Division of Hematology/Oncology, Los Angeles, CA*

Purpose/Objective(s): Head and neck squamous cell carcinoma (HNSCC) is an increasingly prevalent disease but effective targeted therapy is lacking. The use of next-generation sequencing (NGS) in the identification of novel targets has been suggested as a way to potentially expand therapeutic options and thereby improve outcomes. We designed a retrospective study to further characterize the results of blood sample sequencing in recurrent and metastatic (R/M) head and neck cancer (HNC) patients, to determine its ability to identify actionable mutations, and also to further elucidate the utility of liquid biopsies and its role in patient management.

Materials/Methods: Using Guardant360, a 70-gene circulating tumor DNA (ctDNA) NGS platform, molecular profiling of blood samples was obtained from patients with recurrent and metastatic (R/M) head and neck cancers. ctDNA sequencing data was compared to tumor NGS data, when available. Best response to therapy was assessed using RECIST.

Results: Eighty-eight HNSCC patients were evaluated from February 2015 to February 2017. The most common tumor type and histology was oropharyngeal squamous cell carcinoma (n=23), which was commonly human papillomavirus (HPV) positive (n=17). Other cancer types included nasopharyngeal, salivary gland, and thyroid cancers. The most common mutations identified by ctDNA analysis were TP53 (51%) PIK3CA (25%), NOTCH1 (14.8%), and ARID1A (14.8%). Of the 29 matched tumor samples, TP53 (48%) and PIK3CA (24%) were also reported with the highest frequency. Eighty-seven percent of HNSCC, 67% of NPC, 75% of thyroid, and 63% salivary gland cancer patients had actionable mutations. Among these, 10.2% (n=9) received matched targeted therapy (MTT): 1 (11%) had partial response (PR), 5 (56%) had stable disease (SD), and 3 (33%) had progressive disease (PD). Thirty-six (40.9%) patients received immunotherapy: 1 (2.8%) had complete response, 3 (8.3%) had partial response, 15 (41.7%) had stable disease, 16 (44.4%) had progressive disease, and 1 patient is not yet evaluable.

Conclusion: Alterations identified by ctDNA may help inform management decisions in R/M HNSCC. The majority of patients had unique mutations identified on ctDNA. TP53 and PIK3CA mutations were seen at the highest frequency in both ctDNA and matched tumor samples. The utility of ctDNA NGS and its role in patient management should be explored in future studies.

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HPV Structure and Integration Impact the Genomic Profile of HPV-Positive Oropharyngeal Squamous Cell Carcinoma

A. Mazul; *University of North Carolina, Chapel Hill, NC*

Purpose/Objective(s): Although smoking and drinking rates have fallen, oropharyngeal cancer rates have been on the rise due to Human Papillomavirus (HPV). However, to date, few genomic studies have been conducted on primary tumors. The objective of this study is to examine the mutational, structural, and viral profiles for HPV-positive oropharyngeal squamous cell carcinomas (OPSCC).

Materials/Methods: HPV-positive oropharyngeal squamous cell carcinoma samples were obtained from multiple institutions. To be included in the study, tumors must be HPV16 positive and have evidence of HPV to HPV or HPV to chromosomal integration. Tumors with more than 100 HPV16 per million reads were classified as HPV16 positive. DNA was sequenced using hybrid capture technology and Illumina brand paired-end sequencing on the HiSeq2000/2500 and NextSeq500. We focused on 24 genes most commonly mutated genes in head and neck cancer (*AJUBA, CASP8, CCND1, CDKN2A, CUL3, FAT1, FBXW7, FGFR1, FGFR2, HLA-A, HRAS, KMT2C, KMT2D, KRAS, NFE2L2, NOTCH1, NOTCH2, NSD1, PIK3CA, PIK3R1, PTEN, RB1, TGFBR2, TP53, TRAF3*).

Results: A total of 150 HPV-positive OPSCC tumors were included in the study. The most commonly mutated gene was *PIK3CA* (31%), followed by *KMT2D* (24%) and *KMT2C* (22%). There was no statistical difference in the mutational profile between HPV-positive smokers and non-smokers or by pack-year status. HPV genomic integration was observed in 53% (N = 79) of the tumors with the remaining 71 tumors having HPV to HPV integration and classified as episomal. We demonstrate a significant difference in HPV viral read count by integration status; tumors with HPV integration have lower counts of corrected HPV reads (median: 14,598 HPV16 per million reads (Q1-Q3: 2,260-32,825) compared with those with episomal HPV (median: 28,386 HPV16 per million reads (Q1-Q3: 18,723-44,208) ($P < .001$). Although not statistically significant, tumors with HPV integration were more likely (40.5%) to have PIK3CA mutations compared to episomal tumors (25.4%). PIK3CA mutations occurred most commonly in the helical domain (73.4%), followed by kinase domain (10.7%), ABD domain (10.7%), and C2 (5.4%). Tumors with HPV integration were significantly more likely to have helical domain mutations, with 68% of helical domain mutations occurring in integrated cases. There is no association between PIK3CA mutation location and smoking status and corrected HPV read count.

Conclusion: HPV physical state and structure contribute significantly to the mutational profile of HPV-positive OPSCC, particularly with respect to PIK3CA mutational characteristics. These findings demonstrate the potential importance of examining HPV-host tumor interactions as prognosticators in HPV-positive OPSCC.

Author Disclosure: **A. Mazul**: None.

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Whole-Exome Sequencing of Aggressive Cutaneous Head and Neck Squamous Cell Carcinoma

M. Mierzwa,[1] J. Biesiada,[2] X. Zhang,[2] D. Kuhnell,[2] K.P. Redmond,[2] B. Huth,[2] V. Takiar,[2] T. Wise-Draper,[2] N.Hashemi Sadraei,[2] A. Tang,[2] J. Mark,[2] K. Casper,[3] M. Medvedovic,[2] and S. Langevin[2]; *[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]University*

of Cincinnati, Cincinnati, OH, [3]Department of Otolaryngology, University of Michigan, Ann Arbor, MI

Purpose/Objective(s): Cutaneous squamous cell carcinoma of the head and neck (cHNSCC) is a common malignancy in the United States strongly associated with exposure to ultraviolet radiation. Surgical resection is curative in the vast majority of cases, but 15% of patients with cHNSCC exhibit aggressive features with a propensity for locoregional recurrence, distant metastasis, and poor prognosis. Several large-scale whole-exome sequencing studies have provided valuable insight into the mutational landscape of mucosal HNSCC but such information is much more limited for cHNSCC. To address this deficiency, we performed exome-sequencing of cHNSCC to further elucidate potential driver mutations of cHNSCC and bolster our understanding of the molecular underpinnings of these aggressive malignancies.

Materials/Methods: We obtained OCT-embedded tumor tissue and paired blood samples from 21 cases with aggressive cHNSCC from our institutional tumor bank, including tissue from 10 primary tumors, 2 nodal metastases, and 11 recurrent tumors. Genomic DNA (200 ng) was extracted from each sample using the DNeasy Blood & Tissue kit (Qiagen) according to the manufacturer's suggested protocol for purification of total DNA from human tissue and blood, respectively, and sheared to 150-200 bp. The sequencing library was prepared using the Agilent SureSelect Human All Exon V6 Target Enrichment System. Clustered libraries were paired-end sequenced for 2′100 cycles on an Illumina HiSeq platform. Sequencing reads were demultiplexed and mapped to the GRCh37/hg19 human genome assembly using the Burrows-Wheeler aligner. Point mutations were detected via MuTect2 and insertion/deletions were identified via Indelocator using the Genome Analysis Toolkit. Intronic and silent mutations were filtered out prior to reporting. Significantly mutated genes were identified using MutSigCV v.1.41 with significance considered where $P < .001$.

Results: The average depth of coverage was 96.5′. The most common significantly mutated genes were *CSMD3* (18/21 tumors; 85.7%), *TP53* (17/21 tumors; 81.0%), *NOTCH1* (14/21 tumors; 66.7%), and *COL1A2* (13/21 tumors; 61.9%). Moreover, five of the significantly mutated genes previously reported by Pickering et al. (2014) were further validated by our study: *TP53* ($P = 7.77'10^{-16}$), *NOTCH1* ($P = .001$), *NOTCH2* ($P = 0.007$), *FAT1* ($P = .04$), and *CDKN2A* ($P = .02$). The combined fraction of tumors across both studies (n = 60) that harbored a mutation in each of these genes was 90.0%, 61.7%, 48.3%, 45.0%, and 33.3%, respectively.

Conclusion: We were able to validate several previously identified driver mutations, as well as identify novel putative driver mutations, thus advancing our understanding of the somatic mutations involved in the genesis of cHNSCC.

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Galectin-1 Orchestrates Immune Evasion in Head and Neck Cancer by Suppressing T Cell Recruitment to Tumors

D. Nambiar,[1] T.A. Aguilera,[1] J.D. Bloomstein,[1] H. Cao,[1] A.C. Koong,[2] and Q.T. Le[3]; *[1]Stanford University, Stanford, CA, [2]MD Anderson Cancer Center, Houston, TX, [3]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA*

Purpose/Objective(s): It is now appreciated that head and neck cancers (HNCs) display ahighly immune suppressive microenvironment which enables disease development and progression. Concomitantly, recent trials using immune checkpoint inhibitors which reinvigorate the immune system have shown significant benefit in patients. However, these therapies work only in a small number of patients with tumors showing significant T cell infiltration. Characterizing tumor secreted factors which aid immune evasion is highly pertinent to improving treatment response. From our previous studies, we have demonstrated that Galectin-1 (Gal-1) is secreted at high levels in HNCs, which correlates directly to disease progression. Through this study, we aimed to decipher in detail the role of Gal-1 in immune evasion, thereby augmenting cancer progression.

Materials/Methods: Utilizing the CRISPR/Cas9 system, we generated syngeneic models of HNC with/without Gal-1 in HPV negative (MOC1 and MOC2) as well as HPV+ (MEERL) mouse cells. The immune infiltration in tumors was characterized using multicolor flowcytometry. For studying in vitro/vivo migration of T cells, transendothelial migration and adoptive T cell transfer was performed. Blocking antibodies against Gal-1 and PD-1 were also used to study treatment response in the tumors. Lymph node and spleen and peripheral blood were also analyzed to study effect of Gal1 on systemic immune response.

Results: In vivo subcutaneous and orthotopic tumor growth studies showed that Gal-1 KO (knock-out) tumors exhibited marked decrease in tumor growth as well as nodal/lung metastases. These differences were associated with enhanced infiltration of $CD4^+$ and $CD8^+$ T cells in the absence of Gal-1. We show that the presence of Gal-1 in the tumor microenvironment strongly suppresses T cell infiltration into tumors. Further, we found Gal-1 mediated conditioning of tumor endothelium, involving enhanced expression of PD-L1 and Gal-9, was critical in suppressing lymphocytes infiltration. Blocking Gal-1 either genetically or by a blocking antibody led to pronounced effects on T cell infiltration and T cell activation in the lymph node and spleen. Using MOC-2 and MEERL models, which are non-responsive to anti-PD1 therapy, we show that blocking Gal-1 could convert these tumors into PD-1 responsive tumors with a significant decrease in tumor burden. Also, overexpressing Gal-1 in immunogenic MOC1 tumor led to enhanced tumor growth and metastases and immune evasive phenotype. Combining radiation and/or anti-PD1 treatment showed pronounced synergy with Gal-1 blockade.

Conclusion: In summary, our study shows Gal-1 in the tumor microenvironment could create an immune suppressive barrier to lymphocyte infiltration and poor-response to anti-PD1 therapy. Combinatorial approaches of Gal-1 inhibition immune/radiation therapy may enhance therapeutic efficacy in HNC.

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LBA2

Withdrawn

Poster Presentations

LBA3

Withdrawn

LBA4

Prognostic Significance of HPV Positivity and Tobacco Use on Oropharyngeal Squamous Cell Carcinoma Survivorship

P. Morgan, A. Kompelli, W. Harris, R. Boruki, T. Day, and D. Neskey; *Medical University of South Carolina, Charleston, SC*

Purpose/Objective(s): Approximately 12,000 cases of oropharyngeal squamous cell carcinoma (OPSCC) are diagnosed each year in the United States. Historically, these cancers have had a strong association with chronic alcohol and tobacco use. However, recently HPV has been implicated and currently accounts for over 70% of the newly diagnosed cases each year. The prognostic significance of HPV is clear, which has led to significant changes in the 8th Edition of AJCC staging and to the ongoing clinical trials that are investigating de-escalation therapy for patients with HPV related disease. In contrast, the prognostic impact of certain pathologic features, such as extracapsular extension (ECE), perineural invasion (PNI), and lymphovascular invasion (LVI) remains unclear and requires further investigation, particularly in patients with HPV related OPSCC and chronic tobacco use. Therefore, the goal of this study is to determine the prognostic impact of high-risk pathologic features in patients with HPV+ OPSCC who have a history of smoking. We hypothesize that patients with a history of smoking tobacco and adverse pathologic features will have decreased survival outcomes and will be more likely to recur relative to the patient cohort who never smoked.

Materials/Methods: Retrospective chart review of 550 patients treated for oropharyngeal SCC at a tertiary care cancer center from 2008 to 2016. The primary outcome measures were overall and disease-free survival. The endpoints assessed were clinical and pathologic T and N stage, AJCC stage (7e), cigarette pack years, alcohol use, and presence of extracapsular extension (ECE), perineural invasion (PNI), or lympohvascular invasion (LVI). We investigated what pathologic features were associated with decreased survival in both long-term smokers (>20 pack years), compared to short-term/nonsmokers.

Results: Of the 550 patients analyzed, 202 were HPV positive and had a detailed smoking history available. Of these patients, 136 had less than 20 pack years, and 66 had greater than 20 pack years (heavy smokers). In long-term smokers with HPV+ tumors, the presence of ECE ($P = .03$) and LVI ($P = .02$) were associated with significantly decreased overall survival (OS). Furthermore, the presence of ECE was associated with a significantly decreased OS in heavy smokers relative to <20 py ($P = .02$) in HPV+ patients. The decreased survival observed in heavy smokers with HPV+ disease and ECE or LVI was subsequently found to be similar to patients with HPV- tumors, LVI+ ($P = .137$) or ECE ($P = .142$).

Conclusion: In this series, HPV+ patients with a history of long-term tobacco use had a significantly worse OS in the presence of either LVI or ECE. The OS in this patient population was similar to that of patients with HPV- OPSCC. This series highlights the potential need for more aggressive therapy for HPV+ patients with extensive tobacco use in the presence of LVI or ECE.

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LBA5

Phase 2 Trial of Nivolumab, an Anti-PD-1 Monoclonal Antibody, as a Novel Neoadjuvant Pre-surgical Therapy for Locally Advanced Oral Cavity Cancer

J. Kaczmar,[1] A. Kompelli,[2] E. Graboyes,[3] J. Hornig,[2] E. Lentsch,[2] T. Day,[2] C. Paulos,[2] M.R. Young,[2] and D. Neskey[2]; [1]*Hollings Cancer Center, Charleston, SC, United States,* [2]*Medical University of South Carolina, Charleston, SC,* [3]*Medical University of South Carolina, Charleston, SC, United States*

Purpose/Objective(s): Over 300,000 patients develop squamous cell carcinoma of the oral cavity (OCSCC) worldwide and nearly half of these patients die from the disease each year. Treatment of OCSCC often requires complex, multimodality therapy, employing surgical resection followed by post-operative radiation, with the addition of cisplatin-based chemotherapy for patients with high-risk of failure. Despite these comprehensive treatment strategies, OCSCC recurs in 25% to 48% of patients. Given this poor prognosis, it is evident new strategies are needed to treat OCSCC. Neoadjuvant therapy is utilized in multiple cancers and has resulted in improved survival for patients with breast and esophageal cancer. Neoadjuvant chemotherapy prior to definitive surgery has been explored for the treatment of HNSCC with high rates of initial response ranging from 30% to 40%. Because of the combination for the need of new therapies and the benefits of a neoadjuvant treatment strategy, the possibility of immunotherapeutic approaches for HNSCC patients has gained interest.

Materials/Methods: This is an interim analysis of a Phase 2 investigator initiated trial of Nivolumab as a neoadjuvant pre-surgical therapy for patients with locally advanced OCSCC. The primary objective is to determine the pathological overall response rate of neoadjuvant Nivolumab and we hypothesize there will be a 25% to 30% overall response rate. The primary efficacy endpoint is objective response rate defined as pathologic complete response + pathologic partial response.

Results: The trial opened in May 2017 with an anticipated accrual of 17 patients. To date we have enrolled 2 patients. Both patients tolerated the treatment well and did not have dose limiting toxicities. The first patient presented with a 2.5 cm lateral tongue lesion in greatest dimension. Following 4 doses of Nivolumab she had a partial response with a 40% reduction in greatest dimension. The second patient is currently receiving her neoadjuvant therapy and after three doses has had stable disease.

Conclusion: Nivolumab as a neoadjuvant pre-surgical therapy for patients with OCSCC appears to be well tolerated and efficacious. Although these interim results are encouraging, the potential impact of pre-surgical neoadjuvant will not be determined until additional patients are enrolled. Furthermore, correlative studies derived from this ongoing trial will test the hypothesis that neoadjuvant pre-surgical PD-1 inhibition will trigger a memory phenotype in TIL and lead to epigenetic changes within both tumor and T cells that will correlate with clinical response and improved survival in patients with oral cancer.

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LBA6

WEE1 Kinase Inhibition Reverses DNA Damage Checkpoint Activation to Sensitize Oral Cancer Cells to Immunotherapy

C.T. Allen; *National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD*

Purpose/Objective(s): Most head and neck cancers harbor genomically altered *TP53*, resulting in dependence on G2/M DNA damage checkpoint activation for cell cycle control. Here, we describe G2/M DNA damage checkpoint activation as a tumor cell intrinsic mechanism of resistance to cytotoxic T-lymphocyte (CTL) killing.

Materials/Methods: In vitro and in vivo assays.

Results: Using oral cavity cancer cells that express the model antigen SIINFEKL and a real-time impedance-based CTL killing assay, we demonstrated that OT-I CTL specific for SIINFEKL presented on H-2K^b killed all tumor cells at an E:T ratio of 10:1 in a perforin/granzyme B dependent fashion. Killing of cancer cells at lower E:T ratios was enhanced in the presence of AZD1775, a small molecule inhibitor of WEE1 kinase, at low nanomolar concentrations. By mixing antigen-positive and -negative tumor cells, we modeled antigen escape with outgrowth of antigen-negative cells in the presence of 10:1 OT-I CTL. This outgrowth was independent of CTL exhaustion. Remarkably, OT-I CTL killing of antigen-negative tumor cells was also enhanced in the presence of AZD1775. Using depleting antibodies and CRISPR/Cas-9 gene editing, we mechanistically demonstrated that this bystander killing of antigen-negative cells in the presence of AZD1775 was

due to induction of apoptosis and necroptosis in tumor cells by OT-I CTL membrane bound TNFa. Bystander killing of antigen-negative tumor cells was not due to update of antigen released from antigen-positive tumor cells or antigen-MHC complex transfer between tumor cells. We demonstrated that tumor cell exposure to recombinant granzyme B and TNFa caused early and late cell cycle pause and G2/M accumulation, respectively, but minimal DNA damage or death. In the presence of AZD1775, similar insults resulted in significant DNA damage, DNA fragmentation, and cell death. *In vivo*, combination AZD1775 and PD-1 mAb immune checkpoint blockade (ICB) resulted in additive growth control of antigen-negative tumor cells. Conversely, combination AZD1775 and PD-1 mAb ICB synergistically induced rejection of all established antigen-positive tumors. When established tumors comprised of mixed antigen-positive and -negative tumor cells were treated, 80% of tumors with intact TNFR in the antigen-negative cells rejected, whereas tumors with TNFR deleted from the antigen-negative cells grew progressively.

Conclusion: These data suggest that tumor cells resist CTL killing by pausing their cell cycle to allow DNA repair, and that WEE1 kinase inhibition with AZD1775 can reverse this DNA damage checkpoint activation to enhance both antigen-positive and -negative tumor cells to CTL killing via different mechanisms. These results strongly support the clinical combination of AZD1775 and immunotherapy such as ICB.

Author Disclosure: **C.T. Allen**: None.

LBA7

Immunogenomic Correlates of Response to Cetuximab in Head and Neck Squamous Cell Carcinoma

D.L. Faden,[1,2] F. Concha-Benavente,[3] A. Bhaswanth Chakka,[4] and R.L. Ferris[1,2]; [1]*University of Pittsburgh Cancer Institute, Pittsburgh, PA,* [2]*Department of Otolaryngology, Division of Head and Neck Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA,* [3]*Department of Immunology, University of Pittsburgh, Pittsburgh, PA,* [4]*Department of Bioinformatics, University of Pittsburgh, Pittsburgh, PA*

Purpose/Objective(s): Immune evasion is a *sine qua non* for cancer development. Mechanisms of resistance to immune modulating therapeutics in cancer are poorly understood. Less than 20% of patients with HNSCC have a lasting response to cetuximab. We hypothesized that acquired somatic alterations may provide a mechanism of immune evasion in cetuximab failure. Here, using a novel cohort of HNSCC patients treated with neoadjuvant cetuximab, we investigated mechanisms of immune escape from cetuximab therapy.

Materials/Methods: 20 HNSCC tumors (9 non-responders, 11 responders) from a recently completed prospective trial of neoadjuvant cetuximab monotherapy with well annotated response data underwent whole exome sequencing. KIR expression on NK cells, HLA-C expression on HNSCC cells, IFNγ release from NK cells and tumor killing by the anti-KIR monoclonal antibody, lirilumab, were assessed in vitro.

Results: Potentially deleterious somatic alterations (missense mutations and LOH) in HLA-C in non-responders to cetuximab were statistically increased compared to responders and HNSCCs in the TCGA (Table 1). Canonical pathway analysis similarly identified NK cell signaling pathway genes as statistically overly-mutated. HLA-C is the ligand for KIR on NK cells, modulating activation versus latency. To explore this potential mechanism of resistance we examined the relationship between KIR expression and IFNγ release from NK cells, HLA-C expression on HNSCC cells and tumor killing in the presence of lirilumab. We found that NK cells from HNSCC patients maintain expression of KIRs and that cetuximab-activated NK cells induce upregulation of HLA-C on tumor cells, due to cetuximab induced IFNγ release. Blocking NK inhibitory KIR signaling with lirilumab increased cell killing of HNSCC cells.

Conclusion: Somatic alterations in HLA-C may provide a mechanism of immune evasion from cetuximab therapy through disruption of NK cell activation, as supported by the identification of somatic HLA-C alterations in patients who fail cetuximab therapy. In vitro assessment of KIR and HLA-C expression on HNSCC cells, as well as cell killing in the presence of KIR modulation, further support this hypothesis. These findings open the door for additional investigations into the role of HLA alterations in HNSCC and the potential use of HLA-C alterations as a biomarker for cetuximab therapy in HNSCC.

Abstract LBA7; Table 1

Cohort	HLA-C Mutation Rate	*P* value
Non-Responders	67%	<.00001
Responders	9%	
TCGA	2%	

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LBA9

Anti-tumor Effect of PD-L1 Inhibitor Durvalumab Administered Before Surgery in Patients With HPV+ vs HPV- HNSCC

M. Porosnicu,[1] J.D. Waltonen,[2] and P. Triozzi[3]; [1]*Wake Forest University School of Medicine, Winston Salem, NC,* [2]*Wake Forest University School of Medicine, Winston-Salem, NC,* [3]*Wake Forest Baptist Medical Center, Winston-Salem, NC*

Purpose/Objective(s): Immune check point inhibitors tested in neoadjuvant setting before definitive surgery reportedly presented an adequate safety profile and did not delay the surgery. In addition, the window study design offers the opportunity to investigate the tissue response to immunotherapy and to search for predictors of response. We propose to compare the clinical and tissue response in 20 patients with HPV+ versus HPV- HNSCC.

Materials/Methods: We propose to enroll 10 HPV+ and 10 HPV- patients with SCC of the oral cavity (OC) and of the oropharynx (OP) newly diagnosed who are surgically resectable and have an established surgery date that leaves a window of at least 21 days from the time of diagnosis. Patients must have tumor tissue banked for research before registration. Patients will be treated with the PD-L1 inhibitor Durvalumab 750 mg every 2 weeks. Tumor response will be measured with CT scans. PET scans pre- and post-treatment will be obtained in all possible cases. Tumor tissue will be collected from the surgical specimen. Blood and saliva will be collected before and after surgery. HPV, PD-L1 and genomic analysis of the tumor tissue will be performed in all patients. Primary endpoint is the evaluation of different aspects of the immune response measured in tumor, blood and saliva. Objective clinical and radiologic responses as well as safety data will be collected.

Results: Five patients were enrolled so far and 4 patients completed treatment. Two patients had OP and 3 patients had OC SCC. HPV was positive in both patients with OP tumor. Two patients received 2 administrations and 2 patients received 3 administrations of Durvalumab. Treatment was well tolerated and there were no delays in surgery. Treatment-related adverse events appeared in 1 patient: hyperthyroidism and increased amylase and lipase with no clinical symptoms. Both side-effects were encountered after surgery (4 weeks from the last administration of Durvalumab) and both resolved spontaneously. Tumor reduction in response to treatment was noticed in 2 patients and 2 patients had stable disease. Tissue before and after surgery was banked in all patients.

Conclusion: This is an ongoing clinical study. Enrollment and interim results will be updated at the time of presentation. Durvalumab has been well tolerated with no delays in surgery. Tumor tissue, blood and saliva collected before and after surgery are being analyzed for systemic immune response to HPV and tumor associated antigens and impact on immune regulatory mechanisms. Levels of immune-regulatory miRNA in plasma and saliva are being investigated as possible predictors of response. Results will be compared between HPV+ and HPV- patients to identify possible differential effect of treatment with Durvalumab.

Author Disclosure: **M. Porosnicu**: None. **J.D. Waltonen**: None. **P. Triozzi**: None.

LBA10

Two-year Update From CheckMate 141: Outcomes With Nivolumab (Nivo) vs Investigator's Choice (IC) in Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN) in the Overall Population and PD-L1 Subgroups

R.L. Ferris,[1] G.R. Blumenschein,[2] J. Fayette,[3] J. Guigay,[4] A.D. Colevas,[5] L. Licitra,[6] K. Harrington,[7] S. Kasper,[8] E.E. Vokes,[9] C. Even,[10] F. Worden,[11] N.F. Saba,[12] LCIglesias Docampo,[13] R.I. Haddad,[14] T. Rordorf,[15] N. Kiyota,[16] M. Tahara,[17] M. Lynch,[18] L. Li,[18] and M. Gillison[2]; *[1]UPMC Hillman Cancer Center, Pittsburgh, PA, [2]MD Anderson Cancer Center, Houston, TX, [3]Centre Leon Berard, Lyon, France, [4]Centre Antoine Lacassagne, FHU OncoAge, Nice, France, [5]Stanford University, Stanford, CA, [6]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy, [7]Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, London, United Kingdom, [8]West German Cancer Center, University Hospital, Essen, Germany, [9]University of Chicago Medical Center, Chicago, IL, [10]Gustave Roussy, Villejuif Cedex, France, [11]University of Michigan, Ann Arbor, MI, [12]Winship Cancer Institute of Emory University, Atlanta, GA, [13]Hospital Universitario 12 de Octubre, Madrid, Spain, [14]Dana-Farber/Harvard Cancer Center, Boston, MA, [15]Universitätsspital Zurich, Zurich, Switzerland, [16]Kobe University Hospital, Kobe, Japan, [17]National Cancer Center Hospital East, Kashiwa, Japan, [18]Bristol-Myers Squibb, Princeton, NJ*

Purpose/Objective(s): Nivo is the only immuno-oncology (I-O) agent to significantly improve overall survival (OS) in patients (pts) with R/M SCCHN who have progressed on or after platinum-based therapy and for whom long-term prognosis has historically been poor (median OS ≤6 mo). Here we report the first long-term (2-yr) data with immune checkpoint inhibition in pts with R/M SCCHN who have progressed on or after platinum-based therapy from the randomized, open-label, phase 3 CheckMate 141 study (NCT02105636).

Materials/Methods: Eligible pts were randomized 2:1 to nivo 3 mg/kg q2wk (n = 240) or IC (methotrexate, docetaxel, or cetuximab; n = 121). The primary endpoint was OS; other endpoints included progression-free survival (PFS) and safety. Minimum follow-up for the current analysis: 24.2 mo (data cut: Sep 2017).

Results: 2-yr OS rate (95% CI) was 16.9% (12.4, 22.0) with nivo versus 6.0% (2.7, 11.3) with IC. Nivo continued to improve OS significantly vs IC in the overall population (median [95% CI]: 7.7 [5.7, 8.8] mo vs 5.1 [4.0, 6.2] mo; hazard ratio (HR) [95% CI]: 0.68 [0.54, 0.86]). PFS remained similar between treatment arms. Outcomes by PD-L1 and HPV subgroups are shown in the Table 1. In pts with tumor PD-L1 <1%, risk of death at 2 yrs was reduced by 27% with nivo versus IC with the HR trending lower with longer follow-up; HR (95% CI) = 0.89 (0.54, 1.45), 0.83 (0.54, 1.29), and 0.73 (0.49, 1.09) at 6 mo (May 2016 data cut), 1 yr (Sep 2016 data cut), and 2 yrs of follow-up, respectively. Nivo also continued to improve OS versus IC in pts with tumor PD-L1 ≥ 1%. Grade 3-4 treatment-related adverse events occurred in 15.3% (nivo) versus 36.9% (IC) of pts; toxicity-related deaths in 2 pts (0.8%; pneumonitis and hypercalcemia) and 1 pt (0.9%; treatment-related lung infection), respectively.

Conclusion: With longer follow-up (2 yrs), nivo continued to significantly improve OS and maintained a favorable safety profile versus IC in the overall population in CheckMate 141. Nivo is the only I-O therapy to demonstrate OS benefit irrespective of PD-L1 status (<1% and ≥1%) in pts with SCCHN.

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LBA11

Impact of Tobacco Smoking on Mutational Landscape in HPV-Associated Oropharyngeal Cancer

J. Lilja-Fischer,[1,2] B. Ulhøi,[3] J. Alsner,[1] M. Stougaard,[3] P. Lassen,[4] T. Steiniche,[3] and J. Overgaard[1]; *[1]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Otorhinolaryngology - Head & Neck Surgery, Aarhus University Hospital, Aarhus, Denmark, [3]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark, [4]Department of Oncology and Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark*

Purpose/Objective(s): Oropharyngeal cancer (OPC) is now the most common form of head and neck cancer in many western countries due to HPV. Patients with HPV-related (HPV+) OPC have clearly better outcomes after treatment. This has led to a strong wish to individualize treatment for these patients, aiming to minimize morbidity as well as to increase survival. However, patients with HPV+ OPC and a significant history of former or current tobacco smoking (HPV+ smokers) have increased risk of locoregional failure and increased cancer mortality after radiation therapy-based treatment than do non-smokers with HPV+ OPC. These observations, recently confirmed in the MARCH-HPV meta-analysis of individual patient data, has led to the hypothesis that smokers with HPV+ OPC have altered disease biology, possibly through the additional accumulation of somatic tumor mutations through cumulative carcinogenic exposure. The aim of this study was to clarify whether

Abstract LBA10; Table 1 Outcomes by PD-L1 expression and HPV status

	Median OS (95% CI), mo			Median PFS (95% CI), mo		
	Nivo	IC	HR (95% CI)	Nivo	IC	HR (95% CI)
PD-L1 < 1%	6.5 (4.4, 11.7)	5.5 (3.7, 8.5)	0.73 (0.49, 1.09)	2.0 (1.9, 2.1)	2.7 (2.0, 4.6)	1.13 (0.75, 1.71)
PD-L1 ≥ 1%	8.2 (6.7, 9.5)	4.7 (3.8, 6.2)	0.55 (0.39, 0.78)	2.1 (2.0, 3.5)	2.0 (1.9, 3.1)	0.59 (0.41, 0.84)
HPV+	9.1 (6.5, 11.8)	4.4 (3.0, 9.8)	0.60 (0.37, 0.97)	2.0 (1.9, 3.3)	2.0 (1.6, 2.8)	0.75 (0.46, 1.23)
HPV−	7.7 (4.8, 13.0)	6.5 (3.9, 8.7)	0.59 (0.38, 0.92)	2.1 (1.9, 3.1)	3.3 (1.9, 4.0)	1.01 (0.65, 1.56)

HPV+ OPC consists of two different biological subgroups, and whether these could be related to tobacco smoking.

Materials/Methods: We included patients with primary, untreated oropharyngeal squamous cell carcinoma from 2 prospective protocols. Tumors were comprehensively characterized using targeted next-generation sequencing as well as analysis of gene expression related to HPV, hypoxia and radiosensitivity.

Results: 47 patients were included, of which 35 were HPV-positive. Seventeen patients had a history of significant tobacco smoking (≥10 pack-years). Sequencing revealed robust differences between HPV+ and HPV- tumors (*TP53*, $P < .0001$, $q = 0.002$). Also, we found a distinct mutational pattern with genes clustering according to HPV and smoking status, including *KMT2C*, *LTK*, *MET* and *BRAF*, although not reaching statistical significance in this hypothesis-generating study.

Conclusion: HPV+ OPC possibly consists of several biologic subgroups, related to tobacco smoking, explaining the diverse outcomes seen among these patients. These differences warrant further large-scale investigation, as they may inform of treatment sensitivity and serve as biomarkers to guide treatment allocation in future clinical trials.

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LBA12

Defects in NF-kB Pathway Genes Identify a Subset of HPV-associated HNSCC With Improved Survival

W. Yarbrough; *Yale University, New Haven, CT*

Purpose/Objective(s): Using the Cancer Genome Atlas (TCGA) data from the initial cohort of 244 HPV-negative and 35 HPV+ HNSCC, we identified that defects in TRAF3 and CYLD correlated with improved survival, HPV integration, and with activation of the NF-kB.

Materials/Methods: Here, we expanded our analyses to the entire TCGA HNSCC cohort of 463 HPV-negative and 65 HPV+ tumors. Kaplan Meier survival analysis confirmed our earlier findings that in the presence of TRAF3/CYLD mutations patients with HPV+ tumors had markedly improved survival compared to HPV+ tumors lacking mutations ($P = .03$) or HPV-negative tumors ($P = .005$). In fact, HPV+ tumors lacking mutations in TRAF3 or CYLD had survival that was indistinguishable from tumors lacking HPV ($P = .27$). Since additional mutations that lead to the activation of NF-kB have been described in multiple myeloma and nasopharyngeal cancer, we expanded analyses to 8 additional genes that regulate NF-kB (MAP3K14, BIRC3, TRAF2, BIRC2, MYD88, NFKB1A, TNFAIP3, and TRAF6) using a separate cohort of HPV+ HNSCC (n = 27).

Results: Sequencing of tumors found 2 tumors with mutations of MAP3K14 (NF-kappa-B-inducing kinase [NIK]) and 1 tumor each with mutations of BIRC3 and TRAF2. Sequencing from an additional patient revealed 2 mutations in CYLD (S467Ter, and Q716E) and a mutation in MYD88 (S219C). The MYD88 mutation has been recurrently reported in a variety of lymphoid and hematopoietic tumors and testing of this mutant revealed that it is an activating mutant of MYD88 that results in NF-kB activation. Most of these tumors were collected in the last two years, so survival analysis is premature. TCGA data from 65 HPV+ HNSCC revealed few mutations in these genes, but did show that BIRC2 and BIRC3 had deep deletions in 6% of tumors, that TRAF2 was altered in 5%, and that NFKB1A had deletion or truncating mutations in 3% of tumors. Together, these data show that defects in the NF-kB pathway in HPV+ HNSCC may not be limited to TRAF3 and CYLD in HPV-associated head and neck cancer.

Conclusion: HPV has been used as a surrogate of improved survival in HNSCC. Only smoking status has been shown to associate with worsening prognosis in these patients. Data presented here suggest that gene defects in NF-kB regulators are the first molecular markers that correlate with survival in HPV+ HNSCC. Identification of patients with improved survival may be useful to select patients for de-escalation of therapy.

Author Disclosure: **W. Yarbrough**: Provide input from medical professionals in order to continue to develop new technologies; Olympus Corporation.

LBA13

Larotrectinib Is Highly Active in Patients With Advanced Recurrent TRK Fusion Thyroid (TC) and Salivary Gland Cancers (SGC)

L. Wirth,[1] A. Drilon,[2] C. Albert,[3] A. Farago,[1] Wel-Diery,[4] P. Ma,[5] D. Sohal,[6] L. Raez,[7] C. Baik,[8] M.S. Brose,[9] R. Doebele,[10] M. Cox,[11] N. Ku,[11] and D. Hong[12]; *[1]Massachusetts General Hospital, Boston, MA, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]Seattle Children's Hospital, Seattle, WA, [4]Fox Chase Cancer Center, Philadelphia, PA, [5]West Virginia University, Morgantown, WV, [6]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [7]Memorial Cancer Institute, Pembroke Pines, FL, United States, [8]University of Washington/Seattle Cancer Care Alliance, Seattle, WA, [9]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, [10]University of Colorado, Aurora, CO, [11]Loxo Oncology, South San Francisco, CA, [12]M.D. Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): TRK fusions, involving the genes *NTRK1*, *NTRK2*, and *NTRK3*, occur in a broad range of malignancies, including TC and SGC. Larotrectinib is the first selective pan-TRK inhibitor in development, and has demonstrated an overall response rate (ORR) across various TRK-fusion solid tumors of 76% by investigator assessment (Hyman et al, JCO 2017) and an ORR of 75% by independent radiology review. Here we summarize the activity and safety of larotrectinib in advanced TRK-fusion TC and SGC.

Materials/Methods: 19 patients (age 15-75 years) with TRK-fusion TC (n = 7) or SGC (n = 12) were treated with oral larotrectinib (4 in the adult phase 1 study, 2 in the SCOUT global pediatric phase 1/2 study, and 15 in the NAVIGATE global phase 2 study). TRK fusions were identified by local testing. 16 patients received the dose equivalent of 100mg BID on a continuous 28d schedule; 1 patient each was treated with 150 mg BID, 100 mg QD, or 75 mg QD. 17 patients had measurable disease (5 TC and 12 SGC); efficacy was assessed by investigator (INV) and independent review (IRC) using RECIST v1.1.

Results: TC histologies included 6 differentiated (follicular and papillary), and 1 anaplastic. SGC histologies included 6 acinar/mammary analogue secretory carcinoma (MASC), 1 adenoid cystic, 1 adenocarcinoma, 1 mucoepidermoid, 1 sarcomatoid, and 2 NOS. In the 19 patients treated, 4 different fusion constructs were identified with 84% being ETV6-NTRK3 positive. Patients had received a median of 3 prior lines of therapy, including surgery (19), external beam radiation (14), I-131 (4), chemotherapy (8) and tyrosine kinase inhibitors (3). For the 17 patients with measurable disease, larotrectinib treatment resulted in an ORR of 88% by both INV and IRC (3CRs, 12PR, 2PD). ORR for TC was 100% (5/5PR) and ORR for SGC was 83 % (3CR/7PR) by both INV and IRC. Responses occurred within the first 2 months in 87% of patients. At the time of data cut off, treatment is ongoing in 89% of patients, with median follow-up of 10 months. Only 4 patients experienced a grade ≥3 treatment related AE.

Conclusion: TRK inhibition with larotrectinib yields durable high response rates, including CRs, in adolescents and adults with recurrent TRK fusion TC and SGC, regardless of histology. Prolonged larotrectinib therapy is associated with minimal toxicity. Genomic profiling with assays capable of identifying TRK fusions should be strongly considered in patients with recurrent TC and SGC when determining systemic treatment options.

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LBA14

Correlation of Subjective and Objective Swallowing Outcomes in Oral Cancers Following Free Flap Reconstruction

A. Wahi,[1] P. Kaul,[2] A. Bharthuar,[3] and S. Chopra[2]; [1]Patel Hospital, Jalandhar, India, [2]Patel Hospital, Jalandhar City, India, [3]Patel Hospital, Jalandhar, India

Purpose/Objective(s): There is consensus on surgical resection followed by indicated free flap reconstruction (FFR) being standard of care for resectable oral squamous cell carcinoma (OSCC). There exist multiple validated questionnaires for dysphagia; however, there is scant evidence of swallowing outcomes in this patient subset. Aims:

1. To evaluate the influence of patient, tumor, and treatment characteristics on post treatment dysphagia in OSCC patients post FFR.
2. To establish the accuracy of two separate validated dysphagia questionnaires in comparison with videofluoroscopy (VFS) in these patients.

Materials/Methods: Of 170 retrospectively evaluable Stage III-IV OSCC patients post FFR treated at our institution between December 2012 and April 2017; surviving, functional and intelligible patients were contacted about their current swallowing status at a minimum of 6 months post treatment. A trilingual EAT-10 (Eating Assessment Tool, validated for dysphagia screening) questionnaire could be administered confidentially to 45 patients. Forty one (91.1%) patients were able to completely answer all questions. All patients with screening-positive dysphagia (n = 24) underwent further evaluation of quality of life (QoL) by the MD Anderson Dysphagia Inventory (MDADI) and objective evaluation by VFS. Patient-specific cumulative EAT-10 and MDADI scores were correlated with 5 objective parameters of dysphagia/aspiration on VFS. We also studied multiple patient (gender, age, comorbid diabetes), tumor (oral subsite) and treatment (FFR type, adjuvant RT, adjuvant chemotherapy) characteristics for correlation with post treatment dysphagia. Statistical analyses were performed with χ^2 test and Fisher exact t-test.

Results: Oral tongue subsite (in comparison with buccal mucosa, $P = .05$) and fibular FFR (in comparison with radial FFR, $P = .003$) correlated with greater dysphagia on EAT-10 but not on VFS. Patient gender, age and comorbidity did not correlate with dysphagia (P = NS). Adjuvant therapies did not additionally contribute to dysphagia. Considering VFS as standard, the sensitivity and PPV of EAT-10 and MDADI (utilizing recommended score cutoffs of 3 and 80 respectively) for prediction of dysphagia were 45%, 75%, 45% and 69.2% respectively. The median global MDADI score as a QoL indicator was 78 (maximum 100).

Conclusion: OSCC patients are well rehabilitated with contemporary microvascular reconstruction. Tumors of the oral tongue and those undergoing fibular FFR are at higher risk of post treatment dysphagia, thereby mandating more aggressive dysphagia mitigating and rehabilitative strategies. Dysphagia detection by VFS merits careful interpretation. Modest and comparable reliability of the aforementioned questionnaires in predicting dysphagia in OSCC patients in the presence of serviceable QoL indicates the need of a directed head neck specific screening tool.

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Prognostic Role of p16 in Non-oropharyngeal Head and Neck Cancer

A.K. Bryant,[1] L. Vitzthum,[1] K. Zakeri,[1] H. Shen,[1] J.D. Murphy,[1] J.A. Califano,[2] E. Cohen,[3] and L.K. Mell[4]; [1]University of California, San Diego, La Jolla, CA, [2]University of California, San Diego, Moores Cancer Center, Department of Otolaryngology, La Jolla, CA, [3]University of California, San Diego, Moores Cancer Center, Department of Hematology/Oncology, La Jolla, CA, [4]University of California, San Diego, Moores Cancer Center, Department of Radiation Oncology, La Jolla, CA

Purpose/Objective(s): Previous studies have reported conflicting information regarding the prognostic role of p16 in non-oropharyngeal head and neck squamous cell carcinoma (HNSCC). We investigated the association between p16 status and cause-specific mortality in a large sample of United States veterans with oropharyngeal or non-oropharyngeal head and neck cancer (Table 1).

Materials/Methods: Using the United States Veterans Affairs database, we analyzed 8727 patients with locoregionally advanced HNSCC diagnosed between 2005 and 2015 and treated with radiation therapy or chemoradiation therapy. Of these, 1538 had known p16 status, determined by review of clinical notes and pathology reports. We compared outcomes for 1164 patients with oropharyngeal HNSCC and 374 patients with non-oropharyngeal (oral cavity, hypopharyngeal, or laryngeal) HNSCC, using multivariable Cox proportional hazards regression models to test effects on overall survival (OS), cancer-specific survival (CSS), and competing mortality (CM) within strata. We also tested for significant interactions between p16 and non-oropharyngeal primary site for each outcome.

Results: In multivariable models adjusting for treatment, stage, age, comorbidity, and body mass index, patients with p16 positive tumors had improved OS, CSS, and CM compared to patients with p16 negative tumors in both oropharyngeal (OS: hazard ratio [HR] 0.57, $P<.001$; CSS: HR 0.54, $P<.001$; CM: HR 0.63, $P = .04$) and non-oropharyngeal primary sites (OS: HR 0.48, $P<.001$; CSS: HR 0.46, $P = .007$; CM: HR 0.49, $P = .03$). The prognostic impact of p16 status did not significantly differ by primary tumor site for OS, CSS, or CM (interaction P values all $>.05$).

Conclusion: Our findings support the hypothesis that p16 has a similar prognostic role in both non-oropharyngeal and oropharyngeal cancer. Strong consideration should be given to routine testing for p16 in laryngeal, hypopharyngeal, and oral cavity primaries.

Abstract 100; Table 1

		Oropharyngeal		Non-oropharyngeal	
Outcome	Model	Hazard ratio for p16+ (95% CI)	P value	Hazard ratio for p16+ (95% CI)	P value
Overall survival	Unadjusted	0.34 (0.26-0.43)	<.001	0.52 (0.34-0.79)	<.001
	Adjusted	0.61 (0.46-0.80)	<.001	0.47 (0.31-0.73)	<.001
Cancer-specific survival	Unadjusted	0.28 (0.21-0.39)	<.001	0.52 (0.30-0.90)	.02
	Adjusted	0.55 (0.38-0.78)	<.001	0.42 (0.23-0.74)	.003
Competing Mortality	Unadjusted	0.43 (0.29-0.65)	<.001	0.52 (0.28-0.99)	.05
	Adjusted	0.72 (0.46-1.13)	.15	0.53 (0.28-1.02)	.06

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Adaptive Chemoradiation Therapy for Head and Neck Cancer Based on Multiparametric MRI: Interim Results of a Prospective Randomized Trial

P.G. Hawkins,[1] J.Y. Lee,[1] P. Li,[2] C. Lee,[1] M. Mierzwa,[1] M.P. Aryal,[1] G.S. Arnould,[1] F. Worden,[3] P.L. Swiecicki,[3] M.E. Spector,[4] M. Schipper,[1,2] Y. Cao,[1,5] and A. Eisbruch[1]; [1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]Department of Biostatistics, University of Michigan, Ann Arbor, MI, [3]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [4]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [5]Departments of Radiology and Biomedical Engineering, University of Michigan, Ann Arbor, MI

Purpose/Objective(s): Tumor regions characterized by hypoperfusion (HP) and restricted diffusion (RD) by multiparametric MRI have been reported to harbor aggressive disease. We report interim results of a randomized trial assessing boost to these subvolumes in poor-prognosis head and neck cancer (HNC).

Materials/Methods: Patients with HPV-positive, T4/N3 oropharyngeal cancer (OPC); HPV (-), T3-4/N2-N3 OPC; EBV (-), T3-4/N3 nasopharyngeal

cancer; locally-advanced, bulky, or unresectable T3-4 laryngeal or hypopharyngeal cancer; or stage III-IV oral cavity or paranasal sinus cancer who refuse or are unfit for surgery undergo MRI at baseline and 2-weeks midtreatment. Patients with stable HP or RD subvolumes are randomized to boost to these areas to 80 Gy versus standard dose (70 Gy). Cox regression and Kaplan-Meier were used to compare rates of failure. CTCAE v4, and EORTC QLQ-C30 and H&N35 are used to assess toxicity and quality of life (QOL).

Results: At time of analysis, 31 of the planned 80 patients have completed treatment: 15 randomized to boost and 16 to standard therapy. At a median follow-up of 13.3 months, there were 7 (22.6%) locoregional failures (LRFs) in all patients: 5 (31.2%) in the 70-Gy arm and 2 (13.3%) in the 80-Gy arm (HR 0.36, $P = .218$). There were 6 (19.4%) distant failures (DFs): 4 (25%) in the 70-Gy arm and 2 (13.3%) in the 80-Gy arm (HR 0.46, $P = .365$). Rates of HPV positivity were 56.2% and 66.7% in the 70-Gy and 80-Gy arms, respectively ($P = .567$). In HPV (+) patients, there were 2 (10.5%) LRFs: 2 (22.2%) in the 70-Gy arm and 0 in the 80-Gy arm (HR 0.19, $P = .211$). There were 3 (15.8%) DFs: 2 (22.2%) in the 70-Gy arm and 1 (10%) in the 80-Gy arm (HR 0.41, $P = .463$). In HPV (-) patients, there were 5 (41.7%) LRFs: 3 (42.8%) in the 70-Gy arm and 2 (40%) in the 80-Gy arm (HR 0.60, $P = .586$). There were 3 (15.8%) DFs: 2 (22.2%) in the 70-Gy arm and 1 (20%) in the 80-Gy arm (HR 0.59, $P = .670$). On univariate analysis, HPV positivity (HR 0.22, $P = .073$), as well as pretreatment hypermetabolic (HFDG) (HR 1.57, $P = .079$) and union of HP, RD, and HFDG (HR 2.15, $P = .046$) volumes were significant or marginally significant correlates of LRF. There were no significant differences in acute toxicity between arms. "Lost-Weight" QOL scores were worse in the boost arm at baseline and at 4 weeks posttreatment, although the difference at 4 weeks was of lesser magnitude than at baseline. At 72 weeks, "Cough" scores were worse in the boost arm at 2 versus 1.2 on a 4-point scale ($P = .010$).

Conclusion: In this interim analysis of MRI-guided boost in poor-prognosis HNC, there were not yet significant differences in outcomes between arms. However, the HR for LRF was encouraging as it was consistent with the value used to calculate power for the study. Boost was associated with no increased acute toxicity and minimal difference in QOL.

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Impact of Time to Adjuvant Radiation in Oral Cancer Patients With Positive Margins: A Nationwide Population-Based Database Analysis

M.H. Tsai, S.T. Tsai, and Y.H. Wu; *National Cheng Kung University Hospital, Tainan, Taiwan*

Purpose/Objective(s): Secondary analyses of oral cancer patients enrolled in clinical trials showed inferior locoregional control and survival when initiation of adjuvant radiation therapy was delayed to >6 weeks, and current guidelines recommend an interval of ≤6 weeks between resection and postoperative radiation therapy. Whether a shorter (4-5 weeks) or slightly longer (6-7 weeks) interval impacts outcomes is currently unknown. We designed a study to examine the impact of time to adjuvant radiation therapy in patients with positive margins.

Materials/Methods: We queried the Taiwan Cancer Registry for non-metastatic squamous cell carcinoma of the oral cavity (including lip, tongue, gum, floor of mouth, hard palate, buccal, and retromolar area) diagnosed between 2007-2013. We selected patients who received surgery upfront but with positive margins, then proceeded to adjuvant radiation therapy or adjuvant chemoradiation therapy. We investigated the interval of surgery and initiation of radiation therapy on locoregional control, distant metastasis, cancer-specific survival, and overall survival in these patients using the log-rank test and Cox proportional hazards model.

Results: From the initial 24,142 oral cancer patients identified, 607 patients matched our inclusion criteria of positive surgical margins and adjuvant radiation therapy, of which 479 had information on locoregional control and distant metastasis. Patients were grouped by interval of surgery and start of radiation therapy into <4 weeks, 4 to 5 weeks, 5 to 6 weeks, 6 to 7 weeks, and >7 weeks. We found a significant difference in overall survival ($P = .032$) and cancer-specific survival ($P = .020$) between these groups (Table 1). When compared to patients initiating radiation therapy within 4 weeks, the overall survival hazard ratio (95% confidence intervals) for intervals 4 to 5 weeks, 5 to 6 weeks, 6 to 7 weeks, and >7 weeks were 1.02 (0.73-1.42), 1.17 (0.85-1.63), 1.00 (0.65-1.52), and 1.57 (1.13-2.19). The cancer-specific survival hazard ratios were 1.12 (0.78-1.62), 1.23 (0.85-1.77), 1.07 (0.66-1.68), and 1.75 (1.22-2.52), respectively. We did not find a statistically significant correlation between locoregional control or distant metastasis between these groups.

Conclusion: When compared to prompt receipt of adjuvant radiation therapy, an interval of >7 weeks was associated with a worse cancer-specific survival and overall survival. However, oral cancer patients who receive adjuvant radiation therapy within 7 weeks of surgery appears to have comparable cancer-specific survival and overall survival outcomes.

Abstract 102; Table 1

Overall survival Time to adjuvant radiation therapy	Hazard ratio (95% Confidence interval)
<4 weeks	Reference
4-5 weeks	1.02 (0.73-1.42)
5-6 weeks	1.17 (0.85-1.63)
6-7 weeks	1.00 (0.65-1.52)
7 weeks	1.57 (1.13-2.19)

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Phase 1-2 Study of De-intensified IMRT and Concurrent Chemotherapy in Locally Advanced Oropharyngeal Carcinoma

H. Bahig,[1,2] L. Lambert,[2] É. Filion,[2] D. Soulières,[2] L. Guertin,[2] T. Ayad,[2] A. Christopoulos,[2] E. Bissada,[2] M. Alizadeh-Kashani,[3] M. Belair,[2] and P.F. Nguyen-Tan[2]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada, [3]Centre Intégré de Cancérologie de Laval, Laval, Quebec, Canada*

Purpose/Objective(s): To assess tumor control outcomes of de-intensified IMRT (reduced radiation volume and dose) in locally advanced oropharyngeal cancer (LA-OPC) treated with concurrent chemotherapy; as well as to report toxicities and long-term health-related quality of life (HRQoL) outcomes in these patients.

Materials/Methods: Stage III-IVa-b (as per American Joint Cancer Committee) OPC patients treated with IMRT and concurrent carboplatin-5FU were prospectively enrolled in this single-institutional study between 2011 and 2014. De-intensified IMRT consisted in omission of contralateral retropharyngeal and lymph node (LN) level 4, and reduction of dose to low risk LN levels to 43.2 Gy in 24 fractions. Gross tumor volume was treated to 70 Gy in 33 fractions and high-risk LN levels were treated to 59.4 Gy in 33 fractions. All patients were treated using Helical Tomotherapy. Kaplan Meier analysis was used for estimation of locoregional control (LRC) and overall survival (OS). Toxicities were as per CTCAE v.4.0 and HRQoL was assessed using QLQ-C30 and H&N35 questionnaires.

Results: A total of 30 patients were enrolled. Median age was 55 years (range: 44-68); 10%, 83%, and 7% of patients presented with tumor stage III, IVa and IVb, respectively. All but 1 patient had HPV positive disease. Primary tumor subsite included tonsil, base of tongue and lateral pharyngeal wall in 90%, 7% and 1 patient, respectively. Median follow-up was 44 months (range: 22-61). Six patients underwent a planned neck dissection, among which 2 had residual disease on pathology. Two- and 5-year LRC were 100% and 100%; 2- and 5-year OS were 100% and 100%. Acute toxicities included 3 mucositis

in 50% of patients and grade 3 dermatitis in 33% of patients; there were no grade 4-5 toxicities. Fifty percent of patients required nasogastric feeding tube placement for a median time of 36 days (range: 19-63). Per-treatment hospitalisation rate was 23%. Chronic toxicities included 80% and 47% grade 1 xerostomia at 12 months and 24 months, as well as 30% and 13% grade 1 dysgeusia at 12 and 24 months, respectively. One patient required permanent gastrostomy. HRQoL analysis revealed a clinically significant and persistent decline of the following symptom scales at 24 months compared to baseline: swallowing problems (3% at baseline vs 12% at 24 months), dry mouth (14% vs 33%), and sticky saliva (11% vs 28%). All other QLQ-C30 and H&N35 symptom and functional scales returned to baseline or were better than baseline within 8 months of IMRT completion.

Conclusion: De-intensified IMRT with sparing of contralateral retropharyngeal and low-risk LN levels is associated with excellent cancer outcomes and low toxicity rates in HPV positive LA-OPC. A rapid recovery of most HRQoL scales was observed within 8 months of treatment, with the exception of a decline in swallowing and xerostomia related scales, which remained persistent 2 years posttreatment.

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Adjuvant Chemotherapy Utilization According to Treatment Facility Type in Resected Head and Neck Cancer With Negative Surgical Margins and No Extracapsular Nodal Extension

S. Alsidawi,[1] K. Price,[1] R.L. Foote,[2] J.J. Garcia,[3] G.F. Westin,[1] E.J. Moore,[4] and A.V. Chintakuntlawar[1]; *[1]Division of Medical Oncology, Mayo Clinic, Rochester, MN, [2]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, [3]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, [4]Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN*

Purpose/Objective(s): Adjuvant chemotherapy (ACT) after surgical resection of locally advanced head and neck squamous cell carcinoma (HNSCC) is reserved for patients with high-risk features (positive surgical margins or extracapsular nodal extension). Many patients, however, are still considered high risk and continue to receive ACT outside these two indications. We explored the National Cancer Database (NCDB) to compare variations in ACT administration between academic and non-academic institutions in resected HNSCC with negative surgical margins (R0) and no extracapsular nodal extension (no-ENE).

Materials/Methods: Using the NCDB registry, we included adults diagnosed with HNSCC (pathological stages III-IVb) from 2004-2012. Patients had to be treated with upfront surgical resection and have documented R0 and no-ENE. Univariate and multivariate regression analysis were done to calculate odds ratios for receiving ACT. Survival analysis was performed using the Kaplan-Meier method.

Results: A total of 3574 patients met inclusion criteria. ACT is common in patients with R0 and no-ENE with 31.1% and 44.1% of patients receiving ACT at academic and non-academic institutions, respectively. The type of treatment facility (non-academic vs academic) was found to be independently associated with receiving ACT in multivariate regression analysis adjusting for patient variables (age, gender, race, annual income, insurance status, comorbidity score) and tumor variables (primary tumor location, pathological stage, T stage, N stage, lymphovascular invasion, radiation administration) with an odds ratio for receiving ACT at non-academic institutions of 1.83 (95% CI 1.52-2.2, $P < .0001$). Other independent variables for receiving ACT included younger age, advanced N stage, lymphovascular invasion and receiving radiation. In patients with oropharyngeal tumors, the treatment facility type was associated with receiving ACT independent from HPV status with an odds ratio for receiving ACT at non-academic institutions of 2.23 (95% CI 1.55-3.4, $P < .0001$) in multivariate analysis. Despite these differences in ACT administration, median overall survival was not different between academic and non-academic institutions (78 vs 81 months, HR = 0.96, 95% CI 0.85-1.09, $P = .53$).

Conclusion: In patients with surgically resected HNSCC with R0 and no-ENE, treatment at non-academic institutions was independently associated with more common use of ACT in multivariate analysis adjusting for patient and tumor variables. Survival was not different between academic and non-academic institutions in this patient population. More research is needed to investigate the reasons behind these variations leading to more common administration of ACT in non-academic institutions.

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Radiation Treatment Outcome With Reduced Clinical Target Volume in Patients With Oropharyngeal Cancer

A. Vera,[1] A.I. Urdaneta,[1] N.D. Mukhopadhyay,[1] X. Deng,[1] and S. Song[2]; *[1]Virginia Commonwealth University, Richmond, VA, [2]Virginia Commonwealth University Health System, Richmond, VA*

Purpose/Objective(s): Delineation of clinical target volume (CTV) for head and neck cancer radiation treatment varies among institutions and clinical protocols. A 0.5-1.5 cm expansion of gross tumor volume (GTV) to create high-risk CTV for a definitive radiation dose is commonly recommended. At our institution, GTV is treated using IMRT to a definitive dose without CTV expansion. The elective neck regions were treated with expanded skin avoidance to reduce skin reaction. Here we report the outcome of oropharynx cancer treatment using reduced CTV volumes. We hypothesize that patients treated with reduced CTV have similar results to the patients treated with standard expansion.

Materials/Methods: Records of 123 patients with stage I-IVB oropharyngeal cancer treated at our institution from 2005 through 2013 were reviewed. The p16 status was reported in 52 patients. Primary tumor and involved nodes were contoured as GTV and treated to a definitive dose of 68.1 to 70 Gy in 30 to 33 fractions without CTV expansion. High-risk CTV is created with 1 cm of GTV expansion minus bones and air (CTV1), which was treated to 60 Gy. Elective uninvolved nodal regions (CTV2) including the first echelon nodes were treated to 54 Gy. PTV-1, -2 and -3 were created from GTV, CTV1, and CTV2 by adding 5 mm for setup uncertainty. In the uninvolved neck, a 6-mm skin avoidance structure was created to reduce the skin dose. Cisplatin was administered either weekly or every 3 weeks during the course of XRT. Of the 123 patients, 91 were treated with chemotherapy and radiation therapy, 18 with radiation alone, 6 with postoperative adjuvant chemotherapy and radiation therapy, and 8 with post-op radiation therapy. Toxicities were scored according to CTC Ver. 4. The overall survival rate was compared between treatment groups using the log-rank test.

Results: Median follow-up was 4.6 years. For the entire group, the 5.4-year overall survival was 63.11% (71% for stage I/II and 57.56% for Stage III/IV). Among 52 patients with p16 status known, 33 patients had p16 (+) tumors and 19 had p16 (-) tumors. The 5-year overall survival was 84.85% versus 55.56%, respectively ($P = .0169$). There was no significant difference in acute toxicity between our patients and those reported in the literature, with 30.9% experiencing grade 3 or higher mucositis, and 14%

patients with grade 3 radiation dermatitis. A permanent feeding tube was needed in 4.06%, which is lower than those reported in the literature.
Conclusion: Our results compare favorably with the reported outcomes of oropharyngeal cancer treatment in the literature, both in the patient survival and toxicities. Radiation therapy with reduced CTV expansion is safe. While phase 3 dose de-escalation trial is being conducted in patients with HPV (+) or p16 (+) oropharyngeal cancer and is not considered a standard practice at this time, reduction of CTV volume may be used as an alternative approach for dose de-escalation.
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Utilization of Transoral Robotic Surgery in Patients With Oropharyngeal Squamous Cell Carcinoma and Its Impact on Survival and Use of Adjuvant Therapy Compared to Treatment With Definitive Radiation Therapy

S. Baliga,[1] R. Kabarriti,[2] N. Ohri,[1,2] R. Smith,[1] C. Guha,[2] S. Kalnicki,[3] and M.K. Garg[2]; *[1]Montefiore Medical Center, Bronx, NY, [2]Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, [3]Albert Einstein College of Medicine, Bronx, NY*

Purpose/Objective(s): To assess trends in Transoral Robotic Surgery (TORS) utilization and its impact on overall survival (OS) and use of adjuvant therapy compared to treatment with definitive radiation therapy (RT) for patients with oropharyngeal squamous cell carcinoma (OPSCC).
Materials/Methods: We identified all T1-T2, N0-N2b OPSCC patients who received TORS or definitive RT for the upfront management of OPSCC from the National Cancer Database registry between 2010-2014. Trends in TORS use over time and adjuvant chemotherapy or RT use are reported as percentages. Propensity score matching was performed to account for baseline differences between covariates in the TORS versus definitive RT group. OS was measured from time of diagnosis until death or last follow up and the Kaplan Meier method was used to estimate OS. A multivariable logistic regression was performed to assess the impact of TORS on adjuvant chemotherapy and radiation therapy use. Adjustment variables included in the analysis were clinical T and N-stage, oropharynx subsite, overall stage, age, sex, race, median income, facility type, Charlson comorbidity score, diagnosis year, HPV status, and TORS use. The Wilcoxon rank sum test was used for median comparisons between groups, and the χ^2 test was used to compare categorical variables.
Results: A total of 17,150 patients met inclusion criteria. Of these, 2680 (15.6%) received TORS and 14,470 (84.4%) underwent definitive RT. Median follow-up was 31 months. The use of TORS increased steadily from 2010 (13%) to 2014 (27%). Covariates associated with increased TORS use include tonsil subsite, early T stage, higher median income, and younger age. Eighty-two percent of patients treated with RT received chemotherapy, compared to 33% of patients treated with TORS (χ^2, $P < .001$). After adjustment, TORS was still associated with decreased use of chemotherapy compared to definitive RT (Adjusted OR: 0.09, 95% CI 0.08-0.11, $P < .001$). Sixty-one percent of patients treated with TORS were also treated with adjuvant radiation therapy to a median dose of 60 Gy (25th-75th percentile range: 60-66 Gy, IQR 6 Gy). After propensity score matching (n = 845 in each arm), 2-year OS was 93.4% versus 93.0% in the TORS and definitive RT cohort, respectively (HR: 0.86, 95% CI 0.71-1.04; log-rank, $P = .10$). After propensity score matching, TORS use continued to be associated with decreased chemotherapy use (adjusted OR: 0.11, 95% CI 0.09-0.13, $P < .001$). Median RT dose was 69.96 Gy in patients treated with definitive RT versus 60 Gy for those treated with TORS ($P < .001$).
Conclusion: Our findings demonstrate that TORS did not impact OS compared to treatment with definitive RT. We also found an association between TORS use and decreased utilization of chemotherapy as well as the ability to deliver lower RT doses. Prospective trials to compare quality of life and patient reported outcomes in patients treated with and without TORS are needed.
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Comparative Effectiveness of Cetuximab or Cisplatin With Concomitant Radiation for Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck: A Population-Based Analysis

M. Xiang,[1] F.C. Holsinger,[2] M.M. Chen,[2] A.D. Colevas,[2] and B.M. Beadle[1]; *[1]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, [2]Stanford University, Stanford, CA*

Purpose/Objective(s): Cisplatin and cetuximab are the two most widely used systemic therapies given in combination with radiation therapy (RT) for head and neck cancer. While RT with either agent is known to be superior to RT alone, their relative efficacy is uncertain. We hypothesized that the sample size and follow-up afforded by a large, national population-base database would enable a detailed analysis of the comparative efficacies of cisplatin and cetuximab.
Materials/Methods: Patients with locally or regionally advanced (AJCC stage III-IVB) squamous cell carcinomas of the oropharynx, oral cavity, larynx, or hypopharynx from 2004 to 2011 were identified in the SEER-Medicare database. Patients received either cisplatin or cetuximab concurrent with RT, as determined by their Medicare claims. The primary study outcome was head and neck cancer-specific mortality (CSM) analyzed with competing risks. Filtering, propensity score matching, and multivariable Fine-Gray regression were used to adjust for baseline differences between cisplatin and cetuximab groups, including age, comorbidity, and the amount of systemic therapy received.
Results: The total cohort consisted of 1284 patients, of which 693 (54%) received cisplatin and 591 (46%) received cetuximab; median follow-up was 3.9 years. In the cetuximab group, CSM was significantly higher than in the cisplatin group (44% vs 29% at 5 years; $P < .0001$). In the matched cohorts, the adjusted hazard ratio of CSM for cetuximab was 1.74 (95% CI 1.32 to 2.30; $P < .0001$) relative to cisplatin, corresponding to an absolute 10% difference in both CSM and overall survival at 5 years.
Conclusion: In this large, national, population-based database, treatment with cetuximab was associated with significantly higher CSM compared to cisplatin. In the absence of phase 3 randomized data, our results add to a growing body of literature suggesting the non-equivalence of EGFR-targeted and platinum-based therapy concomitant to RT for the treatment of head and neck cancer.
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Withdrawn

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Survival Impact of Treatment Interval Delays in Head and Neck Cancer

A.S. Ho, S. Kim, M. Tighiouart, C. Gudino, A. Mita, K. Scher, J.B. Epstein, N. Ali, C.D. Patio, A. Laury, R. Prasad, H.D. Thompson, A.E. Strouss, J. Mallen-St.Clair, S.L. Shiao, J.E. Van Eyk, and Z.S. Zumsteg; *Cedars-Sinai Medical Center, Los Angeles, CA*

Purpose/Objective(s): Multidisciplinary head and neck cancer management must reconcile increasingly sophisticated subspecialty care with

timeliness of care. Prior studies have examined the individual effects of prolonging diagnosis to treatment interval (DTI), postoperative interval, and radiation interval but not considered them collectively. We investigate the shared impact of these interwoven intervals on head and neck cancer patients completing definitive surgery with postoperative radiation.

Materials/Methods: Head and neck cancer patients undergoing upfront surgical resection with adjuvant radiation were identified in the National Cancer Database between 2004 and 2013. Patients treated with curative intent who completed full-course radiation therapy were included. Diagnosis to treatment interval was defined as the time from diagnosis until surgery. Postoperative interval was defined as the time from surgery to the first day of radiation. Radiation interval was defined as the time from the first to the last day of radiation. Multivariable models were constructed to assess the association between treatment delays and overall survival.

Results: Overall, 15,177 patients were evaluated. Prolonged DTI, postoperative interval, and radiation interval all were associated with impaired survival in univariate analysis. After adjustment for covariates, only prolonged postoperative interval ($P = .006$) and radiation interval ($P < .001$) independently predicted for risk of death, while the association of DTI with overall survival disappeared. Using multivariable restricted cubic spline functions, mortality risk escalated continuously for postoperative interval with each additional day, plateauing at 74 days (cumulative HR 1.25, 95% CI 1.11-1.32, $P < .001$). Similarly, mortality risk increased continuously for radiation interval with each additional day, peaking at 56 days (cumulative HR 1.31, 95% CI 1.22-1.39, $P < .001$). Delays beyond these change points were not associated with additional survival decrements.

Conclusion: Delays in postoperative interval and radiation interval are independently associated with mortality risk. The hazard conferred suggest that attention to these physician-modifiable covariates could considerably improve prognosis. Delays in initiating treatment conversely do not appear to impact survival when appraised in conjunction with the entire treatment course.

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Selecting the Right Patients for Future Trials—Multiple Endpoints Model in 1244 Patients With Oropharyngeal Squamous Cell Carcinoma and Known HPV and p16 Status

J.H. Rasmussen,[1] C.G. Larsen,[1] K.E. Hakansson,[2] J.T. Friborg,[2] I. Vogelius,[2] and C.V. Buchwald[1]; *[1]Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): In the era of precision medicine and HPV-related head and neck squamous cell carcinoma (HNSCC), it is relevant to assess the risk of not only survival, but also the risk of locoregional failure (LRF) and distant metastasis (DM). Traditional staging with AJJC/UICC classification is developed with overall survival as sole endpoint, but the risk of LRF and DM is important to guide who might benefit from local or systemic treatment intensification or de-intensification. The purpose of this study is to develop a multi endpoint model in a large population-based patient cohort with oropharyngeal squamous cell carcinoma (OSCC) and known p16 status.

Materials/Methods: Patients diagnosed with OSCC and treated with curative radiation therapy with or without platin based chemotherapy in eastern Denmark from 2000 to 2014 were included. Patient characteristics including age, gender, UICC-, T, N stage, smoking habits, and performance status (PS) were retrieved from patient charts and both p16 staining and HPV DNA-PCR were performed. The information was used to develop a competing risk model, combining three cause specific Cox models with LRF, DM, and death with no evidence of disease (NED) as endpoints. UICC 8th edition was used and in p16 negative patients N2a and N2b were merged to N2, and N2c and N3 were merged to N3. Patients were categorized in three groups based on both HPV status and p16 status: 1. p16+/HPV+; 2. p16-/HPV+ or p16+/HPV- and 3. p16-/HPV-. The included predefined variables for LRF and DM were: gender, T stage, N stage, smoking habits, HPV/p16 status; and for death NED: age, gender, UICC stage, smoking habits, HPV/p16 status, and PS. Missing values for p16 (32), smoking habits (95), and PS (303) were imputed. The model is presented as an interactive online tool (https://rasmussen.shinyapps.io/Oropharynxmodel/). Absolute risk of LRF, DM, and death of NED after five years was estimated and the performance of the model was compared to UICC classification with cross-validation to test the performance in random subsets of data.

Results: Overall, 1244 patients with OSCC were included and median time to last follow-up was 5.8 years. In LRF, gender, smoking, T stage, N stage, and p16/HPV status were all significant predictors. For DM, smoking, T4 stage, and N stage were significant predictors. For death, NED age, gender, PS, smoking p16/HPV status, and UICC stage were significant predictors. The multi-endpoint model performed better than UICC classification with a clinically relevant higher AUC for all endpoints ($AUC_{LRF} = 65.8\%$ vs 60.8%, $P = .08$; $AUC_{DM} = 65.8\%$ vs 58.4%, $P = .20$, and $AUC_{death\ NED} = 73.3\%$ vs 68.3%, $P = .08$), but was unfortunately only borderline significant in cross-validation.

Conclusion: The multi-endpoint model performed better than traditional staging with the UICC 8th edition and can be used to guide the design of future trials, however the model needs validation in external patient cohorts.

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Outcomes Between Concurrent Cisplatin Versus Carboplatin-Based Chemotherapy in Locally Advanced Oropharyngeal Carcinoma: A SEER-Medicare Analysis

A. Amini,[1,2] M. Eguchi,[1] B.L. Jones,[1] W.A. Stokes,[1] R.M. Lanning,[1] J. McDermott,[1] D. Raben,[1] C.J. Bradley,[1] and S.D. Karam[1]; *[1]University of Colorado School of Medicine, Aurora, CO, [2]City of Hope Cancer Center, Duarte, CA*

Purpose/Objective(s): The comparative efficacy of cisplatin versus carboplatin-based delivered concurrently with radiation therapy (CRT) for locally advanced, non-metastatic, oropharyngeal squamous cell carcinoma (OPSCC) continues to be evaluated. The National Comprehensive Cancer Network guidelines currently recommend cisplatin-based CRT, reserving agents including carboplatin for patients who otherwise cannot tolerate cisplatin.

Materials/Methods: The linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used to identify and compare patient and disease profiles, mortality, toxicity, and overall cost in oropharynx cancer patients undergoing definitive concurrent CRT with cisplatin or carboplatin-based chemotherapy between 2006 and 2011. Unadjusted and adjusted analyses and logistic regression were performed. The primary outcome was 2-year overall survival (OS).

Results: The analytic sample comprised 236 patients; 167 (71%) received cisplatin, and 69 (29%) received carboplatin-based therapy. Age $\geq$ 75 years (OR, 0.23; 95% CI 0.09-0.58; $P = .002$) and treatment in the South (OR, 0.27; 95% CI 0.10-0.72; $P = .009$ were less likely to receive concurrent cisplatin. Treatment given in the more recent years was more likely to consist of concurrent cisplatin versus carboplatin (ORs 4.22-16.98; $P = .001$). There was no statistically significant difference in 2-year OS between cisplatin and carboplatin-based chemotherapy in the Cox proportional hazards model (HR, 1.36; 95% CI 0.70-2.65; $P = .360$). Hospital visits due to neutropenia/thrombocytopenia (7.3% vs 1.8%; $P = .035$) and reported rates of pneumonia (27.5% vs 13.8%; $P < .001$) were higher with

concurrent carboplatin cohort versus cisplatin. Mean total payment by Medicare during the first 12 months from diagnosis was also greater with carboplatin compared to cisplatin ($56,698 vs $42,959).

Conclusion: Older age, region, and year of treatment predicted the use of carboplatin. There was no statistically significant difference in OS between concurrent cisplatin versus carboplatin-based chemotherapy. Concurrent carboplatin was associated with higher hematologic toxicity as well as greater overall cost. Concurrent carboplatin is a reasonable alternative in patients who cannot tolerate concurrent cisplatin in locally advanced OPSCC.

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Impacts of Metformin & Diabetes and Statins & Hyperlipidemia in Head and Neck Cancer: An Analysis of the SEER-Medicare Dataset

W.A. Stokes,[1] M. Eguchi,[1] A. Amini,[1,2] D. Ding,[3] R.M. Lanning,[1] J. McDermott,[1] D. Raben,[1] C.J. Bradley,[1] and S.D. Karam[1]; *[1]University of Colorado School of Medicine, Aurora, CO, [2]City of Hope Cancer Center, Duarte, CA, [3]Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO*

Purpose/Objective(s): Metformin and statins are commonly used to treat diabetes (DM) and hyperlipidemia (HL), respectively, and have both demonstrated antitumor activity in preclinical studies. Their impact on patient outcomes in head and neck squamous cell carcinoma (HNSCC), however, continues to be explored. We aimed to investigate the impact of these medications in a modern cohort of American patients with HNSCC.

Materials/Methods: SEER-Medicare was queried for patients diagnosed with non-metastatic HNSCC from 2008 to 2011 who underwent definitive therapy. Patients were classified first according to DM status and metformin usage: non-DM no metformin (nDnM), DM no metformin (DnM), DM with metformin (D+M); and then according to HL status and statin usage: non-HL no statin (nHnS), HL no statin (HnS), and HL with statin (H+S). Multivariate Cox regression was used to compare overall survival (OS) and cancer-specific survival (CSS) through 2 years from diagnosis, expressed as adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI). Claims data were also used to estimate probabilities of experiencing toxicity events relevant to treatment of HNSCC.

Results: Of 1,644 patients included, 376 were DnM and 124 D+M, while 567 were HnS and 530 H+S. With respect to metformin, there were no significant differences in OS between groups, while CSS was significantly improved among D+M versus nDnM (Table 1). With respect to statins, both OS and CSS were significantly improved among H+S versus nHnS (Table 1). Neither D+M nor H+S were associated with excess toxicity versus either of their respective comparison groups.

Conclusion: HNSCC patients taking metformin or statins have higher rates of survival than nondiabetic or nonhyperlipidemic patients, respectively. Prospective validation is warranted to better establish the role of these medications.

Abstract 112; Table 1*

	OS				CSS			
	OS2 (%)	aHR	95% CI	*P*	CSS2 (%)	aHR	95% CI	*P*
nDnM	65.7	-	-	-	73.9	-	-	-
DnM	57.7	1.16	0.95-1.42	.14	66.0	1.26	0.94-1.69	.12
D+M	73.4	0.90	0.61-1.32	.58	88.8	0.40	0.20-0.81	**.01**
nHnS	58.7	-	-	-	69.3	-	-	-
HnS	61.7	0.81	0.65-1.01	.06	69.2	0.91	0.66-1.26	.57
H+S	73.0	0.57	0.45-0.73	**<.01**	81.2	0.60	0.42-0.86	**.01**

* Adjusted for age, sex, race, marital status, SEER registry, year, primary site, T- and N-classification, comorbidity, hospital type, poverty, surgery, radiation therapy, chemotherapy.

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Phase 2 Trial of Adjuvant Concurrent Cetuximab and Radiation for High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck

M. Mierzwa,[1] K. Casper,[2] K.P. Redmond,[3] W.L. Barrett,[3] V. Takiar,[3] A. Tang,[3] J. Mark,[3] K. Wilson,[3] T. Wise-Draper,[3] N.hashemi Sadraei,[3] and B. Huth[3]; *[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [3]University of Cincinnati, Cincinnati, OH*

Purpose/Objective(s): Aggressive cutaneous squamous cell carcinoma of the head and neck (CSCCHN) is most often treated with surgical resection followed by adjuvant radiation therapy (RT) with or without concurrent chemotherapy and locoregional control (LRC) remains problematic with 2 yr LRC of 60% to 80%. The addition of cytotoxic chemotherapy has not demonstrated benefit over adjuvant RT in randomized trials.

Materials/Methods: NCT01979211 is a multi-institutional single arm phase 2 trial of concurrent adjuvant RT and cetuximab after primary surgical resection for CSCCHN. Eligibility criteria include high-risk (>N1, + PNI, bone or cartilage invasion) or locally recurrent CSCCHN after gross total resection. Primary endpoint is 2 yr LRC. Secondary endpoints include DFS, OS, acute and late toxicities (CTCAE v4.03), and patient reported quality of life with FACT-HN and Dermatology Life Quality Index (DLQI). Correlative studies include whole exome sequencing of primary tumor and nodal metastases.

Results: Twenty-three of planned 40 patients are accrued to date with a median 12 months of follow-up. Eighteen patients have completed all therapy per protocol with minimum 3-month follow-up. Of the patients, 91% were male, mean age 69 (range 50-80), all Zubrod 0-1. Of these, 18 patients, acute toxicities are as follows: 91% had grade 1 toxicities, mostly acneiform rash and mucositis, grade 2 reported in 61% patients including skin (39%), mucositis/oral pain (39%), fatigue (11%), allergic reaction (5%). Three patients had grade 3 skin toxicity, 1 patient had grade 3 mucositis. No grade 4 or 5 toxicities to date. Two patients developed locoregional failures, no one has developed distant metastases. 2 patients have died, 1 related to confirmed LRR. To date, mean baseline DLQI score is 5.5 (+/- 0.5) and at 3 mo post-RT is 3.9 (+/- 0.4), indicating a "small" improvement in skin QOL from postresection, preadjuvant therapy baseline. Mean baseline FACT- HN score is 120 (+/- 18) and 118 (+/- 25) at 3 mo post-RT.

Conclusion: Postoperative concurrent cetuximab and RT for high risk CSCCHN appears well tolerated with favorable LRC thus far in comparison to institutional historic controls and quality of life scores comparable to other trials using concurrent cetuximab and RT for mucosal HNSCC.

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Neoadjuvant Chemotherapy Associated With Improved Survival in High-Risk Nasopharyngeal Carcinoma Patients Treated With Definitive Concurrent Chemoradiation Therapy

J. Han, S.K. Yi, and C.C. Hsu; *University of Arizona Department of Radiation Oncology, Tucson, AZ*

Purpose/Objective(s): Intergroup 0099 established concurrent chemoradiation therapy (CCRT) as the definitive treatment for nasopharyngeal carcinoma (NPC). Despite decreases in toxicity and local failure rates with the advent of IMRT combined with CCRT, patients remain at risk of distant metastases. As a result, several phase 3 trials attempted to compare the efficacy of NAC followed by CCRT to CCRT alone. Sun et al demonstrated a 3-year failure-free survival rate of 80% in the neoadjuvant chemotherapy (NAC) followed by CCRT group compared to 72% in the CCRT alone group. However, trials in a more western and non-endemic

setting have yet to be examined. The purpose of our study is to determine whether NAC followed by CCRT provides an overall survival (OS) benefit, particularly among high-risk patients.

Materials/Methods: We queried the national cancer database for patients with NPC and limited the initial 13,929 patients to those treated with either NAC followed by CCRT or CCRT alone; defining NAC followed by CCRT as chemotherapy initiation ≥21 days prior to RT initiation and CCRT as initiation 20 days prior to and 36 days after RT initiation. After excluding patients with metastatic disease, those treated with surgery or palliative therapy, and without clinical staging, we arrived at a total of 5274 patients. We performed survival analyses using univariate (UVA) and multivariate (MVA) cox proportional analysis to determine if an association between NAC and OS exists.

Results: The median survival of the entire patient cohort was 8.9 years, with a median follow up of 3.3 years. Median survival for the NAC plus CCRT group was 9.4 years and 8.8 years in the CCRT alone group. NAC plus CCRT did not affect OS on UVA (HR 1.01; 95% CI [0.90,1.14)]; $P = .870$) and MVA (HR 0.89; 95% CI [0.79,1.00]; $P = .053$) though trending towards significance. We also stratified patients into risk categories. High-risk included patients with clinical stage IV or keratinizing histology and low all others. NAC plus CCRT improved OS in the high-risk population on MVA (HR 0.86; 95% CI [0.75, 0.98]; $P = .023$) but not in the low risk (HR 1.06; 95% CI [0.80, 1.39]; $P = .692$).

Conclusion: Patients with nonmetastatic NPC treated with NAC plus CCRT trended towards a statistically significant OS benefit on multivariate analysis. However, higher risk patients, who we defined as having clinical stage IV disease or keratinizing histology, benefitted with an improved OS compared to those with low risk disease. Therefore, we conclude that a subset of patients presenting with locally advanced disease who are at a higher risk of distant micrometastases and those with unfavorable histology who are most resistant to radiation therapy may benefit from treatment with NAC plus CCRT, underscoring the necessity of additional future phase 3 trials to confirm these results.

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Final Safety Results of a Phase 1 Clinical Trial of Afatinib in Combination With Docetaxel and Postoperative Radiation Therapy for High-Risk Squamous Cell Carcinoma of the Head and Neck

D.N. Margalit,[1] R.I. Haddad,[2] R.B. Tishler,[1] N. Chau,[3] J.D. Schoenfeld,[1] R.L. Bakst,[4] K. Misiukiewicz,[5] L. Goguen,[6] D. Annino,[6] P. Mchugh,[3] A. Bacay,[3] P. Groden,[3] P.S. Catalano,[7] and G. Rabinowits[8]; *[1]Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [3]Dana-Farber Cancer Institute, Boston, MA, [4]Icahn School of Medicine at Mount Sinai, New York, NY, [5]Mt. Sinai School of Medicine, New York, NY, [6]Division of Otolaryngology, Department of Surgery, Brigham & Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [7]Department of Biostatistics & Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [8]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Purpose/Objective(s): Afatinib is an oral, irreversible EGFR/ErbB family receptor inhibitor with clinical activity in recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN). Previously, EGFR-inhibition with cetuximab in combination with docetaxel and postoperative radiation therapy (PORT) was shown in RTOG 0234 to be well tolerated with higher rates of disease-free survival compared to historical results with cisplatin and PORT. We therefore aimed to assess the tolerability of afatinib in combination with docetaxel and PORT in a cohort of patients with high-risk pathologic features after definitive surgery.

Materials/Methods: This was an open label, non-randomized, phase 1, 3+3 dose-escalation study. Eligible patients had resected stage III-IV SCCHN of the oral cavity, oropharynx, larynx, or hypopharynx with high-risk features of either positive margins (tumor at ink), extracapsular nodal extension, N3 nodal stage, or T4 tumor with bone invasion. Patients received afatinib at an initial dose of 30 mg daily for 1 week prior to PORT and then daily during PORT. Docetaxel 15 mg/m2 was given weekly during PORT. The maximum PORT dose was 66 Gy, 2 Gy/fraction. Toxicities were scored using CTCAE v4.0.

Results: Eleven patients (6 women) were enrolled with a median age of 61 years (44-66 yrs), AJCC stage of III (n = 2) or IV (n = 9) and oral cavity (n = 10) and larynx (n = 1) primary tumors. Seven patients received the starting 30 mg dose including 2 patients that withdrew consent after starting treatment, and 2 that experienced hypersensitivity reactions due to docetaxel and were taken off-study. There were 2 dose-limiting toxicity (DLT) events of grade 3 diarrhea and mucositis at the initial 30 mg dose. Four patients receive the de-escalated 20 mg dose. There were 2 DLT's (grade 3 mucositis). There were no grade 4 or 5 events. The most common toxicity was diarrhea occurring in 9 of 11 patients (grade 3 in 2 patients), and mucositis occurring in 8 of 11 patients (grade 3 in 4 patients).

Conclusion: The combination of afatinib with both PORT and docetaxel for mucosal SCCHN was shown to be difficult to tolerate with a high rate of grade 3 toxicity, mostly mucositis, in this cohort of patients requiring postoperative chemoradiation to the oral cavity. Afatinib may be better tolerated with PORT alone and this is currently being tested in a prospective phase 1 trial in an intermediate-risk cohort. *This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Boehringer Ingelheim Pharmaceuticals, Inc.*

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Survival Outcomes of Primarily Surgically Managed HPV-Associated Oropharyngeal Carcinoma Reported by the New AJCC/UICC 8th Edition Staging System

N. Vawda,[1] B.J. Debenham,[1] and R.N. Banerjee[2]; *[1]University of Alberta, Edmonton, Alberta, Canada, [2]Tom Baker Cancer Centre, Calgary, Alberta, Canada*

Purpose/Objective(s): The 8th edition AJCC Staging manual sought to address the long-standing disparity in the prognosis of human papillomavirus (HPV) associated oropharyngeal carcinoma (OPC) by developing a distinct staging system of OPC based on HPV status. The purpose of this study is to report on survival outcomes of primary surgically managed patients with HPV-associated OPC when categorized by the new pathologic nodal (pN) classification.

Materials/Methods: A retrospective chart review was undertaken on 114 patients with known p16 overexpressing OPC and who were primarily surgically managed between 2006 and 2015, identified from a local database of locally advanced OPC. Patients were stratified on the basis of AJCC 8th edition pN category of ≤4 pathologically involved lymph nodes (pN1) or >4 pathologically involved lymph nodes (pN2). Descriptive summaries were recorded and Overall Survival (OS) and Recurrence Free Survival (RFS) were compared using the Kaplan Meier curves with the log-rank test used to determine statistical significance.

Results: Of the 114 patients, 74.6% (N = 85) were staged pN1. Demographic data was similar between the 2 groups but with regards to

clinicopathological data; patients with pN1 stage had less involved margins (9.4% vs 27.5%, $P = .03$), extracapsular extension (23.5% vs 72.5%, $P < .0001$), perineural invasion (20% vs 41.2%, $P = .04$), and recurrence rates (12.9% vs 41.4%, $P = .00025$) than those with pN2 stage. No differences existed between the groups with regards to pathological tumor stage, grade, presence of lymphovascular invasion, smoking status, adjuvant management, or time to adjuvant treatment. With a median length of follow-up of surviving patients of 3.9 years, the 2- and 5-year overall survival results were significantly improved for patients with pN1 stage (85.2% and 74.7% respectively, $P = .0008$) compared to pN2 stage (64.3% and 41.4%, respectively). Although the 5-year follow-up for pN2 stage was not reached, the RFS results were also significantly in favor of pN1 stage with the 2-year RFS of 88.7% versus 69% ($P = .0005$).

Conclusion: Our local outcomes correlate with the prognostic pathological lymph node groupings of the AJCC 8th edition HPV-associated OPC staging manual, albeit with poorer than expected 5-year survival outcomes for those with pN2 stage. Patients were less likely to present with advanced pathological nodal stage, but when they did, there was a higher incidence of other traditional adverse pathological features which may have contributed to those results. Due to the small numbers in this cohort, definite conclusions cannot be made but a larger cohort may be able to explore the validity of these findings and their impact, if any, on prognosis and adjuvant therapy.

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The Role of Adjuvant Chemotherapy After Definitive Chemoradiation Therapy in Locoregionally Advanced Nasopharyngeal Carcinoma in a Non-endemic Area: Multi-institutional Retrospective Study Using Propensity Score Matching Analysis

Y.S. Kim,[1] Y.C. Ahn,[2] C.G. Lee Jr,[3] K.H. Cho,[4] S.H. Moon,[5] H.G. Wu,[6] Y.T. Oh Sr,[7] and W.K. Chung[8]; *[1]The Catholic University of Korea, Seoul, Korea, Republic of (South), [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South), [3]Yonsei University College of Medicine, Seoul, Korea, Republic of (South), [4]Research Institute and Hospital, National Cancer Center, Goyang, Korea, Republic of (South), [5]Proton Therapy Center, National Cancer Center, Goyang-si, Gyeonggi-do, Korea, Republic of (South), [6]Department of Radiation Oncology, Seoul National University Hospital, Seoul, Korea, Republic of (South), [7]Ajou University School of Medicine, Seoul, Korea, Republic of (South), [8]Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of (South)*

Purpose/Objective(s): It is unclear whether adjuvant chemotherapy (AC) provides an additional survival benefit over concurrent chemoradiation therapy (CCRT) in locoregionally advanced nasopharyngeal carcinoma (NPC). Thus, we evaluated the role of AC after definitive CCRT.

Materials/Methods: We undertook a multicenter retrospective study at 15 institutions. Seven hundred and seven patients of nasopharynx cancer staged T3-4 or N1-3 were collected. They received cisplatin-based CCRT alone or followed by AC consisting of cisplatin and fluorouracil. There were 380 patients in the no AC arm and 327 patients in the AC arm. Patients in both treatment arms were matched using the propensity score matching method, and then the clinical outcomes and toxicities were analyzed in finally matched 478 patients.

Results: At a median follow-up time of 46 months, the AC arm did not show higher overall survival (OS) (86% versus 80%, $P = .0894$) at 3 years. However, the AC arm had a significantly higher failure-free survival (FFS) rate at 3 years than the no AC arm (75% vs 66%, $P = 0.018$). AC was a significant factor for FFS on the multivariate analysis ($P = .046$; HR = 0.77; 95% CI 0.55-0.98). The AC arm did not achieve a significantly higher locoregional FFS rate at 3 years than the no AC arm (91% vs 84%, $P = .1115$). However, the 3-year distant FFS rate in the AC arm was significantly higher than no AC arm (83% vs 78%, $P = .0427$).

Conclusion: AC after definitive CCRT significantly improved FFS, however, which was not translated into the improvement of OS for the patients with locoregionally advanced NPC in a non-endemic region. The observed effect of AC was mainly attributed to the improved distant control, not locoregional control.

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Survival Benefit of Postoperative Chemotherapy for Intermediate-Risk Advanced Stage Head and Neck Cancer

M.M. Chen,[1] A.D. Colevas,[1] U. Megwalu,[1] and V. Divi[2]; *[1]Stanford University, Stanford, CA, [2]Department of Otolaryngology—Head and Neck Surgery, Stanford University, Stanford, CA*

Purpose/Objective(s): The National Comprehensive Cancer Network guidelines state that surgical patients with advanced stage head and neck cancer with risk features other than extracapsular extension (ECE) or positive margins should consider postoperative chemoradiation (CRT). No clinical trial has adequately assessed the survival benefit of adding adjuvant chemotherapy to this subgroup of intermediate risk patients.

Materials/Methods: Adult patients with stage III and IV head and neck squamous cell carcinoma (HNSCC) who received primary surgical treatment with postoperative CRT or RT from 2010 to 2014 were extracted from the National Cancer Database. Patients with pT1-2N1 disease, distant metastases, ECE, and positive margins were excluded. Our main outcome was overall survival (OS). Statistical analysis included χ^2 tests and Cox proportional hazards regression analysis.

Results: We identified 5552 adult patients with intermediate-risk advanced stage HNSCC. Compared to those who received postoperative RT, those who received CRT were more likely to be <70 years of age (86.7% vs 77.6%, $P < .001$), have a Charlson/Deyo comorbidity score of zero (78.5% vs 74.8%, $P = .003$), have pN2-3 disease (70.1% vs 45.1%, $P < .001$), and have private insurance (48.0% vs 41.3%, $P < .001$). Patients at community programs were more likely to receive CRT than those at academic centers (47.5% vs 37.3%, $P < .001$). On multivariable analysis for patients <70 years of age, CRT was associated with improved OS for patients with T1-4N2-3 disease (hazard ratio [HR], 0.73; 95% confidence interval [CI] 0.58-0.93) but was not associated with survival for patients with T3-4N0-1 disease (HR, 0.92; 95% CI 0.71-1.19). For patients ≥70 years of age, CRT was not associated with improved OS for patients with T1-4N2-3 disease (HR, 1.21; 95% CI 0.79-1.86) or T3-4N0-1 disease (HR, 1.08; 95% CI 0.71-1.65). For oropharyngeal cancer patients with human papilloma virus positive disease, CRT was associated with decreased OS (HR, 6.74; 95% CI 2.08-21.87).

Conclusion: Chemoradiation may offer a survival benefit for non-HPV intermediate-risk advanced stage HNSCC patients <70 years of age with T1-4N2-3 disease, but may not benefit those ≥70 years of age or those with T3-4N0-1 disease. Postoperative CRT is more commonly offered than RT in the community than in academic centers for these patients. Further research is needed to improve risk stratification of patients with intermediate risk features and determine who may benefit from CRT.

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De-escalation of Primary Target and Elective Neck Doses in HPV-Positive Oropharyngeal Cancers

G.Q. Yang,[1] D. Gintz,[2] A.O. Naghavi,[1] K. Shah,[3] J. Kennedy,[3] and J.J. Caudell[1]; *[1]H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology, Tampa, FL, [2]Moffitt Cancer Center, Tampa, FL, United States, [3]University of South Florida College of Medicine, Tampa, FL*

Purpose/Objective(s): Human papilloma virus-related oropharyngeal squamous cell carcinoma (OPSCC) is a highly curable malignancy that is increasing in incidence. Primary radiation therapy (RT) with or without chemotherapy currently achieves excellent long-term outcomes; however,

it may be associated with significant acute and long-term side effects. We hypothesized that reductions in dose to the primary target (<69.3 Gy) and elective neck (<50 Gy) would result in similar control and may reduce acute toxicity.

Materials/Methods: After IRB approval was obtained, a database of HPV or p16 positive non-metastatic OPSCC patients treated with definitive radiation therapy with or without chemotherapy was queried. Relevant features of patients in high-dose groups and low-dose groups were compared with Fischer Exact test. Locoregional control (LRC), regional control (RC), and overall survival (OS) were calculated from the end of RT and estimated via Kaplan-Meier method and comparisons made via log-rank test.

Results: A total of 387 patients were available for analysis with a median follow-up was 33 months. Standard doses of ≥69.3 Gy (median 70, range 69.3-75.2) were used in 298 patients, and <69.3 Gy (median 66 Gy, range 58-68 Gy) in 89 patients. Standard elective neck doses of ≥50 Gy (median 56 Gy, range 50-56 Gy) were used in 311 patients and <50 Gy (median 46, range 40-49.6) in 71 patients. Patients in the high-dose range to the primary target or elective neck were more likely to be higher AJCC 8th edition T stage, N stage, and overall stage ($P < .05$ for all comparisons). There was no difference in the 3-year LRC comparing <69.3 Gy and ≥69.3 Gy (95.2% and 91.8% respectively, $P = .67$), no difference in the 3-year RC comparing the <50 Gy and ≥50 Gy arms (94% vs 90% respectively $P = .41$). There was no difference in 3-year OS for both <69.3 Gy (95.3% and 87.3%, respectively, $P = .13$) and <50 Gy (95.6% and 87.9%, respectively, $P = .20$). When stratifying by AJCC 8th edition T, N, overall stages, or concurrent chemotherapy, there was no difference in LRC, RC, or OS at the different dose levels ($P > .22$ for all comparisons). The need for reactive gastrostomy tube (PEG) placements was significantly lower in patients receiving lower doses, 4.4% and 19.5% ($P < .01$). There were 14 (4.9%) grade ≥3 late effects in the ≥ 69.3 Gy arm compared to 1.1% in the <69.3 Gy; however, this was not statistically significant ($P = .32$).

Conclusion: Mild de-escalation of doses to the primary tumor and elective neck does not appear to adversely affect LRC, RC, or OS in patients with AJCC 8th edition I-III HPV-related OPSCC, which remained true after stratification. Patients treated with lower doses had significantly reduced PEG tube rates compared to those in the high-dose group.

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Risk Factors for Locoregional Failure and Survival in Pathologic Node-Negative (pN0) Oral Cavity (OC) Squamous Cell Carcinoma (SCC) Following Resection Alone

J.R. Parkhurst,[1] S. Mott,[2] M. Marquardt,[1] N.S. Andresen,[3] C.M. Anderson,[1] J. Buatti,[1] and J.M. Watkins[1]; [1]*Department of Radiation Oncology, University of Iowa Hospitals and Clinics, Iowa City, IA,* [2]*Holden Comprehensive Cancer Center, University of Iowa Hospitals and Clinics, Iowa City, IA,* [3]*University of Iowa School of Medicine, Iowa City, IA*

Purpose/Objective(s): We aim to identify risk factors for locoregional tumor control and survival in resected, pathologic node-negative (pN0) oral cavity (OC) squamous cell carcinoma (SCC) based upon clinicopathologic risk factors, in order to inform decisions on adjuvant therapy in this setting.

Materials/Methods: A retrospective analysis of clinicopathologic variable association with disease control and survival was completed. Eligible patients had unifocal non-metastatic OC SCC diagnosed between 2002 and 2014, managed surgically, with confirmed pN0 status, and without pre- or postoperative therapy. Patients were excluded for non-SCC histology, insufficient postoperative follow-up (<3 months, unless recurrence or death), and prior head/neck cancer or radiation therapy. Locoregional failure (LRF) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using Cox regression models.

Results: From 2002 through 2014, 770 patients with unifocal non-metastatic OC SCC underwent curative-intent resection, of whom 100 were eligible for analysis. Reasons for ineligibility were: no node dissection (n = 305), pN+ (180), preoperative or adjuvant therapy (74), prior head/neck cancer or radiation therapy (69), unavailable pathology (25), and insufficient follow-up (17). Median age at diagnosis was 60 years (range, 19-88) and a slight majority were male (n = 55). Pathologic stage was pT1-2 for 90 patients and pT3-4 for 10, and tumor grade (G) was 1-2 versus 3 in 87 and 8 cases, respectively (of 95 reported; 92% and 8%, respectively). Surgical margins were close (<1 mm) or positive in 7 cases. Perineural invasion (PNI) was noted in 28 cases, and lymphovascular invasion (LVI) was identified in 10 (of 88 reported; 32% and 11%, respectively). At a median follow-up of 62 months (range, 2-178), 26 patients experienced recurrence and 22 patients had died. The estimated 5-year rates of LRF and OS for the overall population were 26% (95% CI 17%-37%) and 88% (79%-93%). The initial site of disease failure was locoregional in 23 cases (local only in 18, regional nodal only in 2, and both in 3) and distant only in 3 cases. PNI was significantly associated with higher LRF (HR=2.49, 1.06-5.88; $P = .04$); otherwise, none of the variables were associated with LRF or OS. The estimated 5-year LRF rates for patients with versus without PNI were 45% versus 19%, respectively. No statistically significant differences in LRF were detected for other clinicopathologic characteristics, including pT-stage, margin status, LVI, or G3 characteristics. LRF was associated with worse OS ($P = .02$).

Conclusion: PNI was associated with higher rates of LRF. In resected, pN0 OC SCC with PNI, adjuvant therapy may provide an opportunity for improving disease control.

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Carboplatin-Based Chemoradiation Improves Outcomes Compared to Cetuximab Bioradiation in Cisplatin Ineligible Locally Advanced p16 Negative Head and Neck cancer

C. Barney,[1] A. Branstetter,[1] A. Yaney,[1] E. Healy,[1] R. Rupert,[2] A. Neki,[2] S.A. Walston Jr,[1] V.M. Diavolitsis,[1] D.M. Blakaj,[1] J.L. Wobb,[1] D.L. Mitchell,[1] J.C. Grecula,[1] P. Savvides,[3] and A.D. Bhatt[1]; [1]*The Ohio State University Wexner Medical Center, Department of Radiation Oncology, Columbus, OH,* [2]*The Ohio State University Wexner Medical Center, Division of Medical Oncology, Columbus, OH,* [3]*The University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital, Phoenix, AZ*

Purpose/Objective(s): Many patients cannot tolerate standard of care cisplatin (CP) concurrent with radiation therapy (RT) for the definitive treatment of locally advanced (LA) head and neck cancer (HNSCC). In such cases, cetuximab (CTX) bioradiation (bioRT) is an increasingly popular substitute therapy. Yet, mounting evidence suggests that the addition of cytotoxic chemotherapy to RT is needed to optimize clinical outcomes in HNSCC, especially in p16(-) disease. In this regard, concurrent carboplatin-based (CB) chemoradiation (CRT) is another alternative to CP-CRT; however, there are no large trials comparing the efficacy of CTX-bioRT or CB-CRT to CP-CRT in this population. We hypothesized that CB-CRT would result in superior clinical outcomes compared to CTX-bioRT in p16(-) LA-HNSCC.

Materials/Methods: We identified cases of treatment-naïve p16(-) LA-HNSCC (stage III-IVB) of the oropharynx (31%), larynx (55%), and hypopharynx (13%) who received definitive (≥70 Gy) CTX-bioRT (n = 35), CB-CRT (n = 43), or CP-CRT (n = 67) at our institution from 2009 to 2015. Variables with $P < .05$ on log-rank/Kaplan-Meier analysis were included as covariates in Cox proportional hazards modeling to adjust for potential confounders; variables included: concurrent systemic agent, sex, age, smoking history, T stage, N stage, performance status, and primary tumor site.

Results: We identified 145 cases: 107 men (73.7%), median age 60 years (range, 41-87), ≥T3 (63.4%), and ≥N2b (56.6%). There were no statistical differences in sex, age, smoking history, T stage, N stage, performance status, or frequency of primary site among the groups. The most common reasons for CP ineligibility were hearing loss (41.0%), medical comorbidities (35.9%), and renal disease (9%). Median follow up was 3 years. Locoregional control (LRC), distant metastasis-free survival (DMFS), recurrence-free survival (RFS), and overall survival (OS) at 3 years were not statistically different between those treated with CB or CP-CRT. When compared to CTX-bioRT, CB-CRT improved 3-year LRC (81.5 vs 40.0%; $P = .001$), RFS (76.9 vs 38.3%; $P = .009$), and OS (60.0 vs 55.2%; $P = .05$), with a trend toward improved distant metastasis free survival (89.5% vs 65.8%; $P = .06$). On MVA CB-CRT remained associated with improved LRC (HR 0.25, 95% CI 0.10-0.67; $P = .006$), RFS (HR 0.30, 95% CI 0.12-0.76; $P = 0.01$), and OS (HR 0.44, 95% CI 0.20-0.96; $P = .04$) compared to CTX-bioRT. On subset analysis of non-oropharynx primary tumors, concurrent platinum agents (CP or CB) were associated with improved 3-year larynx preservation compared to CTX-bioRT (83.6 vs 47.1%; $P = .02$).

Conclusion: When patients cannot receive CP, CB-CRT is an effective alternative in p16(-) LA-HNSCC. Furthermore, CB-CRT markedly improved LRC, RFS, and OS compared to CTX-bioRT and should be a preferred substitute for CP in this population. Prospective validation of these results is needed.

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What's the Matter With Matted Nodes? Significance of Matted Lymph Nodes in HPV-Related Oropharyngeal Squamous Cell Carcinoma: A Multi-institutional Population-Based Cohort Study

K. Huang,[1] R.N. Banerjee,[1] B. Debenham,[2] A. Patel,[2] F. Sabiq,[2] L. Harold,[1] D.P. Skarsgard,[3] J. Lysack,[2] S. Ghosh,[2] and H.C. Quon[1]; *[1]Tom Baker Cancer Centre, Calgary, Alberta, Canada, [2]Foothills Medical Centre, Calgary, Alberta, Canada, [3]University of Calgary, Calgary, Alberta, Canada*

Purpose/Objective(s): HPV-related oropharyngeal squamous cell carcinoma (OP SCC) is the subject of a number of recent clinical trials. With favorable survival outcomes compared to non-HPV related OP SCC, clinical trials have been aimed at treatment de-escalation or decreasing toxicity without compromising outcomes. The presence of matted lymph nodes has also become an exclusion criteria from such trials, however, its prognostic significance needs to be independently validated and the radiologic criteria for matted nodes needs to be further defined.

Materials/Methods: Patients diagnosed with locally advanced Stage III-IVb OP SCC between 2007 and 2011, p16+, treated with curative intent, were retrospectively reviewed. Pretreatment images were independently scored by two blinded radiologists for the presence of matted nodes according to seven definitions: 2 or ≥3 abutting nodes with or without loss of intervening fat plane; or 1 versus 2 versus ≥3 lymph node with surrounding ECS. Prognostic indicators of overall survival (OS) and recurrence-free survival (RFA) were calculated based on the Kaplan-Meier method. Univariate associations between lymph node status and survival were compared by log-rank test.

Results: Between 2007 and 2011, 161 patients with locally advanced p16+ oropharyngeal squamous cell carcinoma were diagnosed and treated with curative intent. Median follow-up was 55 months and median age was 47 years. Between the presence of the matted nodes group by any definition (MN) and the absence of the matted nodes group by any definition (AMN), OS and RFS at 2 years was 86.5% and 89.4% for the MN group and 87.9% and 85.2%, respectively, for the AMN group ($P = .22, .96$).

Conclusion: In this multi-institutional population-cohort comparison study, the prognostic significance of matted nodes in p16+ locally advanced oropharyngeal squamous cell carcinoma is evaluated. The presence of matted nodes, by a composite definition including all seven imaging categories, was not associated with worse overall survival or recurrence-free survival. Further analysis on specific matted node definitions is ongoing and will be reported. In the era of treatment de-escalation, our study further defines the prognostic significance of matted nodes in HPV-related OP SCC, which represent a relevant proportion of patients in contrast to non-HPV OP SCC counterparts, and can aid clinical decision making.

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Impact of Smoking Status on Survival Outcomes of Human Papilloma Virus (HPV) Positive Locally Advanced Oropharyngeal Carcinoma Stratified by Treatment Modality

N. Vawda,[1] R.N. Banerjee,[2] and B.J. Debenham[1]; *[1]University of Alberta, Edmonton, AB, Canada, [2]Tom Baker Cancer Centre, Calgary, AB, Canada*

Purpose/Objective(s): Both surgery +/- adjuvant therapy or definitive chemoradiation therapy (CRT) are valid options for the management for locally advanced oropharyngeal carcinoma (OPC) with no direct comparisons existing between the two treatment modalities. Tobacco exposure is known to affect the biological behavior of HPV positive OPC with intermediate outcomes relative to tumors that are HPV-associated with no smoking exposure and smoking related HPV negative tumors. We aim to evaluate the impact of smoking on outcomes of patients with HPV-associated locally advanced OPC when stratified by treatment modality.

Materials/Methods: A retrospective chart review was undertaken on 352 patients with known p16 overexpressing locally advanced OPC and who were managed with curative intent therapy between 2006 and 2015. Demographic, clinicopathological data and treatment outcomes were recorded. The impact of smoking status on Overall Survival (OS) and Recurrence-Free Survival (RFS) were compared using the Kaplan Meier curves with the log-rank test used to determine statistical significance. Survival curves were generated for the entire cohort, and then separately for each treatment modality, for different levels of smoking exposure.

Results: Of the 352 patients, 67.6% (N = 238) were managed with primary chemoradiation therapy and 32.4% (N = 114) with primary surgery +/- adjuvant therapy. The median smoking pack-year was 15. Twenty seven percent of patients were active smokers at the time of presentation, with 40.3% identifying as former smokers and 32.7% having never smoked. Median follow-up for surviving patients was 4.2 years. Current smokers had a significantly worse relapse-free survival and overall survival compared to never and former smokers ($P = .03$

and $P = .0001$, respectively), with outcomes significantly worsening with increasing smoking exposure. The 5-year OS for more than 10, 20, and 30 pack-year smoking history was 73.2%, 64.7%, and 59.1% respectively. Current smokers managed with CRT had a 5-year OS of 64.2% compared with former and never smokers (93.1% and 78.2%, respectively). For current smokers managed primarily by surgery, the 5-year OS was 57.6% compared with former and never smokers (69.6% and 73.5%, respectively).

Conclusion: Smoking is an independent prognostic factor in HPV-associated locally advanced OPC. Current smokers and those with higher smoking exposure had poorer outcomes irrespective of their primary modality of treatment, and therefore it is not possible to recommend a preferential modality of treatment for patients with HPV positive tumors who have a significant smoking history. Outcomes were worse for patients managed surgically compared to CRT; however, as this review did not specifically compare outcomes between the two treatment modalities, this requires further evaluation.

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Multidisciplinary Care of Head and Neck Cancer in Elderly Patients

B.K. Leachman, L. DeMora, T.M. Churilla, B. Ebersole, J. Bauman, J.A. Ridge, M. Lango, B. Egleston, and T.J. Galloway; *Fox Chase Cancer Center, Philadelphia, PA*

Purpose/Objective(s): Multidisciplinary care (MDC) of oncology patients optimizes diagnosis, staging, treatment, and outcomes. We sought to characterize the patterns of MDC in US Medicare patients diagnosed with head and neck squamous cell carcinomas (SCC).

Materials/Methods: We examined patients diagnosed with non-metastatic SCC of the oral cavity, oropharynx, hypopharynx, nasopharynx, and larynx from 1991 to 2011 using the Survival, Epidemiology, and End Results (SEER)-Medicare linked dataset (Table 1). MDC was defined as a post-diagnosis, pretreatment evaluation by an otolaryngologist/head and neck surgeon and radiation oncologist for stages 0-II cancer. For stages III-IV cancer, MDC also included evaluation by a medical oncologist. We separately considered evaluation by a speech language pathologist (SLP) prior to definitive therapy in subset analyses (MDC+SLP). Treatment initiation was defined as surgical resection or initiation of chemoradiation within 365 days of diagnosis. Multivariable logistic regression was used to analyze factors associated with receipt of MDC and the Cochran-Armitage trend test was used to examine the use of MDC over time.

Results: We identified 19,874 eligible patients, median age 74 years, 71% male, 56% larynx cancer, 72% patients treated with initial non-surgical therapy. Of 10,445 patients with stages 0-II tumors, 71% received MDC. Of 9429 patients with stages III-IV tumors, 27% received MDC. Use of MDC increased from 30% in 1991 to 57% in 2011 ($P < .001$). Regardless of stage, few patients see SLP (2.2%) and even fewer receive MDC+SLP (1.0%) prior to definitive therapy. Most with early-stage tumors who did not have MDC had initial surgery (with or without adjuvant therapy). Of these 2495 early-stage tumors managed with initial surgery, 13% received MDC. Early stage larynx and oropharynx cancers managed with primary surgery rarely had documented visits to a radiation oncologist prior to surgery (15% and 13% respectively). Of 2989 advanced tumors managed with initial surgery, 23% consulted with a radiation oncologist prior to surgery; 5.8% received MDC. Factors associated with receipt of MDC on MVA are summarized in the Table. Patient race and income did not inform receipt of MDC.

Conclusion: Most early-stage patients are seen by a surgeon and radiation oncologist, but few advanced stage patients meet all members of the MDC team. Regardless of stage, MDC is relatively uncommon among patients treated with initial surgery. Patients with oropharynx or oral cavity tumors are less likely to receive MDC. Consultation with a speech language pathologist prior to definitive therapy for head and neck cancer is very rare.

Abstract 124; Table 1

Factor	OR	95% CI	
Oropharynx	0.82	0.75	0.90
Oral Cavity	0.13	0.12	0.14
Nasopharynx	1.37	1.09	1.72
Male	1.11	1.02	1.20
Age ≥70 years	1.19	1.10	1.29
Charlson CI ≥2	1.13	1.04	1.24
Less Urban/ Rural	0.85	0.75	0.97
Midwest	1.18	1.05	1.32
Stages III-IV	0.10	0.09	0.11

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In the Era of PET Scans, Is Unilateral Radiation Therapy Enough to Treat Squamous Cell Carcinomas of the Head and Neck From an Unknown Primary?

A. Platek,[1] M.D. Mix,[2] V. Chaudhri,[2] M.E. Platek,[3,4] W.L. Hicks,[3] M.A. LaCombe,[2] K.E. Wooten,[3] L.H. DeGraaff,[1] A.J. Iovoli,[1] V. Gupta,[3] A. Hassan,[3] M. Kuriakose,[3] S.S. Hahn,[2] and A.K. Singh[3]; *[1]Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [2]SUNY Upstate Medical University, Syracuse, NY, [3]Roswell Park Cancer Institute, Buffalo, NY, [4]Buffalo State College, Buffalo, NY*

Purpose/Objective(s): The goal of this study was to examine the effects of radiation treatment volume on overall survival and rates of recurrences among a population of head and neck cancer patient with unknown primaries at two different cancer institutes.

Materials/Methods: Clinical characteristics were abstracted from the medical records of 62 patients with unknown primaries of the head and neck treated between 2000 and 2015 at Roswell Park Cancer Institute (Buffalo, NY, n = 33) and Upstate Medical University (Syracuse, NY, n = 29). Patients either received radiation therapy to one side of the head and neck, unilateral radiation (n = 34, RPCI = 28, Syracuse = 6), or radiation therapy to both sides of the head and neck, bilateral radiation (n = 28, RPCI = 5, Syracuse = 23). Mann Whitney U tests for ordinal data and χ^2 and Fischer exact tests for categorical data were conducted to compare demographic and outcome factors between patients treated unilaterally and patients treated bilaterally. Overall survival (OS) and disease-free survival (DFS) trends for unilaterally and bilaterally treated patients were estimated using the Kaplan-Meier method. The effect of treatment volume on overall survival and disease-free survival was examined using multivariate Cox proportional hazard regression models. Models were adjusted for age and nodal stage.

Results: No significant differences in the frequency of local ($P = .32$), regional ($P = .50$), or distant ($P = .76$) failures were observed between patients treated unilaterally and those treated bilaterally. No significant differences were found in OS (3-year OS bilateral = 71.67%, unilateral = 77.90%, $P = .503$) or DFS (3-year DFS bilateral = 77.92%, unilateral = 69.43%, $P = .626$). Results from univariate (HR = 0.74, 95% CI 0.30, 1.80, $P = .504$) and multivariate analysis (HR = 0.74, 95% CI 0.31, 1.81, $P = .511$) for the effect of treatment volume on overall survival showed no significant difference in risk of mortality between the two treatment volumes. There was no statistically significant effect of treatment volume on disease free survival in both univariate (HR = 0.77, 95% CI 0.28, 2.18, $P = .627$) and multivariate (HR: 0.68, 95% CI 0.24, 1.93, $P = .465$) analyses.

Conclusion: Unilateral radiation therapy is as effective in controlling disease as bilateral radiation therapy with similar overall survival in patients with squamous cell carcinomas of the head and neck from unknown primaries. In addition, unilateral radiation therapy may reduce acute and late toxicity effects of treatment as well as lower the risk of toxicity should a contralateral recurrence emerge.

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Survival After Proton and Photon Radiation Therapy in Patients With Head and Neck Cancers: A Study of the National Cancer Database

M.R. Waddle,[1] M. Heckman,[1] N.N. Diehl,[1] W. Stross,[1] D. Miller,[1] T. Kaleem,[1] R.C. Miller,[1] B.C. May Jr,[1] J.L. Peterson,[1] L.A. Vallow,[1] K.S. Tzou,[1] and S. Ko[2]; *[1]Mayo Clinic, Jacksonville, FL, [2]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL*

Purpose/Objective(s): Proton beam radiation therapy (PBRT) utilization has increased over the past ten years for the treatment of head and neck cancers in the United States. Many studies exist evaluating toxicity with PBRT, but few studies have compared relative rates of survival to photon radiation therapy. The goal of this study was to compare survival after radiation therapy between head and neck cancer patients treated with proton versus photon radiation therapy in a large hospital-based population.

Materials/Methods: The National Cancer Database was used to identify patients diagnosed with squamous cell carcinoma or adenocarcinoma of the head and neck who received radiation therapy between 2004 and 2013. Standardized differences in characteristics between groups were estimated before and after propensity score matching. Propensity score matching was performed to create equivalent comparison in a 3:1 fashion for photon to proton therapy patients based on multivariable logistic regression models. The Kaplan-Meier method was used to estimate survival.

Results: A total of 164,580 patients were included in the analysis after exclusions, 271 of which were treated with PBRT. The median follow-up was 2.6 years. PBRT was used most commonly for cancers of the oral cavity (27.7%), nasal cavity (19.9%), Oropharynx/hypopharynx (18.5%), and salivary gland (18.1%). Prior to matching, patients receiving PBRT were more likely to have income >$64,000, to have private insurance, to be treated at an academic hospital, and have less comorbidities. On propensity-matched analysis, the groups showed adequate matching. Propensity analysis showed that PBRT (n = 157) was associated with improved 5-year overall survival compared with the photon radiation therapy group (n = 1400), 66.8% versus 60.0% (HR 0.73, P = .028). PBRT had a similar 5-year overall survival to IMRT treatment (n = 469), 66.8% versus 64.0% (HR 0.78, P = .14).

Conclusion: This is the first study demonstrating increased survival of PBRT when compared with photon based radiation for all types of head and neck cancer. This effect was no longer statistically significant when comparing PBRT to IMRT. The PBRT group showed significant differences in demographic and clinical factors, indicating a possible bias in the use of PBRT. Additional prospective randomized studies are warranted to investigate further the potential benefits of PBRT.

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Addition of Chemotherapy is Associated With a Survival Detriment for Early Stage (T1-2N0M0) Glottic Squamous Cell Carcinoma Treated With Definitive Radiation Therapy

C. Wang,[1] A.U. Kishan,[2] A. Raldow,[3] P.J. Beron,[4] D.J. Wong,[5] M. St.John,[6] M.L. Steinberg,[7] and R.K. Chin[8]; *[1]UCLA Department of Radiation Oncology, Los Angeles, CA, [2]Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA, [3]Harvard Radiation Oncology Program, Boston, MA, [4]University of California, Los Angeles-David Geffen School of Medicine, Los Angeles, CA, [5]UCLA David Geffen School of Medicine, Department of Medicine, Division of Hematology/Oncology, Los Angeles, CA, [6]UCLA David Geffen School of Medicine, Department of Head and Neck Surgery, Los Angeles, CA, [7]University of California, Los Angeles, Los Angeles, CA, [8]UCLA David Geffen School of Medicine, Department of Radiation Oncology, Los Angeles, CA*

Purpose/Objective(s): The role of chemoradiation therapy (CRT) in treating patients with early-stage glottic squamous cell carcinoma (SCC), especially for T2N0 glottic SCC with impaired vocal cord mobility, remains unexplored. We sought to evaluate the impact of CRT on survival in early-stage glottic SCC by employing the Surveillance, Epidemiology, and End Results (SEER) program database.

Materials/Methods: We included patients with localized (T1-4N0M0) glottic SCC (n = 5046) diagnosed between 2004 and 2014, and treated with definitive radiation therapy (RT) alone, CRT, or laryngectomy alone in the SEER database. Disease-specific mortality (DSM) was evaluated via multivariate regression using a competing risk model that accounts for other-cause mortality (OCM) as a competing risk event for DSM. One-to-one propensity score matching (PSM) between CRT and RT cohorts was also performed to facilitate comparison of cumulative DSM and OCM incidences stratified by T stage.

Results: After stratification by T stage, CRT was associated with increased DSM in T1 and T2 glottic SCC (AHRs of 4.202 and 2.081, respectively; P<.001 for both). For T2N0 glottic SCC with and without impaired vocal cord mobility, CRT resulted in significantly increased DSM compared to RT alone in both cohorts (AHR of 2.440, P < .001 and AHR of 2.087, P = .046 respectively). After PSM, cumulative incidence plots demonstrated a statistically significant increase in DSM associated with CRT compared to RT alone for both T1 and T2 glottic SCC.

Conclusion: CRT for T1-2N0M0 glottic SCC resulted in a statistically significant increase in DSM compared to RT alone. This pattern persisted upon further stratification based on vocal cord mobility status for T2N0M0 glottic SCC. This finding warrants additional investigation to elucidate the cause of the increase in DSM associated with chemotherapy in early-stage glottic SCC.

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p16 and HPV-DNA Tests Discordance in Human Papilloma Virus (HPV)-Associated Oropharyngeal Cancer: Results From a Case-matched Study

T. Lin,[1] A.S.R. Mohamed,[2] H. Elhalawani,[3] A. Jethanandani,[4] C.D. Rock,[5] B. Williams,[6] G.B. Gunn,[3] A.S. Garden,[2] D.I. Rosenthal,[2] and C.D. Fuller[7]; *[1]Baylor College of Medicine, Houston, TX, [2]MD Anderson Head and Neck Cancer Symptom Working Group, The University*

of Texas MD Anderson Cancer Center, Houston, TX, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]The University of Tennessee Health Science Center College of Medicine, Memphis, TN, United States, [5]The University of Texas MD Anderson Cancer Center, Division of Radiation Oncology, Houston, TX, [6]Furman University, Greenville, SC, [7]MD Anderson, Houston, TX

Purpose/Objective(s): HPV-associated oropharyngeal cancer (OPC) has been associated with improved prognosis compared to HPV-negative OPC. Concomitant HPV DNA and p16 testing has been shown to improve sensitivity and specificity; however, the prognostic significance of discordant testing (i.e., p16+/HPV DNA or p16-/HPV DNA+) in OPC patients has not been quantitatively studied due to inadequate sample sizes. We aim to determine whether there is a prognostic significance for discordant p16/HPV-DNA test results for OPC patients receiving curative intent radiation treatment.

Materials/Methods: A case-control study design was used to retrospectively analyze 136 patients with pathologically proven oropharyngeal cancer (OPC) treated with curative intent radiation therapy at our institution between the years 2005 and 2012. HPV DNA status was evaluated using in-situ hybridization (ISH) methods, and p16 status was identified via immunohistochemistry (IHC). Two subgroups were identified: concordant (p16+/HPV DNA+) and discordant (p16+/HPV DNA- or p16-/HPV DNA+) subgroups, with the former serving as control. Characteristics including sex, age at diagnosis, ethnicity, smoking status, cancer stage, and treatment modality were identified. Kaplan-Meier survival analysis and univariate Cox proportional hazard analysis were performed.

Results: Patient characteristics, including age, sex, smoking status, stage, pathological grade, tumor subsite within oropharynx, treatment modality, and follow-up duration were well-matched between the concordant and discordant subgroups. Survival analysis failed to show any statistically significant difference between the concordant and discordant subgroups in terms of overall survival, local, locoregional, or distant control. The discordant subgroup was comprised entirely of p16+/HPV DNA- patients; no patients in the discordant subgroup were found to be p16-/HPV DNA+. Univariate analysis demonstrated statistically significant correlation between overall survival and N-category in the discordant group ($P = .024$ by Effect Wald Test), in contrast to the concordant group ($P = .18$).

Conclusion: This study suggests that HPV test discordance is not correlated with differential treatment outcomes as compared to HPV test concordance. p16 testing by IHC has been previously shown to be more sensitive and specific than HPV DNA testing by ISH. This study further validates this observation and suggests that p16 may be used as a standalone test in the diagnosis of HPV in HNC patients.

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Pre-radiation Therapy Tumor Volume as a Predictor of Local Control in Squamous Cell Carcinoma of the Supraglottic Larynx: A 30-Year Experience

S.R.W. Nurkic,[1] T. Nurkic,[2] C.G. Morris,[1] R.J. Amdur,[1] and W.M. Mendenhall[3]; *[1]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [2]Department of Radiology, University of Florida College of Medicine, Gainesville, FL, [3]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL*

Purpose/Objective(s): To examine the utility of pretreatment CT in predicting local control (LC) in patients with squamous cell carcinoma (SCC) of the supraglottic larynx treated with primary radiation therapy (RT).

Materials/Methods: 167 patients treated with primary RT for supraglottic larynx SCC between 1983 and 2013 were reviewed. Patients had received pretreatment diagnostic CT imaging of the larynx and neck with intravenous contrast from which the primary tumor volume was delineated. The mean dose was 74 Gy; 20% received concurrent chemotherapy. LC, larynx function at last follow-up, and RT complications were recorded. Tumor volume was evaluated with respect to outcome.

Results: Median age, 61 years. Mean follow-up, 96 months. Of these, 43% had T1-T2, 46% had T3, and 11% had T4 disease; 49% had N0 disease. Median tumor volume, 5.1cm^3 (0.4-188 cm^3). The 10-year LC for the entire patient population was 78.9%. LC at 5 and 10 years was stratified by tumor volume: 0-4.9 cm^3, 5-8.9 cm^3, and 9 cm^3 and greater. LC by tumor volume among all patients at 10 years were as follows: 0-4.9 cm^3, 90.8%; 5-8.9 cm^3, 67.3%; and 9 cm^3 and greater, 69.4%. LC with preserved larynx function by tumor volume at 10 years was as follows: 0-4.9 cm^3, 76.7%; 5-8.9 cm^3, 61.5%; and 9 cm^3 and greater, 53.4% LC and LC with preserved larynx function was significantly different between primary tumor volume groups ($P < .001$). On multivariate analysis, primary tumor volume was the only significant predictor of LC and LC with preserved larynx function ($P < .005$). T stage, N stage, pre-RT larynx dysfunction, chemotherapy, and RT dose did not significantly influence outcome. Six patients developed soft-tissue necrosis; 2 suffered fatal carotid blowouts. Patients with grade 5 complications were treated with concomitant chemotherapy. Four patients required total laryngectomy for a non-functional larynx; 14 required permanent tracheostomy or gastrostomy tube.

Conclusion: Pretreatment primary tumor volume helps identify patients most likely to experience LC with primary RT alone or combined chemoradiation. LC for supraglottic larynx SCC is optimal if the primary tumor volume is <5.0cm^3.

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Performance of an Oral Rinse Point-of-Care Assay to Aid in the Diagnosis of Head and Neck Squamous Cell Carcinoma in a High-Risk Danish Ear-Nose Throat Clinic

D. Hellelstrup,[1] M. Donovan,[2] E. Franzmann,[3] and M. Klokker[1]; *[1]University of Copenhagen, Copenhagen, Denmark, [2]Icahn School of Medicine at Mt. Sinai, NYC, NY, [3]University of Miami, Miami, FL*

Purpose/Objective(s): Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cause of cancer mortality. The ability to detect HNSCC an earlier stage could have significant impact on overall outcome. Previous studies demonstrated that a point-of-care (POC) lateral flow assay and an ELISA LAB test measuring CD44 and total protein (TP) aid in the diagnostic process for HNSCC. We sought to better understand the prospective performance of the POC assay in a hospital-based high risk oral clinic in Denmark.

Materials/Methods: Oral rinses were obtained from 150 consecutive patients presenting for physical exam and biopsy in a high-risk ENT clinic (Rigshospitalet, Copenhagen, Denmark). Operators were provided POC visual tools to record assay results. A positive POC test is a visible CD44 band or level of TP (i.e. color-graded scale from 1-5, recommended cutoff >/=2 or adjusted >/=3), with Sensitivity (Se), Specificity (Sp), NPV to evaluate correlation with biopsy.

Results: We had 131 evaluable patients, 30% with HNSCC. Average age: 57 years, 43% male, 100% white and 59% smokers. Using POC levels of

CD44 or a TP cutoff of 3, the assay achieved a Se of 73% and Sp50%. Applying a TP of 2 for non-smokers and 4 for smokers further improved assay performance: Se 80% and Sp 43%. With a prevalence of 9.27%, the NPV was >90%.

Conclusion: POC assay performed well for discriminating HNSCC. Additional studies are underway to further confirm these results and compare with the LAB test.

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Prognostic Impact of HPV-Associated p16 Expression and Smoking Status on Outcomes Following Radiation Therapy for Oropharyngeal Cancer: the MARCH-HPV Project

P. Lassen,[1] B. Lacas,[2] J.P. Pignon,[3] A. Trotti,[4] B. Zackrisson,[5] Q. Zhang,[6] J. Overgaard,[7] and P. Blanchard[8]; *[1]Department of Oncology and Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Biostatistics and Epidemiology, Gustave-Roussy, Paris-Saclay University, Paris, France, [3]Department of Biostatistics and Epidemiology, Gustave-Roussy, Paris-Saclay University, Paris, France, [4]Moffitt Cancer Center and Research Institute, Tampa, FL, [5]Department of Radiation Sciences - Oncology, Umeå University, Umeå, Sweden, [6]NRG oncology, Philadelphia, PA, [7]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [8]The University of Texas MD Anderson Cancer Center, Division of Radiation Oncology, Houston, TX*

Purpose/Objective(s): To evaluate the prognostic and predictive impact of HPV-associated p16-expression and to assess the combined prognostic impact of p16 and smoking on altered fractionated radiation therapy (RT) for oropharyngeal cancer (OPC) within the frames of the update of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH).

Materials/Methods: Patients with OPC, known tumor p16 status, and smoking history were identified from the MARCH update, resulting in a dataset of 815 patients from four randomized trials (RTOG9003, DAHANCA6&7, RTOG0129, ARTSCAN). HPV status was determined according to p16 immunohistochemistry. Analysis was performed using a Cox model stratified by trial and adjusted on gender, age, T stage, N stage, type of radiation therapy fractionation, p16 status, and smoking. Primary endpoint was progression-free survival (PFS).

Results: In total, 465 patients (57%) of the patients had p16-positive tumors and 350 (43%) p16-negative. Patients with p16-positive tumors were significantly younger (mean: 56 vs 59 years, $P = .0002$), in better performance (PS = 0: 74% vs 50%, $P < .0001$), had smaller tumors (T1-2: 46% vs 33%, $P < .0001$) and more advanced N stage (N+: 87% vs 76%, $P <. 0001$) compared with the p16-negative subgroup. p16-positive patients had significantly better PFS (HR = 0.42 [95% CI 0.34-0.51], 28.9% absolute increase at 10 years) and OS (HR = 0.40 [0.32-0.49], 32.1% absolute increase at 10 years) than patients with p16-negative tumors. No interaction between p16-status and fractionation schedule was detected. Smoking negatively impacted outcome; in the p16-positive subgroup, never smokers had significantly better PFS than former/current smokers (HR = 0.49 [0.33-0.75], 24.2% survival benefit at 10 years).

Conclusion: The strong prognostic impact of p16-status was confirmed and especially p16-positive never smoking patients have superior outcome after RT.

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Bolus Versus Weekly Chemotherapy in Definitive Chemoradiation for Nasopharyngeal Cancer

V.W. Osborn,[1,2] C.J. Tsai,[2] E. Sherman,[3] D.G. Pfister,[4] S.S. Baxi,[4] L. Dunn,[4] A. Ho,[4] L. Michel,[3] N. Riaz,[2] D.S. Higginson,[2] J.E. Leeman,[2] S. Patel,[4] P. Xie,[2] X. Li,[2] N. Lee,[2] and S. McBride[4]; *[1]SUNY Downstate Medical Center, Brooklyn, NY, [2]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [3]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [4]Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Ongoing randomized controlled trials for nasopharyngeal carcinoma (NPC) utilize administration of weekly concurrent cisplatin (cis), although there is limited data comparing its outcomes with bolus dosing. We therefore set out to compare efficacy of weekly versus bolus cisplatin in chemoradiation therapy (CRT) for the definitive treatment of NPC.

Materials/Methods: We conducted a single institution retrospective review of patients undergoing definitive CRT for NPC with IMRT and/or protons between January 1, 2003, and December 31, 2016. Patients receiving induction chemotherapy or who did not receive cis were excluded. Dosing regimens were recorded as well as age, smoking status (≥10 pack-years vs <10), Charlson Comorbidity Index (CCI) (0, 1, or ≥2), stage grouping (I, II-III, IVA, or IVB), EBV (EBER) status and receipt of adjuvant chemotherapy. Bolus and weekly cis were grouped as intent-to-treat. The Kaplan-Meier method was used to compare locoregional control (LRC), progression free survival (PFS), distant metastasis (DM) and overall survival (OS). Univariate and multivariate Cox regression analysis were also performed to assess for factors impacting the same aforementioned outcomes.

Results: 159 patients were identified of whom 89 received bolus and 51 received weekly cis. Median age was 51.71% of patients were male. Median follow up was 53.5 months (range 2.7-147.0), 53.5 months for bolus and 16.9 months for weekly cis. 17 patients cumulatively received <200 mg/m2 of cisplatin, 8% of the bolus group and 17% of the weekly group. 98% of patients' radiation therapy was delivered to a dose of at least 6996 cGy (or equivalent). 10 patients receiving bolus and 9 patients receiving weekly cis had documented locoregional failures. Two-year LRC was 95% with bolus and 79.2% with weekly cis ($P = .005$). Two-year PFS was 85.1% with bolus versus 69.2% with weekly cis ($P = .064$). DM or OS were not significantly associated with use of bolus versus weekly cis ($P = .83$ and .417 respectively). On multivariate analysis, both lower stage grouping ($P = .003$) and bolus cis ($P = .008$) were associated with significantly improved LRC, but not receipt of ≥200 mg/m2 cis ($P = .297$), age, smoking status, KPS, EBV or use of adjuvant chemo. There was improved PFS with lower stage grouping ($P = .009$), and lower CCI (.039) and a trend toward improvement with bolus cis ($P = .069$), but not receipt of ≥200 mg/m^2 cis ($P = .263$).

Conclusion: This single institution retrospective analysis demonstrated a significant improvement in 2-year LRC associated with bolus CRT compared to weekly that was independent to total dose within the narrow range of total dose administered within this cohort. The results are hypothesis-generating, and further prospective investigation into comparing the two regimens is likely warranted.

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Impact of Treatment Duration on the Outcomes of Patients With Locally Advanced Head and Neck Cancer Undergoing Surgery and Postoperative Radiation Therapy

H. Bahig,[1] A.S.R. Mohamed,[1] A.S. Garden,[1] S.P. Ng,[1] S. Lai,[1] R.S. Weber,[1] C.D. Fuller,[1] and D.I. Rosenthal[2]; [1]*The University of Texas MD Anderson Cancer Center, Houston, TX,* [2]*MD Anderson Head and Neck Cancer Symptom Working Group, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): We aim to determine the impact of treatment duration on the oncologic and survival outcomes of patients with locally advanced head and neck cancer undergoing surgery and postoperative radiation therapy (PORT).

Materials/Methods: A retrospective analysis of 500 patients with stage III or IV squamous cell carcinoma of the oral cavity or larynx that underwent surgery and PORT from 1984 to 2011 at MD Anderson Cancer Center was conducted. Fifty-one percent of patients had larynx cancer and 49% had oral cavity cancer; median dose was 60 Gy (53-69 Gy) in 30 fractions (30-41 fractions). Kaplan-Meier curves were used for locoregional (LRC), recurrence-free survival (RFS), and overall survival analysis (OS). Cox proportional hazard ratio models were used for univariate and multivariate analysis of potential predictive variables. Variables related to time (diagnosis-to-PORT completion, diagnosis-to-surgery time, treatment package time, and PORT duration) found to be associated to an outcome on univariate analysis were used in subsequent recursive partitioning analysis (RPA) to identify appropriate cutoff point.

Results: Actuarial 5- and 10-year LRC, RFS and OS were 82% and 75%, 65% and 59%, and 54% and 38%, respectively. On univariate analysis, there was a trend for a significant association between diagnosis-to-surgery time and LRC ($P = .07$) and diagnosis-to-PORT completion time and LRC ($P = .08$); PORT duration was significantly associated with OS ($P = .01$). Diagnosis-to-PORT completion time of ≥ 82 days was identified as a significant cutoff point for adverse LRC outcomes using RPA; no cutoff point could be identified for diagnosis-to-surgery time and PORT duration time. On multivariate analysis, only node positive disease ($P = .001$) and T stage 3-4 ($P = .006$) were associated with worse LRC, whereas node positive disease ($P = .001$), T stage 3-4 ($P = .001$) and longer PORT duration time (0.048) were associated with worse OS.

Conclusion: This study confirms high long-term cancer control outcomes achieved by our institution in patients with oral cavity and larynx cancer undergoing PORT. In addition to the known effect of RT duration time and tumor stage on outcomes, our study suggests that diagnosis-to-PORT completion time as well as diagnosis-to-surgery time may be predictors of LRC outcomes in these patients.

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Evaluation of the AJCC 7th, ICON-S, and HPV-Path Staging Systems for Surgically Managed HPV/p16+ve Oropharyngeal Squamous Cell Carcinoma Patients

P. Gupta,[1] J.C. Migliacci,[1] A. Hay,[1] M. Rosenthal,[1] N. Lee,[2] R.J. Wong,[3] J. Shah,[1] S. Patel,[1] and I. Ganly[1]; [1]*Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY,* [3]*Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): The differences in the outcome of HPV positive and the HPV negative patients have led to a separate staging system for oropharyngeal squamous cell carcinoma (OPSCC). The changes have been driven by the ICON-S Trial (clinical staging) and the HPV-Path Study (Pathological System) both of which have been incorporated in the new AJCC 8th edition. The purpose of our study is to evaluate the two staging systems along with the previously used AJCC 7th edition, in terms of predicting outcomes, in patients undergoing surgery as the initial treatment at one institute.

Materials/Methods: A retrospective review of IRB-approved patient database at one institute, from 1985 to 2015, was used to identify patients with HPV/p16+ve OPSCC. Patients that had received any form of neoadjuvant therapy, had HPV negative or unknown status, or with metastatic disease at presentation were excluded from the study. The clinicopathological data were utilized to categorize patients based on the AJCC 7th edition, ICON-S, and HPV-Path Staging systems. The survival data were analyzed using Kaplan-Meier methods. The Breslow test was used for univariate analysis to evaluate staging systems.

Results: A total of 218 patients were found eligible for the study. The baseline characteristics of the study cohort were similar to the ICON-S trial and the HPV-Path study. The AJCC 7th staging system failed to predict outcomes and did not serve as a good model for the survival data. The ICON-S system performed better than the AJCC-7th by the reclassification of the nodal categories, but it failed to show a significant difference in 5-year OS for Stage I and II ($P = .192$). The HPV-Path system accounting for the number of nodes involved served as the best fit, with a consistent decline in survival across all stages with no overlap (Table 1).

Conclusion: The current analysis shows the improvement of both the ICON-S and HPV-Path staging system over the current AJCC 7th edition. It also serves as a strong evidence of better performance of the pathological staging system over the newly adopted clinical staging system in patients with surgery as the initial treatment.

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Abstract 134; Table 1 Evaluation of different staging systems with respect to 5-year OS and 5-year DSS

AJCC − 7th edition				
Staging System	5-year OS	*P* Value	5-year DSS	*P* Value
Stage 1	33.3%	NA	0	NA
Stage 2	86.5%	Ref	86.5%	Ref
Stage 3	81.7%	.241	82.8%	.446
Stage 4	79.2%	.947	89.7%	1.863
ICON-S system				
Staging System	5-year OS	*P* Value	5-year DSS	*P* Value
Stage 1	82.4%	Ref	89.4%	Ref
Stage 2	76.9%	.192	79.1%	.059
Stage 3	54.5%	.009	71.4%	.621
HPV-Path System				
Staging System	5-year OS	*P* Value	5-year DSS	*P* Value
Stage 1	86.9%	Ref	93.1%	Ref
Stage 2	67.2%	.002	75.2%	.005
Stage 3	30.0%	<.001	40.0%	.000

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Do Subgroups (T3-T4 Versus Nodal Metastases) of Intermediate-Risk Head and Neck Cancer Matter in Empirical Treatment With Postoperative Radiation Therapy?

F.L. Ampil,[1] G. Caldito,[1] G. Ghali,[1] C.A.O. Nathan,[2] G. Mills,[1] D. Kim,[1] T. Richards,[1] M. Vora,[1] T. Lian,[1] and E. Milligan[1]; [1]*Louisiana State University Health Sciences Center, Shreveport, LA,* [2]*Louisiana State University Health Shreveport, Shreveport, LA*

Purpose/Objective(s): In head and neck cancer (HNC), the high-risk (for recurrence) category is defined by histopathology showing nodal metastasis with extracapsular spread (ECS) and/or tumor-positive surgical margins. The low-risk class is indicated by stage I-II disease, low grade tumor, negative surgical margins, and the absence of ECS as well as any other adverse pathologic features. The intermediate-risk (IR) designation is characterized by pathology other than those mentioned in the preceding risk groups. The goals of this retrospective study were to determine the long-term results of postoperative radiation therapy (PORT) administered to individuals with IR-HNC and to compare the outcomes in two histopathologic subgroups of IR-HNC to assist in defining which patients are more appropriate candidates for PORT.

Materials/Methods: Histopathology reports of patients who underwent surgery for stage I-IV HNC during a period of over 30 years (1977-2013) were retrospectively reviewed. After identification of 134 IR-HNC study participants, the patients were assigned to subgroups with documented nodal metastases/pN+ (65 patients) or with advanced T3/T4 primary tumors (69 patients). Endpoints of the analysis included the frequency of locoregional and distant failures, and Kaplan-Meier survival and morbidity rates.

Results: At a median follow-up of 24 months, the overall locoregional and distant relapse rates were 20% and 18%, respectively. The overall survival rate at 5 years was 35%, and the observed morbidity rate was 5%. Locoregional relapse occurred less often in the advanced tumor patient subgroup than in the nodal metastases cohort (16% vs 24%, respectively; $P = .29$); the corresponding proportions of distant metastases relapses were 21% and 15%, respectively ($P = .66$). PORT conferred a 5-year survival advantage for T3-T4 subgroup compared to the node positive subset (43% vs 26%, respectively; $P = .03$). After adjusting for potential confounding variables such T3-T4 and pN+ categories as well as the number of positive nodes, the presence of nodal metastases proved to be the independent predictor of prognosis.

Conclusion: Although the value of PORT in IR-HNC cannot be definitively supported by the present findings, the use of adjuvant irradiation in people with IR-HNC resulted in acceptable long-term outcomes with minimal morbidity satisfying the quality-of-life consideration. Our comparative analysis findings underscore the importance of further studies to improve our understanding of the influence of selection criteria in the postoperative radiotherapeutic management of patients with IR-HNC.

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Cervical Esophageal Cancer: A Comparison of Outcomes by Treatment Paradigm, Tumor Location, and Histology Using the National Cancer Database

A.M. Torgeson,[1] S. Francis,[2] S. Lloyd,[3] Y.J. Hitchcock,[3] G.M. Cannon,[4] and V. Avizonis[4]; [1]*Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT,* [2]*Huntsman Cancer Institute, Salt Lake City, UT,* [3]*University of Utah Huntsman Cancer Institute, Salt Lake City, UT,* [4]*Intermountain Healthcare, Salt Lake City, UT*

Purpose/Objective(s): The most appropriate treatment for cervical esophageal cancer (CEC) remains controversial, with some favoring a head & neck (H&N) paradigm (>60 Gray [Gy] and single-agent chemotherapy) and others favoring an Esophageal paradigm (60 Gy or less and multi-agent chemotherapy). We used the National Cancer Database (NCDB) to compare survival outcomes between these two paradigms for both cervical esophageal cancer and upper 2/3 esophageal cancers.

Materials/Methods: Stage II-III esophageal cancer patients with adenocarcinomas or squamous cell carcinomas (SCC) were identified in NCDB. CEC patients were grouped into either H&N or Esophageal groups. Survival was compared using univariate (UVA) and multivariate analysis (MVA), followed by propensity score matching. The analysis was then expanded to include all upper 2/3 tumors, and survival outcomes were compared for the H&N and Esophagus paradigms as an overall cohort and by location and histology. Subgroup analysis of patients who underwent esophagectomy was done for both CEC and the overall cohort.

Results: There were 4248 patients, 340 were CEC. There was no difference by treatment group in survival for CEC patients either on UVA or after propensity score match (HR 1.39, $P = .40$) and no improvement in survival for the 13 CEC esophagectomy patients (HR 0.93, $P = .42$). On MVA of upper 2/3 tumors, there was no survival benefit by treatment group (HR 0.94, $P = .66$) but there was for esophagectomy (HR 0.63, $P<.001$). On subgroup analysis, patients with adenocarcinomas experienced a trend towards improved survival with the Esophagus paradigm (HR 0.53, $P = .07$) compared to H&N. There was no survival difference for SCC by group, and no difference by location (upper/middle third).

Conclusion: There is no survival difference by treatment group for CEC or upper 2/3 patients, and no difference between groups for specific locations. A trend was noted for improved outcomes in upper 2/3 adenocarcinomas treated with the Esophagus paradigm.

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Human Papillomavirus Is Associated With Improved Overall Survival in Patients With Non-Oropharyngeal Squamous Cell Carcinomas Presenting With Metastatic Disease

A. Burr,[1] P.M. Harari,[2] H.C. Ko,[2] S. Chen,[3] M. Yu,[4] A.M. Baschnagel,[2] R.J. Kimple,[2] and M.E. Witek[2]; [1]*Department of Human Oncology, University of Wisconsin Hospital and Clinics, Madison, WI,* [2]*Department of Human Oncology, University of Wisconsin, Madison, WI,* [3]*Department of Statistics, University of Wisconsin School of Medicine and Public Health, Madison, WI,* [4]*Department of Statistics, University of Wisconsin School of Medicine and Public Health, Madison, WI*

Purpose/Objective(s): Human papillomavirus (HPV) is a favorable prognostic marker for patients with oropharyngeal squamous cell carcinoma (OPSCC) and non-metastatic non-OPSCC of the head and neck. We evaluated the impact of HPV status on overall survival (OS) for patients with Stage IVC non-OPSCC.

Materials/Methods: Patients diagnosed between 2010 and 2013 with Stage IVC non-OPSCC and known HPV status were identified in the National Cancer Database. Univariate and multivariate analyses were performed with Cox proportional hazards to determine factors associated with OS. Propensity score-weighted Kaplan-Meier estimation was used to adjust for confounders in OS analyses. The multiple imputation method was used for sensitivity analysis.

Results: We identified 708 patients with Stage IVC non-OPSCC with 30% being HPV positive. Unadjusted median survival was 10.3 months for HPV-negative patients and 21.4 months for HPV-positive patients ($P < .0001$). Age ≥ 65 (HR: 1.47; 95% CI 1.08-2.01) and tumor diameter (HR: 1.13; 95% CI 1.03-1.25) were associated with worse OS while

treatment (HR 0.29; 95% CI 0.19-0.43) and HPV-positive status (HR 0.43; 95% CI 0.29-0.64) were associated with improved OS on multivariate analysis. Adjusted median survival for patients with HPV-negative and HPV-positive disease was 11.1 months and 23.8 months, respectively ($P < .01$). On subgroup analysis, patients with HPV-positive oral cavity disease exhibited improved outcomes ($P < .0001$) while HPV-positive hypopharynx and larynx patients exhibited a trend for improved OS compared to HPV-negative patients. The survival advantage associated with HPV positivity was maintained on sensitivity analysis (HR 0.66; 95% CI 0.48-0.92).

Conclusion: These data demonstrate a clinically meaningful association between HPV status and overall survival in patients with non-oropharyngeal squamous cell carcinomas presenting with Stage IVC disease. In the absence of randomized data, these findings support active consideration of HPV status in clinical decision making, clinical trial design, and patient counseling regarding prognosis.

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The Effect of Delay Between Diagnosis and Initiation of Treatment on Outcomes in Patients With Head and Neck Squamous Cell Carcinoma

L.H. DeGraaff,[1] A. Platek,[1] A.J. Iovoli,[1] M.E. Platek,[2] K.E. Wooten,[2] A. Hassan,[2] V. Gupta,[2] W.L. Hicks,[2] and A.K. Singh[2]; [1]*Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY,* [2]*Roswell Park Cancer Institute, Buffalo, NY*

Purpose/Objective(s): Delayed initiation of treatment after a patient is diagnosed with head and neck squamous cell carcinoma (HNSCC) may have detrimental effects on the patient's outcome. This study aims to quantify the effect that a delay in the initiation of treatment after diagnosis has on the clinical outcomes and overall survival of patients with HNSCC treated at one institution.

Materials/Methods: This is a retrospective analysis of 633 patients treated in the radiation medicine department at one institution for HNSCC between 2004 and 2017. Dates regarding diagnosis and treatment, as well as descriptions of outcomes, were abstracted from the medical records. Overall survival (OS) curves and multivariate cox proportional hazard ratios were determined for each time to treatment quartile.

Results: The median time to treatment was 41 days. Comparison of OS curves for each time to treatment quartile revealed that patients treated 42 to 60 days after diagnosis had the best OS, and patients treated after 60 days had the worst OS ($P = .0164$). This trend between treatment time quartiles held for the majority of the analyses in this study. When stratified by primary tumor site, differences in OS between treatment time groups were significant for hypopharyngeal primaries only ($P = .0065$). Delaying treatment initiation did not have a significant effect on OS for patients treated with chemoradiation therapy, but for patients treated with radiation therapy alone, the difference in OS between groups was significant ($P = .0009$).

Conclusion: For the majority of the situations examined, delaying treatment initiation by several weeks did not have a detrimental effect on the outcome of treatment. Therefore, the quality of planning and delivering treatment for patients with HNSCC should not be sacrificed in an effort to begin treatment more rapidly after diagnosis. Instead, this information can be used to help calm patients' anxieties about having to wait for treatment to begin.

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Withdrawn

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Outcomes Between Concurrent Cisplatin Versus Cetuximab in Locally Advanced Oropharyngeal Carcinoma: A SEER-Medicare Analysis

A. Amini,[1,2] M. Eguchi,[1] B.L. Jones,[1] W.A. Stokes,[1] R.M. Lanning,[1] J. McDermott,[1] S. Bhatia,[1] D. Raben,[1] C.J. Bradley,[1] and S.D. Karam[1]; [1]*University of Colorado School of Medicine, Aurora, CO,* [2]*City of Hope Cancer Center, Duarte, CA*

Purpose/Objective(s): The comparative efficacy of cisplatin (CDDP) versus cetuximab (CTX) delivered concurrently with radiation for locally advanced, non-metastatic, oropharyngeal squamous cell carcinoma (OPSCC) continues to be evaluated.

Materials/Methods: The linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used to identify and compare patient and disease profiles, mortality, toxicity, and overall cost in oropharynx cancer patients undergoing definitive concurrent chemoradiation (CRT) with CDDP or CTX between 2006 and 2011. Unadjusted and adjusted analyses and logistic regression were performed. The primary outcome was 2-year overall survival (OS).

Results: The analytic sample comprised 348 patients. The sample was nearly evenly split between those who received CDDP and CTX. Older age (OR, 0.15; 95% CI 0.08-0.30; $P < .001$), African American race (OR, 0.22; 95% CI 0.05-0.84; $P = .027$), and those with a Charlson Comorbidity Index ≥ 2 (OR, 0.26; 95% CI 0.12-0.59; $P = .001$) were less likely to receive concurrent CDDP. Two-year OS was inferior with CTX in the Cox proportional hazards model (HR, 1.91; 95% CI 1.20-3.05; $P = .006$). Antiemetic use was statistically significantly higher with CDDP (92% vs 44%; $P < .001$). In the multivariate model, mean per patient spending for CTX was significantly higher than CDDP ($61,621 versus $47,216, $P = .002$).

Conclusion: Older age, African American race, and worse co-morbidity status predicted the use of CTX. CDDP is associated with improved OS, slightly lower overall cost, and higher antiemetic usage. Concurrent CDDP may be the favored chemotherapy agent, with CTX based therapy reserved for those who otherwise cannot tolerate concurrent CDDP in locally advanced OPSCC.

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Prediction of PEG Tube Rates in the Era of Constrictor and Laryngeal Sparing

G.Q. Yang,[1] D. Gintz,[2] A.O. Naghavi,[1] J. Kennedy,[3] K. Shah,[3] and J.J. Caudell[1]; [1]*H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology, Tampa, FL,* [2]*Moffitt Cancer Center, Tampa, FL, United States,* [3]*University of South Florida College of Medicine, Tampa, FL*

Purpose/Objective(s): While definitive radiation therapy (RT) for human papilloma virus-related oropharyngeal squamous cell carcinoma (OPSCC) achieves excellent rates of long-term disease control, it may be associated with significant acute and long-term sequelae. For example, placement of percutaneous endoscopic gastrostomy (PEG) tubes during treatment is occasionally necessary to alleviate weight loss and dehydration. Over the last decade, dysphagia associated organs at risk and their threshold doses for significant toxicity have been identified. We sought to determine the risk of reactive PEG (rPEG) placement in a

modern cohort of patients treated with IMRT with uniform sparing goals of dysphagia organs at risk.

Materials/Methods: After IRB approval was obtained, a database of HPV or p16 positive non-metastatic OPSCC patients treated with definitive radiation therapy with or without chemotherapy was queried. For consistency of contouring and dosimetric goals, a single radiation oncologist's cases were selected. PEG tubes placed after 10 days after initiation of treatment were considered reactive, and clinical features were compared using Fischer exact test and dosimetric values were evaluated with the Mann-Whitney U test. Dosimetric data include mean dose to inferior (IPC), middle (MPC), and superior (SPC) constrictor muscles, larynx, lowest mean dose to one submandibular gland (SMG), lowest mean dose to one parotid, oral cavity (OC), and esophagus.

Results: A total of 137 patients were identified, of whom 14 had prophylactic PEG tubes placed. Of the remaining 123 patients, 17 (13.8%) underwent reactive PEG tube placement during or after treatment. Patients requiring a reactive PEG placement were more likely to have higher mean dose to the IPC (4086 vs 3551 cGy, $P = .016$) or SMG (4673 vs 3580 cGy, $P = .037$). Clinical factors associated with rPEG placement included female gender ($P = .043$), AJCC 8th edition stage II and III disease ($P = .044$), concurrent chemotherapy ($P = .011$), radiation doses $\geq$6930 cGy ($P < .01$), and elective neck dose $\geq$5000 cGy ($P < .01$). On multivariate logistic regression only a prescribed radiation dose $\geq$6930 cGy remained associated with rPEG placement (HR = 5.6, CI 1.13-27.1, $P = .034$).

Conclusion: In this modern data set of patients receiving radiation therapy for HPV-related OPSCC with a priori effort using IMRT with rigorous criteria to spare dysphagia associated organs at risk, rates of reactive PEG placement were low. Prescribed doses in excess of 6930 cGy were associated with PEG placement, giving further impetus for consideration of dose de-escalation.

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Prognostic Impact of Leukocyte Counts Before and During Radiation Therapy for Oropharyngeal Cancer

G.L. Jensen,[1] P. Blanchard,[2] G.B. Gunn,[3] A.S. Garden,[4] C.D. Fuller,[2] E.M. Sturgis,[1] M. Gillison,[1] J. Phan,[5] W.H. Morrison,[4] D.I. Rosenthal,[4] and S.J. Frank[2]; *[1]MD Anderson Cancer Center, Houston, TX, [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]MD Anderson Head and Neck Cancer Symptom Working Group, The University of Texas MD Anderson Cancer Center, Houston, TX, [5]The University of Texas MD Anderson Cancer Center, Division of Radiation Oncology, Houston, TX*

Purpose/Objective(s): Peripheral blood count components are accessible and evidently predictive in other cancers but have not been explored in oropharyngeal carcinoma. We examine if there is an association between the use of intensity-modulated radiation therapy (IMRT) or intensity-modulated proton therapy (IMPT) and lymphopenia, as well as if there is an association between baseline neutrophilia, baseline leukocytosis and lymphocyte nadir in oropharyngeal cancer.

Materials/Methods: Analysis started with 150 patients from a previous case to case study design, which retrospectively identified adults with oropharyngeal carcinoma, 100 treated with IMRT in 2010 to 2012 and 50 treated with IMPT in 2011 to 2014. Pretreatment leukocyte, neutrophil, lymphocyte, and hemoglobin levels were extracted, as were neutrophil and lymphocyte nadir levels during radiation therapy. We retained 137 patients with recorded pretreatment leukocyte and neutrophil levels for associated analysis and 114 patients with recorded lymphocyte levels during radiation and associated analysis. Multivariate survival analyses were done with Cox regression.

Results: The radiation therapy type (IMRT vs IMPT) was not associated with lymphopenia (grade 3, $P>.99$; grade 4, $P = .55$). In univariate analyses, poor overall survival was associated with pretreatment neutrophilia (hazard ratio [HR] 5.58, 95% confidence interval [CI] 1.99-15.7, $P = .001$), pretreatment leukocytosis (HR 4.85, 95% CI 1.73-13.6, $P = .003$), grade 4 lymphopenia during radiation therapy (HR 3.28, 95% CI 1.14-9.44, $P = .03$), and possibly smoking status >10 pack-years (HR 2.88, 95% CI 1.01-8.18, $P = .05$), but only T status was possibly significant in multivariate analysis (HR 2.64, 95% CI 0.99-7.00, $P = .05$). Poor progression-free survival was associated with pretreatment leukocytosis and T status in univariate analysis, and pretreatment neutrophilia and advanced age on multivariate analysis.

Conclusion: Treatment modality did not affect blood counts during radiation therapy. Pretreatment neutrophilia, pretreatment leukocytosis, and grade 4 lymphopenia during radiation therapy were associated with worse outcomes after, but establishing causality will require additional work with increased statistical power.

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Clinical Profile and Outcome of Viral-Mediated Pharyngeal Carcinoma at a Western Institution

S.H. Huang,[1] J.N. Waldron,[2] J. Su,[3] S. Bratman,[4] J.H. Kim,[5] A. Bayley,[6] J.G. Ringash,[4] M.E. Giuliani,[5] A.J. Hope,[5] J. Cho,[4] A. Hansen,[7] R. Jang,[8] J. de Almeida,[9] B. Perez-Ordonez,[5] I. Weinreb,[5] L. Tong,[5] W. Xu,[3] and B. O'Sullivan[10]; *[1]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada, [2]University of Toronto, Toronto, Ontario, Canada, [3]Division of Biostatistics, Princess Margaret Cancer Centre, Toronto, Ontario, Canada, [4]Department of Radiation Oncology, Princess Margaret Cancer Centre/University of Toronto, Toronto, Ontario, Canada, [5]Princess Margaret Cancer Centre, Toronto, Ontario, Canada, [6]Department of Radiation Oncology, Princess Margaret Cancer Centre/ University of Toronto, Toronto, Ontario, Canada, [7]Department of Medical Oncology, Princess Margaret Cancer Centre/University of Toronto, Toronto, Ontario, Canada, [8]Division of Medical Oncology, Princess Margaret Cancer Centre/ University of Toronto, Toronto, Ontario, Canada, [9]Department of Surgical Oncology, Princess Margaret Cancer Centre/University of Toronto, Toronto, Ontario, Canada, [10]Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, Ontario, Canada*

Purpose/Objective(s): To compare clinical profile and outcome between viral-mediated oropharyngeal (OPC) and nasopharyngeal carcinoma (NPC) at a western institution.

Materials/Methods: All newly diagnosed nonmetastatic viral-mediated OPC and NPC treated with IMRT from 2005 to 2014 were reviewed. Viral etiology was confirmed by p16 immuno-staining for HPV and EBER in situ hybridization for EBV. Demographics, the 8th edition TNM for HPV+ OPC (ICON-S) and NPC, failure patterns, and outcomes were compared between OPC and NPC.

Results: A total of 802 OPC (801 HPV+; 1 EBV+) and 369 NPC (360 EBER+ and 9 HPV+) were viral-mediated. NPC patients were mostly Asian (75% vs 4%) while most OPC were Caucasian (94% vs 20%) (both $P < .01$). Compared to NPC, OPC patients were older (median 59 vs 52 years, $P < .001$), predominantly male (83% vs 67%, $P < .001$), and had more advanced stage ($P < .001$). Median follow-up was 5.0 years for the entire cohort. Compared to NPC, OPC had similar 5-year overall survival (OS) (80% vs 87%, $P = .073$), regional control (96% vs 94%, $P = .230$) and distant control (88% vs 88%, $P = .530$). Local control was higher in OPC (96% vs 91%, $P < .001$) and remained significant after adjusting for T/smoking/age (HR = 0.43, $P = .004$). Late toxicity rates were marginally lower with OPC (19% vs 25%, $P = .062$). Similar 5-year RFS was found according to the same TNM stage grid: T1-2N0-1 disease (i.e. early disease: stage I OPC; stage I-II NPC) (91% vs 90%, $P = .26$), T1-2N2 or T3N0-2 disease (intermediate disease: stage II OPC; stage III NPC) (84% vs 87%, $P = .95$), and T4 or N3 disease (advanced disease: stage III OPC; stage IVA-IVB NPC) (69% vs 63%, $P = .56$). Distant metastasis (DM) was the main form of failure and occurred in 92 (11%) OPC and 51 (14%) NPC patients. Most DMs (85% OPC and 76% NPC) did not have locoregional failure ($P = .22$). Multisite involvement was common in those with DM (51% OPC and 35% NPC) and most evident in lung, liver, and bone. Interestingly, DM to brain was more frequent in OPC versus NPC (13% vs 2%, $P = .03$). OS after DM for OPC and NPC were similar (5-year: 17% vs 22%, $P = .20$). Of patients with DM, 24 of 92 (26%) OPC and 15 of 51 (29%) NPC survived more than 2 years after DM.

Conclusion: This large western cohort study shows that ethnic susceptibility remains after inter-continental migration. Viral type has a distinct anatomic preference. HPV usually causes OPC, but may occasionally cause NPC. The outcome and pattern of failure are very similar by the 8th edition TNM classification. However, local control is slightly lower in NPC, likely reflecting anatomic challenges in NPC. DM is the main form of failure for both NPC and OPC but long-term survivors after DM are seen in the 2 diseases. Such similarities in clinical behavior could reflect common mechanisms of oncogenesis, metastasis, and radio-/chemo-sensitivity and/or resistance induced by HPV and EBV.

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The Impact of a Dedicated Multidisciplinary Care Team on a High-Risk Head and Neck Cancer Population

A. Kaplon,[1] E. Blackman,[2] C. Miyamoto,[1] D. Savior,[1] C. Ragin,[2] and J.C.J. Liu[1]; *[1]Temple University School of Medicine, Philadelphia, PA, [2]Fox Chase Cancer Center, Philadelphia, PA*

Purpose/Objective(s): While the Multidisciplinary Tumor Board (MTB) is the accepted best practice for the management for head and neck cancer, there is a paucity of evidence demonstrating its impact on treatment outcomes. Our goal was to investigate the impact of MTB following the hiring of a fellowship trained head and neck surgeon and implementation of an expanded MTB. As minorities and underinsured patients have consistently had worse outcomes and survival in HNSCC, we hypothesized that these changes would improve survival in our high-risk cohort.

Materials/Methods: A review of head and neck squamous cell carcinomas (HNSCC) treated at our institution between 10/2006 and 5/2015 was performed. The cohort was divided into historical (10/06-2/11) and contemporary (2/11-5/25) cohorts. Prior to 2/2011, the MTB at that time did not consistently include a dedicated surgeon or additional members. In 2/2011 a dedicated fellowship trained head and neck surgeon joined the MTB, and the MTB was expanded with additional members including: speech/swallow therapy, social work, neuroradiology, pathology, and dental. Patients without a HNSCC primary, who were not managed by an otolaryngologist within the institution, had inadequate records, or did not receive any treatment, were excluded.

Results: A total of 224 patients were included, with 98 patients in the historical cohort and 126 in the contemporary cohort. 139 (62%) of the patient cohort were black and 91 (40%) were Medicaid or uninsured. Average follow-up time was 2.87 years. Of the overall cohort, 25% were stage I/II and 68% were stage III/IV. OS and DSS in the contemporary cohort were statistically significantly improved over the historical cohort on univariate analysis, and also on multivariate analysis when controlling for age, sex, race, and tobacco use. On Kaplan-Meier evaluation, OS and DSS were significantly different with 5-year DSS of 52% versus 75% ($P = .003$), respectively. This OS and DSS difference persisted when evaluating only stage III/IV cancers ($P = .02$). When excluding oropharynx cancers to eliminate potential imbalance from HPV-associated oropharynx cancers, DSS remained statistically significant ($P = .02$). Average time to treatment was not significantly different. Surgery was more commonly employed for advanced HNSCC treatment in the contemporary group ($P = .0067$)

Conclusion: Implementation of an expanded MTB and dedicated head and neck surgeon had significant impact on OS and DSS for advanced HNSCC. Our study corroborates the belief that treatment of HNSCC by a dedicated multidisciplinary team results in best outcomes for patients. Implementing expanded MTB and specialty surgeon support should be considered to help address HNSCC racial disparity outcomes.

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What Is the Benefit of Adjuvant Radiation Doses Above 60 Gy in Head and Neck Cancer Patients?

V. Avkshtol, E. Handorf, J.A. Ridge, J.C.J. Liu, J. Bauman, and T.J. Galloway; *Fox Chase Cancer Center, Philadelphia, PA*

Purpose/Objective(s): Radiation dose response data in the post-operative management of Head and Neck Squamous Cell Carcinoma (HNSCC) are limited. We compared radiation dose trends and outcomes of HNSCC treated with adjuvant radiation, with or without concurrent chemotherapy.

Materials/Methods: Patients with non-metastatic HNSCC who were treated between 2004 and 2014 with primary site surgery, lymph node dissection, and adjuvant radiation with an equivalent dose in 2 Gy (EQD2) of $\geq$ 56.64 Gy (equivalent to 57.6 Gy in 32 fractions) and $\leq$ 72 Gy were identified in the National Cancer Database. Radiation doses of EQD2 $<$ 56.64 Gy and $>$ 72 Gy were respectively interpreted to reflect incomplete radiation courses or attempted salvage of gross recurrences prior to the initiation of radiation and were excluded. Standard dose radiation was

defined as an EQD2 of ≥ 56.64 Gy and ≤ 60 Gy and high dose radiation as an EQD2 of > 60 Gy and ≤ 72 Gy. Radiation regimens employed in < 10 patients were excluded. We used multivariate logistic regression to model receipt of high dose radiation, and multivariate cox proportional hazards regression to assess the association between dose and survival within the cohorts of interest.

Results: We identified 19,492 patients managed with adjuvant radiation. Oral cavity, oropharynx, larynx, hypopharynx, and nasal cavity comprised 43%, 38%, 14%, 3%, and 2% of the primary sites, respectively. HPV status was available for 3496 (47%) oropharynx patients. High dose radiation was prescribed to 52% of patients. Factors that predicted for increased use of high dose radiation included extra-nodal extension (ENE), positive or unknown surgical margins, fewer examined lymph nodes, increased number of positive lymph nodes, increased N staging, concurrent chemotherapy, and non-tonsil primary site. When adjusted for known poor prognostic factors to control for high dose being prescribed to a worse prognosis cohort, there was a decrease in overall survival (OS) in the high dose group (HR = 1.10; 95% CI 1.03-1.17). High dose radiation was independently associated with worse OS in HPV positive oropharynx patients when controlling for poor prognostic factors (HR = 2.03; 95% CI 1.22-3.37). In non-oropharynx primary or HPV negative oropharynx primary that had positive margins, ≥ 5 positive lymph nodes, and/or ENE, high dose radiation was not associated with improvement in OS (HR 1.03; 95% CI 0.94-1.13).

Conclusion: Factors known to predict for poor outcomes are associated with higher rates of high dose adjuvant radiation in this large national cohort. However, when controlling for poor prognostic factors, there was no survival benefit from postoperative dose escalation above EQD2 of 60 Gy.

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Skin Cancer of the Nose: Outcome in 405 Cases Treated With High Dose Radiation Therapy

N.E. Flores,[1] T.A. Mian,[2] and D. Liu[1]; [1]*Arizona Dermatology, Phoenix, AZ,* [2]*Medical Radiation Physics Inc., Scottsdale, AZ, United States*

Purpose/Objective(s): To determine the clinical outcome of patients treated with radiation therapy for skin cancer of the nose.

Overview: Between 2013 and 2016, we treated approximately 1500 cases of primarily basal and squamous cell skin cancers utilizing high dose radiation therapy. In this series, 405 cases involved the nose. Patient selection was limited to age >35 years, tumor size <40 mm in diameter and <5 mm thick.

Demographics: Pathology: 86.7% basal, 12.8% squamous, one lymphoma, one melanoma. Size by treatment field: 66.9% 10 mm, 28.1% 20 mm, 4.7% 35 mm and <1% 50 mm. Age: 76.8 years median (37.3-99.7 years).

Materials/Methods: Radiation therapy was administered per recommendations by ASTRO and AAPM and performed with either a 50 kV x-ray device or a 6 MeV LINAC electron beam. The majority of patients received a total of 4000 cGy in 500 cGy fractions given twice weekly. Prescribed treatment depth was 0 mm for non-bulky disease. Bolus was used for all electron beam treatments. Wax-coated nasal plugs were used for lateralized or large midline lesions. Sloughing tumor was debrided and/or treatment depth modified during treatment as necessary. Treatment interruptions were rare, usually due to infection or contact dermatitis and limited to less than two weeks.

Results: Ninety-nine percent of patients maintained a complete response at 2 years (0.2-3.7 years) median follow-up with one edge-of-field progression and one in-field recurrence. *Side Effects:* Transient nasal mucositis (10%) limited to lateralized or large midline lesions, superficial infection (<1%) limited to patients with a history of moderate to severe acne and/or patients applying cosmetic concealers during treatment. No chronic nasal dryness, cartilage necrosis, ophthalmic injury, nasolacrimal disruption, or dental complications. *Patient Satisfaction/Cosmesis*: Self-scored functional and cosmetic outcomes ranged from very good to excellent in 100% of patients.

Conclusion: Radiation therapy utilizing either High Dose Rate Electronic Brachytherapy or High Dose LINAC Electron Therapy is an effective and well-tolerated treatment option for carefully selected patients with basal and squamous cell skin cancer of the nose. When compared to more extensive surgery, radiation therapy results in high patient satisfaction without the need for extended postoperative care or reconstruction. Response rates for both electron beam and low-energy x-rays at this prescribed dose schedule were comparable to previously published studies. When compared to conventional radiation therapy, the high response rates, smaller field size capability, shorter treatment times, and reduced radiation dose to adjacent critical tissues make electronic brachytherapy a useful addition to standard techniques.

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Periocular Nonmelanoma Skin Cancers: Outcome in 86 Cases Treated With High Dose Rate Electronic Brachytherapy

N.E. Flores,[1] D. Liu,[1] T.A. Mian,[2] and F. Muratovic[3]; [1]*Arizona Dermatology, Phoenix, AZ,* [2]*Medical Radiation Physics Inc., Scottsdale, AZ, United States,* [3]*Ironwood CRC, Glendale, AZ, United States*

Purpose/Objective(s): To determine the clinical outcome of patients treated with radiation therapy for periocular nonmelanoma skin cancer (NMSC).

Overview: Eighty-six cases of periocular NMSC were treated with an accelerated radiation therapy schedule utilizing High Dose Electronic Brachytherapy. Patient selection was limited to age >40 years, and tumor size <40 mm in diameter and < 5 mm thick. Treatment sites included the upper or lower eyelids, medial or lateral canthus, or supra-orbital ridge in patients considered poor surgical candidates or who declined surgery. Demographics: Pathology: 82.6% basal, 17.4% squamous. Size by treatment field: 76.7% 10 mm, 19.8% 20 mm and 3.2% 35 mm. Location: 48.8% lower lid, 25.6% medial canthus, 23.3% upper lid, 2.3% lateral canthus. Age: 73.5 years median (40.8-99.6 years).

Materials/Methods: Radiation therapy was administered per recommendations by ASTRO and AAPM and performed with a 50 kVx-ray device. All treatments were delivered within a single dermatology practice over a four-year period. A total of 4000 cGy in 500 cGy fractions were given twice weekly. Prescribed treatment depth was 0 mm for non-bulky disease. Bulky disease was debrided and/or treatment depth modified during treatment as necessary. Treatment interruptions were rare, usually due to infection or contact dermatitis and limited to less than two weeks.

Results: Ninety-nine percent of patients maintained a complete response at 2 years (0.2-3.7 years) median follow-up with one edge-of-field progression and no in-field recurrences.
Side Effects: Transient low-grade conjunctivitis when using gold eye shields, minimal loss of eyelashes for treatment involving the ciliary rim. No long-term vision changes, dry eye, corneal injury, retinitis, dacrocystitis, orbital bone injury, or impairment of eyelid motion.
Patient Satisfaction/Cosmesis: Self-scored functional and cosmetic outcomes ranged from very good to excellent in 100% of patients.
Conclusion: Radiation therapy utilizing High Dose Rate Electronic Brachytherapy offers a unique patient option for selected NMSC arising in the periocular space. When compared to multistage surgery, electronic brachytherapy results in improved patient comfort without the need for extended postoperative care or reconstruction. When compared to conventional radiation therapy, the high response rates, small field sizes, reduced treatment time, and lower radiation dose to adjacent critical tissues make electronic brachytherapy a useful addition to electron therapy or superficial x-ray (orthovoltage) techniques.
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Hepatocyte Nuclear Factor 4 Alpha Overexpression Confers Resistance to Radiation in a Human Oral Cavity Squamous Cell Carcinoma Cell Line

J.D. Smith, C. Matovina, S.K. Foltin, A.C. Birkeland, and J.C. Brenner; *University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Human whole-genome lentiviral open-reading frame (ORF) pools allow for large-scale, efficient functional screening for genetic drivers of specific oncologic phenotypes in vitro (e.g. resistance to chemo-radiation). We sought to identify and validate candidate genes whose ORF overexpression confers resistance to radiation treatment in an oral cavity squamous cell carcinoma cell line.
Materials/Methods: UM-SCC-49 cell line was transduced with the MISSION TRC3 human whole-genome lentiviral ORF pool (Sigma-Aldrich) at an MOI = 0.3 under puromycin selection. ORF-expressing cells were treated with radiation according to dose sensitivity of control UM-SCC-49 cells, followed by derivation of monoclonal cell populations from ORF-expressing cells resistant to radiation. Validation of monoclonality and identity of ORF construct in radiation-resistant cell populations was determined by sanger sequencing of unique ORF barcode and target gene. Clonogenic cell survival assays were utilized to confirm radiation resistance phenotype in monoclonal ORF populations.
Results: Three separate monoclonal, radiation-resistant cell populations expressing the ORF for hepatocyte nuclear factor 4 alpha (HNF4a) were identified. Initial clonogenic cell survival assays showed increased growth and viability of HNF4a-expressing cell populations relative to UM-SCC-49 cells alone and containing the whole-genome ORF pool at increasing doses of 2, 4, 6, and 8 Gray radiation. Hepatocyte nuclear factor 4 alpha (HNF4a) is a nuclear transcription factor with crucial roles in embryologic differentiation of the liver and gut, and hepatocyte metabolism and homeostasis, and may be involved in colorectal carcinogenesis through interaction with Wnt/b-catenin pathway members.
Conclusion: HNF4a overexpression conferred a radiation-resistance phenotype in an in vitro model of oral cavity squamous cell carcinoma. This gene is a promising new target for preclinical mechanistic studies of radiation resistance in squamous cell carcinomas of the oral cavity.
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A Dosimetric Comparison of Split-Field IMRT, Whole-Field IMRT, and Volumetric Modulated Arc Therapy for Patients With Early-Stage Tonsillar Cancer

A.C. Moreno,[1] C.T. Wilke Jr,[2] H. Wang,[3] and J. Phan[4]; [1]*University of Texas MD Anderson Cancer Center, Houston, TX,* [2]*University of Minnesota, Minneapolis, MN,* [3]*The MD Anderson Cancer Center, Houston, TX,* [4]*The University of Texas MD Anderson Cancer Center, Division of Radiation Oncology, Houston, TX*

Purpose/Objective(s): Three of the most widely used techniques in the treatment of head and neck malignancies include split-field intensity-modulated radiation therapy (SF-IMRT) in which the low neck is treated with a single anterior-posterior beam matched above the glottis, whole-field IMRT (WF-IMRT) where the entire target volume is treated with a single IMRT plan using a static beam arrangement, and volumetric modulated arc therapy (VMAT). We have recently demonstrated that comparable laryngeal sparing in the setting of bilateral neck radiation can be achieved using all three techniques for the treatment of advanced oropharyngeal cancers. Due to continued improvements in radiation therapy planning, we sought to determine if WF-IMRT and VMAT could yield further reductions in dose to organs-at-risk (OARs) compared to SF-IMRT when treating early-stage oropharyngeal cancers with unilateral neck radiation therapy.
Materials/Methods: We analyzed 40 consecutive patients with tonsillar cancer (20 left-sided, 20 right-sided) who received definitive radiation therapy to the unilateral neck using an SF-IMRT technique. Each patient underwent replanning using both WF-IMRT and VMAT techniques with evaluation of the doses to various OARs including the larynx, esophagus, spinal cord, and brainstem. The larynx was defined both by the Radiation Therapy Oncology Group 1016 criteria (RTOG larynx) and as previously described by our institution (MDACC Larynx). Comparisons were made using the Tukey-Kramer method with $P < .05$ considered statistically significant.
Results: There was no significant difference in coverage of the target volume between the three plans; however, the heterogeneity index was improved using WF-IMRT and VMAT as compared with SF-IMRT (1.10 vs 1.07 vs 1.37; $P < .05$). WF-IMRT and VMAT plans were both associated with significantly lower mean doses to the supraglottic larynx (18.5 vs 17 vs 31 Gy; $P < .01$), MDACC larynx (10.5 vs 9.8 vs 13.4; $P < .01$), RTOG larynx (12.1 vs 11.1 vs 15.8; $P < .01$), and brainstem (10.7 vs 9.5 vs 14.7; $P < .01$). The improved laryngeal sparing observed with WF-IMRT and VMAT plans remained significant when stratified by the presence of mid-low neck nodal disease. Mean esophageal dose was significantly worse with WF-IMRT and VMAT (12.2 vs 11.1 vs 5.9; $P < .01$) but only in the absence of lower neck disease. VMAT plans were associated with the shortest treatment times (1.5 vs 8 vs 7.1 minutes; $P < .01$) and required the least amount of monitor units (502 vs 831 vs 614 MUs; $P < .01$) compared to the SF-IMRT and WF-IMRT plans, respectively.
Conclusion: For treatment of early-stage tonsillar cancers, WF-IMRT and VMAT plans can be optimized to result in significantly improved dose to the laryngeal structures as compared to SF-IMRT. VMAT offers further advantages including shorter treatment times and fewer required monitor units.
Author Disclosure: **A.C. Moreno**: None. **C.T. Wilke**: None. **H. Wang**: None. **J. Phan**: None.

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The Value of the Body Weight, Body Mass Index , and Nutritional Markers in Predicting Outcomes of Radiation Therapy—Treated Head and Neck Cancer

J. Lee and J. Kim; *Ewha Womans University Medical Center, Seoul, Korea, Republic of (South)*

Purpose/Objective(s): Patients with head and neck cancer commonly experience weight loss and malnutrition both before and during the course of treatment. This study aimed to investigate the prognostic value of body weight, body mass index (BMI), and nutritional markers in patients with radiation therapy (RT)—treated head and neck cancer (HNC)

Materials/Methods: This study included 176 patients with nonmetastatic HNC who underwent either postoperative or definitive RT from March 2000 to June 2016. Body weight and BMI were evaluated at baseline, 2 weeks, 2 months, 5 months, 8 months, and 1year post-RT. Albumin and total protein were measured at baseline and after RT.

Results: The median follow-up period was 61 months (range, 10 - 208). Five-year overall survival (OS), disease-free survival (DFS), and locoregional recurrence—free survival (LRRFS) were 75.5%, 71.2%, and 88.3%, respectively. In univariate analysis, patients with low body weight (<64 kg) and low BMI (<22.9 kg/m2) before treatment had inferior OS ($P=.027$ and $P=.019$, respectively) and DFS ($P=.038$ and $P=.004$, respectively). Pretreatment hypoalbuminemia (<4 g/dL) and hypoproteinemia (<6.5 g/L) were significantly associated with poor OS ($P=.008$ and $P=.003$, respectively), DFS ($P=.005$ and $P=.010$, respectively), and LRRFS ($P=.007$ and $P=.025$, respectively). Patients who had recovered their weight in 1 year after RT had superior OS ($P=.026$). In multivariate analysis, low body weight (<64kg) before treatment remained independent predictor for OS (HR 1.78: 95% CI, 1.02-3.09; $P=.043$). Weight and BMI change during treatment did not affect outcomes.

Conclusion: Pretreatment low body weight was a significant predictor for survival in patients with RT-treated HNC in this study. Early nutrition assessment with intervention before treatment and weight change surveillance and care after RT might be needed to improve survival outcomes.

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Patterns of Loco-Regional Failure In HPV-Associated Oropharyngeal and Unknown Primary Cancers After Definitive Chemoradiation: Implications For Elective Nodal Coverage

N.M. Woody,[1] B.A. Harr,[1] J. Bodmann,[2] J. Ferrini,[2] J. Heney,[3] D. Ives,[2] J. Hamker,[4] J.L. Geiger,[2] N.P. Joshi,[1] S. Koyfman,[1] and D.J. Adelstein[2]; *[1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [4]Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Clinical trials in HPV-associated oropharyngeal (OP) cancer are exploring both deintensification of radiation therapy (RT) dose and reduction in RT treatment volumes. A baseline prevalence of and pattern of recurrence relative to high dose and lower dose electively treated areas for patients treated with chemoradiation (CRT) are needed as comparison for such trials.

Materials/Methods: From an IRB approved database, we identified all HPV+ patients with either OP or unknown primary cancer treated with definitive CRT with intensity modulated radiation therapy (IMRT) between 11/2009 and 3/2016. Patients were treated with full dose (~70 Gy) to gross disease and (~56 Gy) to elective nodal regions. Patients had to have initial follow-up with negative PET CT to eliminate the cases of primary disease progression. Patients with subsequent suspicion for local regional recurrence underwent reimaging and biopsy. Location of recurrence relative to initial treatment high dose and elective dose regions were recorded as well as recurrence nodal station relative to known initial grossly involved nodal stations.

Results: A total of 156 patients were identified meeting study criteria with 22.4% having T3-T4 disease and 81.4% had ≥N2b disease. Concurrent therapy was cisplatin (67.9%), cetuximab (19.2%), or platinum doublet (12.8%). Median age was 58.6, median f/u with CT neck imaging was 17.8 months (range 2.7-65.1). Only three patients developed locoregional failure: one primary tumor only recurrence at 40.3 months, one nodal only recurrence at 16.5 months, and one with primary tumor and nodal recurrence at 5.7 months post-RT. Only a single patient with N2c disease treated with concurrent cetuximab experienced nodal failure in the elective dose region. This recurrence was in the same nodal region as a grossly involved node at the time of initial treatment. One- and 2-year locoregional controls were 99.3% and 98.1%, respectively.

Conclusion: Locoregional failure in HPV-associated oropharyngeal and unknown primary cancers treated with definitive CRT is very low. Recurrences in the elective dose region are uncommon, and no recurrences occurred in the elective dose region outside of nodal regions grossly involved at the time of initial treatment. Trials exploring reduction in RT dose in elective areas and restricting elective volumes to involved/adjacent nodal regions are rational.

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Treatment Outcomes of Squamous Cell Carcinoma of the Oral Cavity in Young Adults

M.E. Gamez,[1] R.D. Kraus,[2] M.L. Hinni,[3] E.J. Moore,[4] D.J. Ma,[5] S. Ko,[6] J.C. Rwigema,[1] L.A. McGee,[1] M.Y. Halyard,[1] M.R. Buras,[7] and S.H. Patel[1]; *[1]Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, [2]University of Southern California, Keck School of Medicine, Los Angeles, CA, [3]Department of Otorhinolaryngology, Mayo Clinic, Phoenix, AZ, [4]Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN, [5]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, [6]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, [7]Division of Health Sciences Research, Mayo Clinic, Scottsdale, AZ*

Purpose/Objective(s): In recent years, an increased incidence of squamous cell carcinoma of the oral cavity in younger adults has been reported. Controversy exists in the optimal management of this entity. This series is an updated report on the treatment outcomes in patients with oral cavity squamous cell carcinoma age ≤40 years.

Materials/Methods: We performed a retrospective IRB approved analysis of 124 consecutive patients with primary oral cavity squamous cell carcinoma treated at our Institution from 1980 to 2014. Median age was 35 years (range, 19-40 years). The most common primary site was oral tongue: 107 patients (86.3%). 74 patients (59.7%) were male. Twenty-six patients (29.9%) had >10-year smoking pack history. Of the patients, 117 (94.4%) had surgery, with 101 (81.5%) undergoing wide local excision. Surgery alone was the curative treatment in 77 (62.1%) patients. Forty-seven (37.9%) patients received radiation and 26 (21%) received chemotherapy as part of their treatment. The majority of patients had early T stage: pT1 in 65 (52.4%) and pT2 in 29 (23.4%). Forty-six (37.1%) of the patients were lymph node positive. Univariable (UA) log-rank tests and multivariable (MVA) Cox proportional hazard regressions were performed to associate patient characteristics to treatment outcomes. Variables considered for analysis were gender, smoking history, primary site (oral tongue vs other), pathologic T and N stage, treatment type (surgery alone vs surgery + other), tumor grade (G1-2 vs G3-4), margin status (negative vs close/positive), perineural invasion, extracapsular extension, and development of disease recurrence following curative treatment.

Results: Median follow-up was 9 years (range, 0.1 − 36.1 years). The 5- and 10-year OS were 78.1% and 76.9%, respectively. The 5-year DFS, LC, and LRC were 66.6%, 87.6%, and 78.5%, respectively. Factors associated with worsened OS on UA were higher pathologic T stage (T3-T4) ($P=.003$), lymph node positivity ($P\leq.001$), higher tumor grade (G3-4) ($P=.002$), positive margins ($P=.01$), patients requiring adjuvant therapy ($P\leq.001$), and recurrent disease ($P\leq.001$). The same variables were also associated with a statistically significant worsened DFS on UA except for tumor grade and margin status. On MVA factors associated with worsened OS and DFS were higher pathologic T stage ($P=.008$), lymph node positivity ($P\leq.001$) and recurrent disease ($P\leq.001$).

Conclusion: The outcomes of this series continues to support treating young patients with primary oral cavity squamous cell carcinomas using a similar treatment paradigm to older adults. A decision-making strategy for adjuvant therapy based on pathologic criteria is justified.

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Dosimetric and Volumetric Effects of Induction Chemotherapy in the Treatment of Locally Advanced Squamous Cell Carcinoma of the Oropharynx

E. Healy, D. Christ, A. Cetnar, D.J. DiCostanzo, J.L. Wobb, D.L. Mitchell, J.C. Grecula, A.D. Bhatt, and D.M. Blakaj; *The Ohio State University Wexner Medical Center, Department of Radiation Oncology, Columbus, OH*

Purpose/Objective(s): Induction chemotherapy (ICT) is not considered the standard of care in the treatment of locally advanced squamous cell carcinoma of the head and neck (LASCCHN). However, in very advanced cases, abnormally large tumor volumes often preclude adequate tumor coverage due to dose limitations of normal tissues and organs at risk (OARs). In these cases, ICT is often utilized to decrease gross tumor burden prior to definitive chemoradiation (CRT). We hypothesized that ICT would have a significant dosimetric and volumetric effect on primary tumor volume (GTVp), nodal volume (GTVn), and OARs.

Materials/Methods: Between January 2013 and December 2015, 40 patients were treated at our institution with ICT for LASCCHN. Of these, 19 with oropharyngeal primaries were reviewed. GTVp and GTVn were contoured using PET/CT-based contouring on both the pre- and post-ICT images. For the dosimetric analysis, a pre-ICT plan was generated using the deformable registration tools in Velocity™. Hounsfield units from the post-ICT plan were mapped onto the pre-ICT PET/CT to create a synthetic plan CT. Both target volumes and OARs were contoured on the synthetic pre-ICT planning CT. All plans were reoptimized and calculated in Eclipse and normalized to 100% prescription covering 95% of the high-risk PTV volume. Integral dose (ID) was calculated using the product of mean dose and structure volume. Paired t-tests were used to analyze differences in pre- and post-ICT volumes and doses.

Results: Of the 19 oropharyngeal patients, 8 (42%) had clinical T4 disease, 7 (37%) had N3 disease, and 3 patients (16%) had T4/N3 disease. Seventeen patients (89.5%) were p16 positive. Most patients (N = 15, 79%) received 3 cycles of TCF/TPF as ICT. The mean pre-ICT GTVp was 57.5cc (6.3-130.8cc) and the mean post-ICT GTVp was 21.4cc (0-122.6cc). The mean pre-ICT GTVn was 183.5cc (30.8-756.9cc) and the mean post-ICT GTVn was 34cc (0-107.6cc). We found that ICT prior to CRT resulted in an average decrease in the GTVp of 68.8% (± 29.6%, $P=.0004$) and an average decrease in the GTVn of 77% (± 23%, $P=.0005$). Eight patients were included in the dosimetric analysis. On dosimetric analysis, ICT significantly reduced the average ID to the brachial plexus, larynx, mandible, and parotids by 20%, 24%, 17%, and 16%, respectively ($P=.0077$, .0003, .0067, .0168). Differences in average esophagus, pharynx, and spinal cord ID were not significant ($P>.05$). Dose constraints were successfully met in all pre-ICT and post-ICT plans.

Conclusion: Our findings show that in very locally advanced cases of oropharyngeal cancer, ICT is a feasible approach prior to definitive CRT. Use of ICT was associated with a significant decrease in both primary and nodal disease volumes. Furthermore, this tumor volume decrease resulted in reduced integral dose to most OARs without any compromise of plan target coverage.

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Treatment Compliance and Insurance Status in Head and Neck Radiation Therapy Patients

C. Yarn[1] and D.L. Schwartz[2]; [1]*UTHSC School of Medicine Memphis, TN,* [2]*University of Tennessee West Cancer Center, Department of Radiation Oncology, Memphis, TN*

Purpose/Objective(s): Poor treatment compliance with head and neck (H&N) radiation therapy leads to poor cancer outcomes. Our prior work has suggested inferior radiation therapy (RT) compliance in Medicaid/uninsured populations in North Texas. Our aim was to confirm if under-/uninsured populations in the mid-south are at higher risk for H&N radiation therapy treatment delays than insured patients. We hypothesize that this may be a potential mechanism contributing to poor cancer control rates in at-risk populations across different geographic U.S. regions.

Materials/Methods: This was a chart review of 217 H&N RT patients treated at UTHSC-West Cancer Center with curative intent from January 2011 through January 2017. Data analysis was performed with JMP Pro 13 and Tableau.

Results: A total of 7574 treatment appointments were scheduled. Nine-hundred fourteen (12%) appointments were cancelled, and 675 treatment interruptions were patient-related (i.e. "Cancel," or "No Show"). Only 67/217 patients finished treatment with no treatment delays. Of the 217, 150 patients had one or more treatment delay. Medicaid/uninsured patients were at significantly higher risk for treatment delays than privately insured ($P=.0007$) or Medicare patients ($P=.0094$). Widowed status ($P=.005$) and chemotherapy administration ($P=.02$) were also associated with treatment interruption. Geographic mapping confirmed tight correspondence between total number of missed appointments and median income in home ZIP code.

Conclusion: We confirm significant correlation between H&N RT treatment delay and health insurance status. Geographic data qualitatively demonstrate how treatment delays track with known financial disparities in the Memphis region. This work sets the stage for prospective identification of patients at high risk for treatment attrition and focused interventional trials.

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Reducing Radiation Treatment Volumes in the N0 Contralateral Neck for HPV-Positive Oropharynx Patients

H.C. Ko, P.M. Harari, H.B. Musunuru, P. Yadav, P.M. Hill, and M.E. Witek; *Department of Human Oncology, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Patients with HPV-positive oropharyngeal squamous cell cancers (HPV+ OPSCC) exhibit favorable clinical outcomes warranting the development of strategies to reduce toxicity. Patients at risk for bilateral nodal disease are conventionally recommended by RTOG guidelines to undergo elective contralateral nodal irradiation of levels II-IV. We postulate that this elective treatment volume in the N0 neck can be safely reduced, as foretold by examining N2c patients presenting with a single contralateral nodal metastasis. By detailing the anatomic location of the single contralateral node in early N2c patients treated at our institution, we generated a novel elective target volume (eCTV), which would

diminish normal tissue toxicity while still treating the dominant risk region for occult tumor spread in the contralateral neck.

Materials/Methods: We identified 25 patients with early OPSCC N2c disease, as defined by a single contralateral node, and related this node location to common anatomic landmarks. These were plotted on a representative CT neck scan and used to define anatomic borders of the eCTV. We compared normal tissue complication probabilities (NTCP) for 10 HPV+ OPSCC patients planned with both elective RTOG volumes and eCTV.

Results: The eCTV was defined anteriorly by the posterior border of the submandibular gland, posteriorly by the posterior edge of the internal jugular vein, superiorly by 2mm above the C2 transverse foramen, inferiorly by the caudal edge of the cricoid, medially by the internal carotid artery, and laterally by the sternocleidomastoid head. The mean RTOG contralateral neck treatment volume was 253.7cc, while the mean eCTV volume we identified was 101.7cc (one-tailed paired t-test, $P<.05$). The mean dose predicted to the contralateral parotid gland (cPG) using RTOG volumes and eCTV was 21.0 Gy vs 15.1 Gy, respectively (one-tailed paired t-test, $P<.001$). The mean NTCP of the cPG was 6.9% calculated using the RTOG volumes, and 3.6% using the eCTV volumes (0.52 relative risk, one-tailed paired t-test, $P<.001$).

Conclusion: A highly predictable localization pattern was found for early contralateral neck nodal positivity in patients with HPV+ OPSCC. Reducing the contralateral neck elective target volume as defined by the eCTV lowered the putative NTCP for the contralateral parotid gland and other normal structures. These data support systematic investigation of target volume reduction in the contralateral N0 neck for HPV+ OPSCC patients in future clinical trials.

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Prognostic Impact of Quantitative Imaging Analysis of Lean Body Mass After Chemoradiation Therapy for Patients With Advanced Nasopharyngeal Cancer

H. Inokuchi, K. Okano, K. Takehana, K. Tsutsui, and M. Hiraoka; *Department of Radiation Oncology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan*

Purpose/Objective(s): Severe body weight loss and lean body mass changes occur in the majority of patients treated with chemoradiation therapy (CRT) for advanced head and neck cancer patients, especially those undergoing more intense treatment regimens. The aim of this study is to assess the prevalence of weight loss and the isolated loss of lean body mass in nasopharyngeal cancer (NPC) patients treated with definitive radiation therapy with concurrent chemotherapy and to clarify the impact of these changes on clinical outcome

Materials/Methods: From 2001 through 2015, the data of advanced NPC patients who underwent at least one cycle of platinum-based chemotherapy and definitive radiation therapy to median dose of 70 Gy (range, 60 to 72 Gy) were retrospectively analyzed. Their weight changes throughout the duration and after CRT and skeletal muscle index (SMI) measured on the cross-sectional CT scan area at the L3 vertebral level were retrospectively assessed according to the Prado et al method. We evaluated the effect of pre- and post-CRT sarcopenia on survival outcomes. Survival curves were constructed using the Kaplan-Meier method and log-rank test was used to compare their outcomes.

Results: A total of 36 patients were identified, and the median follow-up was 60.3 months. The mean SMI was 45.2 cm^2/m^2 for pre-CRT and 38.2 cm^2/m^2 for post-CRT ($P<.05$). Therefore, sarcopenia was identified in 23 patients (63.8%) on the pre-CRT and an additional 29 of 36 patients (80.5%) on the post-CRT scan. Patients who developed sarcopenia on the post-CRT had decreased locoregional control (LRC), overall survival (OS), and disease-free survival (DFS) compared with those in the non-sarcopenia group ($P<.05$ for all). Patients with severe skeletal muscle mass decrease of over 20% that was identified on the post-CRT scan showed lower 5-year OS and DFS ($P<.05$). Positive correlation between percent weight loss and decreased SMI from baseline was shown (Pearson r = 0.40, P = .028).

Conclusion: Our results suggest that skeletal muscle mass change may be a prognostic factor after CRT for NPC patients. Further analysis is needed to clarify whether aggressive nutritional intervention during CRT improves skeletal muscle mass and thus contributes to reducing recurrence in sarcopenic patients.

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Treatment Intensification for HPV-Unrelated Head and Neck Squamous Cell Carcinoma With *Nab*-Paclitaxel-Based Chemotherapy followed by Cisplatin and Radiation Therapy

D. Adkins,[1] J. Ley,[2] P. Oppelt,[3] H.A. Gay,[4] M.D. Daly,[4] R.S. Jackson,[2] J. Rich,[5] P. Pipkorn,[5] R.C. Paniello,[5] J.P. Zevallos,[2] and W.L. Thorstad[4]; *[1]Washington University in St. Louis, Department of Medical Oncology, St. Louis, MO, [2]Washington University School of Medicine, St. Louis, MO, [3]Washington University School of Medicine, St. Louis, MO, [4]Washington University in St. Louis, Department of Radiation Oncology, St. Louis, MO, [5]washington university school of medicine, St. Louis, MO*

Purpose/Objective(s): In human papillomavirus (HPV)-unrelated head and neck squamous cell carcinoma (HNSCC), locoregional relapse (LRR) is the most common cause of treatment failure. Following cisplatin and radiation therapy (CisRT), the LRR rate at two years is 25%-35% (RTOG 0129, 0522, 91-11). We present our experience of treatment intensification for HPV-unrelated HNSCC with *nab*-paclitaxel-based chemotherapy followed by CisRT.

Materials/Methods: In this retrospective analysis, we identified patients with HPV-unrelated HNSCC treated with *nab*-paclitaxel and cisplatin-based chemotherapy over nine weeks followed by CisRT (High Dose [x3] Cisplatin + 70 Gy IMRT). Efficacy endpoints included LRR rate, progression-free (PFS) and overall survival (OS).

Results: Thirty-eight patients were the subject of this analysis. Patient characteristics included mean age 58 years, smoker 95%, male gender 76%, PS 0 (76%), and ACE comorbidity scores moderate/severe (45%). Tumor characteristics included T3/4 (81%), > N2c (58%), and larynx/hypopharynx sub-sites (71%). Median follow-up was 27 months. LRR occurred in 4 (11%) patients. Two-year PFS was 75% and OS was 83%. Causes of death included relapse (4 patients), second cancer (2), co-morbidity (5), and other (2).

Conclusion: In HPV-unrelated HNSCC, the LRR risk two years following *nab*-paclitaxel-based chemotherapy and CisRT was only 11%, which is much lower than historical comparisons from the literature. This exploratory analysis suggests that intensification of CisRT with *nab*-paclitaxel-based chemotherapy may lower the risk of LRR in these high-risk patients.

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Understanding Patient's Refusal of Laryngectomies and the Survival Implications

S. Massa,[1] S. Mehrotra,[2] L. Cass,[1] G. Ward,[2] and R. Walker[2]; *[1]Saint Louis University School of Medicine, Saint Louis, MO, [2]Saint Louis University, St Louis, MO*

Purpose/Objective(s): Despite the increasing utilization of non-surgical therapies for advanced laryngeal cancer, total laryngectomy is recommended for some patients. A recent national database study associated refusal of surgery for advanced laryngeal cancer with a 10% 5-year survival decrease. However, important confounders could not be assessed

with the registry data. The present study was undertaken to confirm the national database findings and better understand patients' decision process.
Materials/Methods: Adult patients with stage II-IVa laryngeal squamous cell carcinoma diagnosed from 2006-2014 were identified from an institutional cancer database. Demographic and oncologic data were obtained from the database, then confirmed and augmented via comprehensive chart review. Patients who did not undergo curative treatment were excluded. Patients refusing laryngectomy in favor of chemoradiation were compared to those receiving surgery using paired t-tests and chi-squared tests for continuous and categorical variables, respectively. Patients refusing laryngectomy were then matched to those undergoing laryngectomy using propensity scoring with a 1:3 case:control ratio. Kaplan-Meier curves were developed for overall survival and compared by log-rank testing.
Results: The study cohort consisted of 141 patients with median of 67 months follow-up. Six patients were identified as refusing surgery from registry data and an additional 3 from chart reviews, representing 12.6% refusal among 70 patients recommended surgery. Compared to patients undergoing laryngectomy, the 9 refusing patients were more often black (66.7% vs 18.0%, $P=.006$), female (55.6% vs 26.2%, $P=.161$) and current alcohol users (88.9% vs 44.3%, $P=.086$). Age, subsite, and comorbidities were similar between groups. Overall survival curves were similar between patients refusing laryngectomy and matched controls (median 69 vs 51 months, $P=.470$). Reasons for refusing laryngectomy included fear of surgery, uncertainty of recovery, and a stated desire to avoid a permanent stoma.
Conclusion: Many patients who may benefit from laryngectomy are apprehensive about surgery, and a subset will refuse this treatment despite the recommendation of their treatment teams. After controlling for potential confounding factors, including those not available in prior registry-derived studies, no survival difference was found associated with refusal.
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Withdrawn

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Outcomes of Stage I-II Squamous Cell Carcinoma of the Oral Tongue Managed With Surgery Including an Elective Nodal Dissection: Potential Indications for Postoperative Radiation Therapy

M. Zhi[1] and S. Iganej[2]; [1]*Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA,* [2]*Southern California Permanente Medical Group, Los Angeles, CA*

Purpose/Objective(s): Patients with pathologic T1-2N0 oral tongue squamous cell carcinoma (OTSCC) are considered "low risk" and typically do not receive adjuvant treatment. We sought to characterize the outcomes of patients managed with surgery alone, their recurrence patterns, and any prognostics factors predictive of recurrence and/or survival.
Materials/Methods: We retrospectively reviewed the records of 84 consecutive patients with newly diagnosed, early-stage pT1-2N0 OTSCC who underwent partial glossectomy and ipsilateral elective neck dissection from 2007-2013 at our institution. Patients who received PORT were excluded as well as those who had positive margins, pathological nodal involvement, or a history of prior or synchronous head and neck primaries.
Results: The cohort was 60% male and was comprised of 62% pT1 and 65% grade 2-3 tumors. Of the patients, 51% were current or former smokers. Median age was 58.5 (range: 20-87 years). With a median follow-up of 58 months (range: 3-131 months), 13 (16%) patients developed a relapse. The site of first relapse was isolated local in 5 patients, isolated regional in 2 patients, and combined locoregional in 6 patients. No patients developed a distant recurrence, either isolated or combined, at the time of first relapse. Regional recurrences were ipsilateral in 75% and contralateral in 25% of patients. Overall, the 5-year rates for local control (LC), regional control (RC), locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) were 89%, 91%, 86%, 80%, 93%, and 87%, respectively. Pathologic T2 status was a predictor for worse outcomes across all endpoints. Perineural invasion (PNI) was a predictor for worse RC ($P=.04$), DSS ($P=.001$), and OS ($P=.001$). Margin $\leq$2 mm was a predictor for worse LC ($P=.0001$) and PFS ($P=.0011$). Nine of the 49 (18%) patients with depth of invasion (DOI) $\geq$4 mm suffered locoregional relapses (LRR). Of the 5 patients with pT2 and PNI, 2 (40%) developed isolated regional relapses. Of the 24 patients with pT2 and DOI $\geq$4 mm, 5 (21%) had regional failures. Patients who developed neck recurrences experienced a significantly worse DSS (5-year: 38% vs 100%; $P<.0001$) and OS (5-year: 38% vs 92%; $P<.0001$) compared to those who did not. All relapses underwent further salvage treatment; 8 (62%) patients were successfully salvaged with no evidence of disease at last follow-up.
Conclusion: At our institution, patients with early-stage, pT1-2N0 OTSCC exhibited relatively low rates of LRR and good overall prognosis. Regional relapse, however, significantly impacts OS adversely. Patients with pT2 disease who have PNI and/or DOI $\geq$4 mm appear to be at considerable risk of regional relapse and should be counseled regarding PORT. When feasible, wider margins >2 mm should be obtained surgically.
Author Disclosure: **M. Zhi**: None. **S. Iganej**: None.

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Prognostic Factors Associated With Progression-Free Survival in Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma Treated With Induction Chemotherapy Followed By Chemoradiation Therapy

N. Sobrevilla, A. Martínez, M.A. Alvarez, O. Macedo, L. Mendoza, M. Granados, and J.L. Aguilar; *Instituto Nacional de Cancerología, Mexico, Mexico*

Purpose/Objective(s): Chemoradiation therapy (CRT) is the standard of care for locally advanced head and neck squamous cell carcinoma (LAHNSCC). Induction chemotherapy (IC) with TPF (taxane, CDDP, FU) has shown benefit compared to PF (CDDP, FU), but its use is controversial. Response to IC may be associated with further response to CRT. We hypothesized that response to IC is an independent prognostic factor associated with PFS. Objective: to analyze the PFS of patients with LAHNSCC (larynx[L], hypopharynx[HP], oropharynx [OP], oral cavity[OC]), treated with IC followed by CRT, according to response to IC and CRT.
Materials/Methods: Retrospective review of patients with LAHNSCC treated with IC followed by CRT from January 2010 to December 2014. Demographic characteristics, basal blood test results, type of IC, type of CRT, responses, and adverse events were collected. Patients were classified according to overall response rate (ORR) to IC and CRT, no ORR to IC but ORR to CRT, ORR to IC but not to CRT and no ORR to IC or CRT. Kaplan-Meier analysis for PFS was performed. Multivariate analysis with Cox regression was performed with variables with a P value >.1.
Results: Fifty patients were included. Mean age 54.7 yr (28-76), 36 (72%) males, 27 (54%) smoking history. OC 20 (40%), L 13 (26%), HP 10 (20%), OP 7 (14%). CS III 16 (32%), IVA 23 (46%), IVB 11 (22%). 46 (92%) ECOG 1, 4 (8%) ECOG 2. 49 (98%) TPF with cisplatin, 40 (80%) weekly (wk) taxane, 44(88%) paclitaxel, 6 (12%) docetaxel. ORR IC 80%: CR 12%, PR 68%, SD 18%, PD 2%. CRT with CDDP 41 (82%), 9 (18%) CBP. CDDP wk 20 (40%), CDDP 3wk 21 (42%). Mean CDDP dose wk 218.6 (91.37-320.71), median CDDP dose 3 wk 203.55 (94.1-308.7). Median RT dose 70 Gy (42-74), Median protraction time 8.78 wk (5-12.57). ORR CRT 84%: CR 44%, PR 40%, SD 10%, PD 6%. Univariate and multivariate results for PFS are shown in the table. Five (55%) patients with SD post-IC and 1 (100%) patient with PE post-IC achieved ORR with CRT.
Conclusion: Response to CRT is an independent prognostic factor from response to IC for PFS. Patients responding to both treatments have the best prognosis. Patients that do not respond to IC still can benefit from CRT. CRT with CDDP should be pursued in all fit patients.

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Variable	Univariate PFS (m)(IC95%)	p	Multivariate HR (IC95%)	p
ORR IC and CRT ORR IC not CRT No ORR IC but ORR CRT No ORR IC or CRT	55.05 (43.85-66.25) 9.94 (7.19-12.69) 33.45 (15.03-51.87) 9.61 (6.37-12.85)	<.0001 NS .02	1.12 (.65-1.93)	NS
ORR (CR+PR) CRT SD PD	53.63 (43.12-64.14) 11.17 (8.87-13.47) 7.31 (5.9-8.71)	.03 <.0001	3.72 (1.47-9.43)	.006
Female Male	36.22 (38.2-58.35) 45.38 (36.2-54.57)	.08	1.31 (.48-3.54)	NS
CS III Other	63.55 (48.49-78.61) 35.48 (25.71-45.2)	.03	.26 (.081-.84)	.02
3wk CDDP Other	48.86 (37.76-59.97) 39.99 (27.21-52.78	.07	.29 (.11-.76)	.01
Protraction time >8wk Protraction time ≤ 8 wk	42.2 (30.5-53.84) 54.1 (40.1-68.9)	.08	2.37 (.60-9.33)	NS

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Outcomes of Tomotherapy for Advanced Cutaneous Scalp Squamous Cell Carcinoma

M.K. Abdelhakiem, A.D. Currey, and J.R. Robbins; *Medical College of Wisconsin, Milwaukee, WI*

Purpose/Objective(s): Advanced cutaneous scalp squamous cell carcinoma can often be challenging to treat due to large size, convex anatomy, and potential regional spread. Tomotherapy has emerged as a technique that can technically provide coverage for these lesions. This study assesses outcomes and patterns of failure for cutaneous scalp squamous cell carcinoma in patients treated with Tomotherapy as definitive or adjuvant therapy.

Materials/Methods: Between 2007-2015, 16 patients were treated with Tomotherapy for advanced cutaneous SCC of the scalp at our institution. Retrospective data were collected on each patient by chart review and included the primary site of the lesion, date of diagnosis, start/end radiation treatment dates, any diagnosed recurrences including local/regional/distant, last known follow-up date, and patient survival. Local control, regional control, distant control, and overall survival following treatment of the primary lesion were specifically investigated.

Results: The treated tumors were all complex and advanced. The average size was 5 cm. Twenty-five percent were recurrent lesions. Half of the lesions had upfront surgery (Mohs or wide excision) and were treated postoperatively due to high risk features (perineural invasion, bone/periosteal invasion, multifocal disease, metastasis to regional lymph nodes). Two of the patients were immunocompromised. Dose ranged from 54-66 Gy in the postoperative cases and 60 to 70 Gy in definitive cases. Median time to last follow-up was 25.2 months (range, 6.2-111.3 months). In total, there were 6 local, 4 regional, and 2 distant recurrences, with two patients having both local and regional recurrences. All patients with bone invasion developed a recurrence. Local control at 2 years was 69%, while regional control and distant control were at 81.25% and 87.5% respectively. Overall survival at 2 years was 75%. Four patients passed away by the 2-year mark with the causes of death being metastatic disease, local recurrence with one immunocompromised patient developing sepsis, and another patient having tumor versus abscess spread into the CSF, and the fourth patient dying from non-cancerous cause without recurrence. The overall recurrence rate (local, regional, distant) following Tomotherapy for advanced cutaneous scalp SCC was 44% at two years.

Conclusion: Advanced cutaneous scalp SCC can be challenging to treat. Patients treated with Tomotherapy did have reasonable control given the advanced nature of their diseases. Further work to more fully establish this therapy as part of the standard therapy for these lesions is needed.

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Head and Neck Squamous Cell Carcinoma in Organ Transplant Recipients: A Single Institutional Experience

J.L. Geiger,[1] C.A. Reddy,[2] N.M. Woody,[2] S. Koyfman,[2] N.P. Joshi,[2] J. Bodmann,[1] B.A. Harr,[2] J. Ferrini,[1] D. Ives,[1] B.B Burkey,[3] B. Prendes,[3] E. Lamarre,[3] J. Scharpf,[3] and D.J. Adelstein[1]; *[1]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Immune suppression following solid organ transplantation with antimetabolites and other antirejection medications is a risk factor for the development of squamous cell carcinoma. While outcomes of cutaneous squamous cell cancers in organ transplant recipients (OTRs) have been reported, there is a paucity of such data in those patients who develop mucosal squamous cell carcinomas of the head and neck (HNSCC). We report the Cleveland Clinic experience with this patient population.

Materials/Methods: Patients who developed HNSCC after solid organ transplant between 2000 and 2016 were retrospectively identified in an IRB-approved database. Adults maintained on immunosuppressive medications for their transplant with biopsy-proven HNSCC were included. Patterns of disease recurrence were evaluated by cumulative incidence, and progression-free survival (PFS) and median overall survival (OS) were analyzed by the Kaplan-Meier method.

Results: Seventeen patients met inclusion criteria for evaluation with a median time from organ transplant to diagnosis of HNSCC of 4.9 years. Transplanted organs included: lung (6), kidney (5), liver (4), heart (1), heart/lung (1). Ten patients (59%) were never smokers. Primary tumor site was distributed among all head and neck sites, including 7 patients with oral cavity disease, 3 with oropharynx (all of which were HPV-positive disease), 1 larynx, and 3 each of major salivary gland and unknown primary. Of the patients, 59% (10/17) presented with Stage III or IV disease; 24% (4/17) and 17% (3/17) had Stage I and II disease, respectively. Seventy-six percent (13/17) of patients were treated with primary surgical resection, and 77% (10/13) subsequently received adjuvant treatment: 8 patients received radiation therapy (RT) alone and 2 patients were treated with adjuvant chemoradiation therapy (CRT). Four patients (24%) were treated with definitive RT; only one patient received definitive CRT. There were no cases of organ transplant rejection with cancer treatment. The 5-year OS rate was 50%; median PFS was 37.6 months. Six patients (35%) developed recurrent disease; two 12%) with locoregional recurrence, one (6%) with distant metastatic disease, and three patients (17%) who recurred both locoregionally and distantly.

Conclusion: OTRs on chronic immunosuppression can develop mucosal squamous cell carcinoma in any of the head and neck anatomic locations. While treatment appears well-tolerated with a low risk of transplant rejection, the likelihood of locoregional and distant recurrences in this patient population remains high. Further data is needed to better define the risk of HNSCC development in OTRs, study outcomes in this disease and population, and develop improved treatment strategies.

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Prognostic Factors and Treatment Outcomes of External Auditory Canal Carcinoma

I.J.H. Jang,[1] C.E.H. Teo,[2] Z.Y. Tay,[2] and K. Sommat[3]; *[1]Singapore Health Services, Singapore, Singapore, [2]Singapore General Hospital, Singapore, Singapore, [3]National Cancer Centre Singapore, Singapore, Singapore*

Purpose/Objective(s): External auditory canal (EAC) carcinoma is rare, and despite multiple different staging systems proposed, prognosis is poor. Presently, there are no standard guidelines on treatment modalities as well. Hence this study aims to investigate the prognostic factors and treatment outcomes in patients with EAC carcinoma.

Materials/Methods: All patients diagnosed with primary EAC and treated with curative intent at a single tertiary institution were retrospectively reviewed over a 22-year period. Patients were staged with the modified Pittsburgh staging system. Thirty-seven patients (77.5%) were treated with surgery alone or combined with postoperative radiotherapy (RT) and/or concurrent chemotherapy (CRT). Nine patients (22.5%) received definitive RT or CRT. Baseline and clinical characteristics were collected, and survival outcomes analyzed using the Kaplan−Meier method. Comparisons were made using log-rank test. Median follow up was 8.3 years.

Results: There were 40 patients with EAC carcinoma in our cohort. The 5-year overall survival (OS), 5-year disease specific survival (DSS) and 5-year locoregional free survival (LRFS) were 66% ± 9%, 70% ± 9%, and 60% ± 11% respectively. Majority (92%) of relapses were locoregional. On univariate analysis, the factors predictive of OS were age and surgical treatment (P=.027 and P=.049, respectively). Although facial nerve palsy did not show a significant difference in OS (P=.091), it showed a significant difference in DSS and LRFS (P=.005 and P=.000, respectively). Group stage, T-stage, N-stage, histology grade, histology margins, ECOG performance status, and ACE-27 comorbidity scores did not show a significant difference in OS, DSS, and LRFS.

Conclusion: Younger age, absence of facial nerve palsy, and surgical treatment showed significantly better survival outcomes in patients with EAC carcinoma.

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TPF Induction Chemotherapy Prior to Chemoradiation for Locally Advanced Nasopharyngeal Carcinoma

S.M. Davidson,[1] D.A. Palma,[1] S. Kuruvilla,[2] V.M. Venkatesan,[1] N. Read,[1] J.A. Hammond,[1] A. Nichols,[3] K. Fung,[3] D. MacNeil,[3] J. Yoo,[3] A. Warner,[4] and E. Winquist[2]; *[1]Department of Oncology, Division of Radiation Oncology, Western University, London, ON, Canada, [2]Department of Oncology, Division of Medical Oncology, Western University, London, ON, Canada, [3]Department of Otolaryngology, Western University, London, ON, Canada, [4]London Regional Cancer Program, London, ON, Canada*

Purpose/Objective(s): Platinum-based chemoradiation (CRT) with or without adjuvant chemotherapy is considered standard treatment for locally advanced nasopharyngeal carcinoma (LA NPC). Recently, a large randomized trial reported overall survival benefit with TPF induction chemotherapy (IC) prior to CRT compared to CRT alone. We have used TPF IC prior to CRT selectively in patients (pts) with symptomatic LA NPC and report our outcomes with this approach.

Materials/Methods: Eligible pts were retrospectively identified from electronic records, had a pathological diagnosis of stage III-IVB NPC, and received TPF IC at our large academic institution. TPF consisted of docetaxel 75 mg/m^2 and cisplatin 100 mg/m^2 IV day 1 plus 5-FU 1000 mg/m^2/d x 96 hours by IV infusion q21days x 3 cycles given with antibiotic prophylaxis or G-CSF. Radiation entailed 70 Gy in 35 daily fractions using IMRT with lower doses to elective regions. Data were extracted and time-to-event outcomes reported using the Kaplan-Meier method.

Results: Of 2997 pts seen in our Head & Neck MDT clinic 2009-2016, 51 (1.7%) had NPC. Thirteen eligible LA NPC pts were identified (25.5%); median age 55 (range: 17-61), stage III/IVA/IVB (23%/69%/8%), 11 were male. Median follow-up was 26 months. Nine pts received TPF to relieve symptoms: cranial neuropathy +/- headache (5 pts), trismus (2 pts), bradycardia (1 pt), and orthopnea (1 pt). Two pts were treated to reduce RT dose to brain stem/optic chiasm, and 2 pts at the oncologist's discretion. All except 3 pts received 3 TPF cycles. Two pts received only 1 TPF cycle; 1 pt died of cardiac arrest and the other elected to discontinue all treatment with subsequent death due to uncontrolled NPC. One pt did not complete the 3rd cycle due to hearing loss. Eleven pts (85%) experienced at least grade 3 toxicity during TPF with volume depletion, nausea/vomiting, and infection being most common. Prior to CRT the objective partial response rate to TPF was 92.3%. Cancer symptoms improved in all pts. Four pts have died: 1 toxic death, 1 non-cancer death, and 2 due to uncontrolled NPC. Progression-free and overall survival at 3 years were 58% and 67%, respectively. Grade 3 late toxicity has been reported in 4 pts (hearing loss, dental caries, and weight loss).

Conclusion: TPF induction chemotherapy prior to CRT was highly active in symptomatic LA NPC pts and induced tumor and symptom remission prior to CRT. Consistent with prior reports, TPF was associated with significant adverse effects in most pts and 1 toxic death, and it should be used by experienced clinicians in suitable pts. Our data support use of TPF IC prior to CRT as a treatment strategy in pts with advanced symptomatic NPC to provide symptom relief prior to CRT, allow more effective delivery of systemic chemotherapy, and potentially improve overall survival. Further research to identify both the optimal TPF regimen and the patient subgroups who benefit most is needed.

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Tomotherapy Versus 3D Conformal Radiation Therapy in Patients With Head And Neck Cancer Treated With Definitive (Chemo) Radiation Therapy

J. Kovarik,[1] M. Cunnell,[1] G. Shaikh,[1] C.G. Kelly,[2] and M.S. Iqbal[1]; *[1]Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [2]Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom*

Purpose/Objective(s): Since the introduction of Tomotherapy in our center, it has not been possible to treat all head and neck cancer (HNC) patients on it due to logistic reasons. It was a unique situation where HNC patients were treated simultaneously by the same specialists using two different radiation therapy techniques in the same institute. The objective of this study is to evaluate the efficacy and toxicity of two techniques, i.e. Tomotherapy and 3D conformal radiation therapy in HNC patients treated with definitive (chemo)radiation therapy.

Materials/Methods: Between March 2009 to February 2013, 165 consecutive patients with a biopsy proven squamous cell carcinoma of head and neck region treated with definitive radiation therapy 65 Gy in 30 fractions ± weekly cisplatin/cetuximab chemo(bio)therapy were included. The data was collected retrospectively, log-rank test was used for survival analysis; chi-square and Fisher's exact test were used for group analysis.

Results: Ninety-seven patients received 3D conformal radiation therapy (3D CRT group) and 68 patients were treated with Tomotherapy (Tomo group). Median age was 63 years (range: 37-89) in 3DCRT and 58 years (range: 19-77) in the Tomo group. In both groups, oropharynx was the most common primary subsite (54% in 3D CRT and 63% in Tomo).

Majority of the patients in both groups were of stage (TNM 7th edition) IVa (54% in 3D CRT and 66% in Tomo) followed by stage IVb (10% in each group). Of the patients in 3D CRT, 56.7% received concurrent chemotherapy (95% cisplatin, 5% cetuximab) while 86.8% of Tomo group received chemotherapy (92% cisplatin, 8% cetuximab). In 3D CRT, 67.3% of the patients completed all 6 cycles of chemotherapy compared to that 74.6% in Tomo group. Response was achieved in 93.8% cases in 3D CRT and 97.1% cases in Tomo group. In 3D CRT, 17 patients recurred locally and 8 developed distant metastases as compared to 14 and 10 respectively in Tomo group. With a median follow up of 42 months (range: 1-83), 1-year and 5-year disease-free survival were 80% and 63.7% in 3D CRT vs 88.1% and 77.1% in Tomo group. One-year overall survival and 5-year survival were 85.5% and 54.2% in 3D CRT group vs 85.3% and 62.1% in Tomo group. The incidence of acute toxicities was higher in Tomo group given the higher percentage of patients received concurrent chemotherapy. However, there was a trend of lower incidence of late toxicities in the Tomo group: bone necrosis (7 patients in 3D CRT vs 3 in Tomo, $P = .52$), complete xerostomia (18 vs 8, $P = .24$), and laryngeal cartilage necrosis (5 vs 1, $P = .40$). A significant difference was observed in late swallowing dysfunction requiring intervention (27 in 3D CRT vs 5 in Tomo, $P = .02$).

Conclusion: There was no statistical difference in DFS and OS between two groups; however, we observed a trend of lower incidence of late toxicities in patients treated with Tomotherapy, with a significant difference in late swallowing dysfunction.

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Development of Care Pathway Models to Standardize and Optimally Integrate Multidisciplinary Services in the Management of Head and Neck Cancer

A.G. Sacco,[1] C. Coffey,[2] P. Sanghvi,[3] G.P. Rubio,[4] J.A. Califano,[2] J. Athas,[4] G.J. Tamayo,[1] K. Linnemeyer,[4] R.K. Orosco,[2] K. Brumund,[2] E. Cohen,[1] K.A. Gold,[1] L.K. Mell,[3] A. Sharabi,[3] G. Daniels,[1] Y. Abbott,[4] R. Collins,[5] K. Clynch,[4] M. Noboa,[4] and L. Blumenfeld[4]; *[1]UC San Diego, Moores Cancer Center, Department of Hematology/Oncology, La Jolla, CA, [2]UC San Diego, Moores Cancer Center, Department of Otolaryngology, La Jolla, CA, [3]UC San Diego, Moores Cancer Center, Department of Radiation Oncology, La Jolla, CA, [4]UC San Diego, Moores Cancer Center, La Jolla, CA, [5]UC San Diego Health System, La Jolla, CA*

Purpose/Objective(s): Multidisciplinary care is a cornerstone of head and neck cancer (HNC) management, with prior studies highlighting improved functional and survival outcomes when utilizing an integrated approach. While the National Comprehensive Cancer Network (NCCN) guidelines recommend that "all patients need access to the full range of support services and specialists with expertise" in the management of HNC, the timing and frequency of these interventions has not been clearly defined. The Care Pathway Model (CPM) is a clinical roadmap that defines and standardizes the patient care experience throughout treatment and survivorship, permitting predictable and consistent prescription of multidisciplinary services. In line with the clinical vision of our Head and Neck Cancer Center of Excellence, we sought to develop CPMs to standardize our patient-centric, multidisciplinary approach to HNC care.

Materials/Methods: Representatives across all disciplines participated in the CPM decision-making process. These included physician providers from Medical, Radiation and Surgical Oncology, supportive service providers (Nursing, Speech Language Pathology, Nutrition, Physical/Occupational Therapy, Social Work, Patient Navigation) and our program administrator. Multiple small group discussions were required to create the CPMs, with decisions surrounding timing and frequency of visits based on specialty clinical expertise, recommendations from the available literature, and feasibility based on our program's infrastructure.

Results: Four CPMs were devised and implemented, including pathways for definitive chemoradiation, surgery followed by adjuvant radiation, surgery alone, and radiation alone. Order sets for each pathway were built into the electronic medical record to facilitate referral generation. A patient navigator program was developed to assist with care transitions. An education course was designed for new HNC patients to facilitate early introduction of the multidisciplinary paradigm. An education booklet will provide pertinent resources specific to HNC patients. Survivorship follow-up plans based on NCCN guidelines were created, with handouts provided to patients. Additionally, a nurse practitioner-driven survivorship clinic is underway.

Conclusion: These pathways have provided the framework for implementation of integrated, highly coordinated multidisciplinary care. Our future directions include rigorous evaluation of how these CPMs impact functional and survival outcomes as well as overall patient experience.

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Towards A Personalized Radiation Therapy Dose-Prescription in Locally Advanced Nasopharyngeal Carcinoma

N. Alsafadi,[1] M. Khan,[1] Y. Barakati,[2] F. Saeedi,[1] S. Jaber,[1] and E.N. Ismail[1]; *[1]Princess Norah Oncology Center, Jeddah, Saudi Arabia, [2]Princess Norah Oncology Center, jeddah, Saudi Arabia*

Purpose/Objective(s): Nasopharyngeal carcinoma frequently affects young adults who often present with locally advanced disease. The combination of intensity modulated radiation therapy (RT) and chemotherapy (CT) improves the outcome. However, the RT dose required for disease control is close to the tolerance of the surrounding normal tissues. We have been treating patients with intracranial extension and patients under 25 years of age with hyperfractionated RT (HRT) aiming at reducing the severity of the late toxicity. The purpose of this study is to compare HRT to conventionally fractionated RT (CRT) using a biological model with the endpoints of tumor control probability (TCP) and normal tissue complication probability (NTCP)

Materials/Methods: We reviewed the plans of 5 patients treated radically with HRT and CT. A control plan using CRT was created for each patient treated with HRT for the purpose of this study. The biological evaluation was done using the software provided by Eclipse, version 13.7. The mean prescribed dose for the CRT was 67.6 Gy and 57.6 Gy (range 66-70 and 56-60) in 33-35 once-daily fractions for High Risk and Low Risk Planning Target Volume (HR-PTV & LR-PTV). The corresponding mean HRT dose was 72.6 Gy and 63.8 Gy (range 69-75.4 and 60-67) in 60-66 twice-a-day fractions. The dose-fractionation protocol was chosen clinically to best fit the tumor extension, taking into consideration the patient age. All patients were treated using Volumetric Modulated Arc Therapy (VMAT; RapidArc. Varian Medical Systems, Palo Alto, CA, USA) using the concomitant boost technique. We introduced two new organs at risk, the internal carotid artery (ICA) and soft tissues of the neck (STN), which we consider as an important source of late morbidity/mortality in young patients. We assumed a D50 of 65 Gy and $\alpha/\beta = 3$ for both of these volumes.

Results: HRT yielded higher TCPs in all patients. The mean TCP (HRT vs. CRT) for HR-PTV, LR-PTV, and the composite TCP (C-TCP) were 81% vs. 73% ($P = .029$), 94% vs. 85% ($P = .008$), and 76% vs. 64% ($P = .027$) in favor of HRT. The NTCPs were in favor of the HRT. Notably, the NTCP

for the ICA and STN were significantly improved using HRT, 21% vs. 36%, $P=.002$ and 18% vs. 31% $P=.018$, respectively. The temporal lobe and optic chiasm NTCPs were non-significantly improved with HRT compared to CRT (Mean 0.97% vs. 2.93%, $P=.097$, and 0.36% vs. 10.38%, $P=.27$).

Conclusion: In the present study, HRT provided significantly better TCPs and favorable NTCPs indicating an enhanced therapeutic ratio. The improved NTCPs for the ICA & STN is interesting, and is most important in this young population with high cure rate. Using feedback from the biological model, we are now individually personalizing the HRT dose prescription aiming at maximizing the C-TCP while maintaining clinically acceptable NTCPs.

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Organ Preservation With External Beam Radiation and Systemic Therapy in Patients With Locoregionally Advanced Laryngeal Cancer: An Institutional Experience

L. Callan,[1] T. Zhang,[2] H. Low,[3] D. Yeh,[4] R. Araslanova,[4] S. Kuruvilla,[5] E. Winquist,[5] J.A. Hammond,[6] N. Read,[6] D.A. Palma,[6] A. Nichols,[4] and V.M. Venkatesan[1]; *[1]Department of Radiation Oncology, Western University, London, ON, Canada, [2]London Regional Cancer Program, London, ON, Canada, [3]Chris O'Brien Lifehouse, Sydney, Australia, [4]Department of Otolaryngology, Western University, London, ON, Canada, [5]Department of Oncology, Division of Medical Oncology, Western University, London, ON, Canada, [6]Department of Oncology, Division of Radiation Oncology, Western University, London, ON, Canada*

Purpose/Objective(s): To retrospectively evaluate the outcomes of combined radiation therapy and systemic treatment in patients with locoregionally advanced laryngeal cancer.

Materials/Methods: Using an institutional database, 456 patients with laryngeal cancer treated between 2002 and 2014 were identified. Of the 171 patients with Stage III or IVa disease, 67 were treated with curative intent using combined external beam radiation therapy and systemic therapy for organ preservation. Fifty patients remained eligible for analysis after excluding the following patients: cartilage invasion (n=8), non-squamous cell pathology (n=2), failure to complete a minimum of 10 fractions of radiation (n=2), treatment at a different institution (n=4), and simultaneously treatment for a synchronous malignancy (n=1). The Kaplan-Meier method was used to estimate time-to-event outcomes, with censorship at the time of last known follow-up. The endpoints were 3- and 5-year Overall Survival (OS), Laryngectomy-Free Survival (LFS), Disease Specific Survival (DSS), Locoregional Control Rate (LCR), and Laryngeal Preservation Rate (LPR). Gray's test was used to compare survival curves between patients based on prognostic factors including T3 vs. T4a disease, node positive vs. node negative disease and glottic vs. supraglottic primary disease site.

Results: The median follow-up for the 50 analyzed patients was 68 months (range: 42-119). Primary disease site was supraglottic in 68% of patients (n=34) and glottic in the remainder. 62% of patients (n=31) were Stage III and 38% (n=19) were Stage IVa. T and N status were distributed as follows: T2 12% (n=6), T3 78% (n=39), T4a 10% (n=5), N0 52% (n=26), N1 16% (n=8), N2a 4% (n=2), N2b 16% (n=8), N2c 12% (n=6), N3 0% (n=0). At last known follow-up, 56% of patients (n=28) were alive and well, 14% (n=7) had died due to their disease or treatment complications, 24% (n=12) had died from other causes and 6% (n=3) had died of unknown causes. The 3- and 5-year OS, LFS, and DSS were 77.7% and 60.2%, 67.6% and 52.3%, and 83.3% and 74.8%, respectively. LPR was 88.7% and 85.4% at 3 and 5 years, respectively. LCR and distant metastasis free rate at 3 and 5 years were 88.8% and 85.6%, and 91.0% and 91.0%, respectively. Comparisons between prognostic groups, patterns of failure, and functional outcomes will be presented.

Conclusion: Our study demonstrates that through careful selection, patients with locoregionally advanced laryngeal cancer can be offered organ preservation with non-surgical therapy without compromising oncologic, survival or functional outcomes.

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Oral Cavity Cancer Institutional Database Evaluating Characteristics Predictive for Cancer Recurrence and Survival

D. Ding,[1] W.A. Stokes,[2] M. Eguchi,[2] J. McDermott,[2] R.M. Lanning,[2] J.A. Goddard,[3] H. Somerset,[4] D. Raben,[2] C.J. Bradley,[2] and S.D. Karam[2]; *[1]Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]Department of Otolaryngology, University of Colorado School of Medicine, Aurora, CO, [4]University of Colorado School of Medicine, Denver, CO*

Purpose/Objective(s): Despite significant advancements made in cancer diagnostic and treatment strategies, oral cavity squamous cell carcinoma (OCSCC) continues to have one of the highest rates of mortality among head and neck cancer sites even after trimodality care (surgery, radiation, and chemotherapy). In this retrospective study, we aim to identify factors that predict outcomes and to provide prognostic information to better assist clinicians in making treatment-related decisions

Materials/Methods: We retrospectively reviewed records of patients with pathological diagnosis of OCSCC between 1999 and 2015. Demographic, histopathologic, and toxicity- and treatment-related parameters were extracted. Univariate and multivariate Cox proportional hazard ratios (HRs) were calculated for locoregional control (LRC) and overall survival (OS). Univariate association with nodal involvement was also assessed. Survival curves were generated using the Kaplan-Meier method.

Results: A total of 148 patients without a previous diagnosis of OCSCC were analyzed. The 5-year LRC and OS rates were 62% and 35%, respectively. In univariate analysis, being uninsured ($P=.005$) or insured with Medicaid (0.040), >10% lymph node involvement ($P=.005$), T3-T4 pathological stage ($P=.01$), positive margin ($P=.008$), +PNI ($P=.03$) and +LVSI ($P=.014$) were associated with worse overall survival. In multivariate analysis, T3-T4 pathological stage ($P=.006$) and being uninsured ($P=.0004$) were independent predictors of poor overall survival. Worse OS also held for Medicaid patients compared to privately insured patients but did not reach statistical significance ($P=.12$). In terms of nodal involvement, the presence of LVSI or ECE was associated with more extensive nodal involvement ($P<.0001$). Finally, 54 patients with a recurrent OCSCC lesion were analyzed for overall survival. The 5-year OS rates between patients who received surgery only for the previous lesion (55.3%) and patients who received radiation previously (46.9%) were not significantly different ($P=.543$).

Conclusion: Our findings suggest that the presence of LVSI or ECE predict more extensive nodal involvement and should prompt a thorough neck evaluation. More advanced pathological stage as well as being uninsured are associated with worse outcomes. In the salvage setting, prior receipt of radiation treatment for the primary OCSCC lesion, as opposed to surgery alone, does not seem to compromise the treatment outcome of the recurrent lesion.

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Primary (Chemo)Radiation Therapy Versus Surgery Followed by Adjuvant (Chemo)Radiation Therapy in Stage IVA (TNM 7th edition) Squamous Cell Carcinoma of the Tonsil

J. Kovarik,[1] G. Shaikh,[1] J. O'Hara,[2] A. Greystoke,[1] N. Willis,[1] C.G. Kelly,[3] W. Dobrowsky,[1] and M.S. Iqbal[1]; *[1]Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [2]Department of ENT, Freeman Hospital, Newcastle upon Tyne, UK, Newcastle upon Tyne, United Kingdom, [3]Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom*

Purpose/Objective(s): To compare the treatment outcome and toxicity between patients with stage IVA (TNM 7th edition) squamous cell carcinoma of the tonsil treated with either primary (chemo)radiation therapy or surgery followed by adjuvant (chemo)radiation therapy.

Materials/Methods: Between March 2009 to February 2013, 52 consecutive patients with a biopsy-proven squamous cell carcinoma of the tonsil, stage IVA (TNM 7th edition), were analyzed retrospectively. Group CRT (primary radiation therapy ± chemotherapy, n = 37) was compared against group S+CRT (surgery followed by adjuvant radiation therapy ± chemotherapy, n = 15). The two groups were well-matched in terms of patient's age (median age 57 years in group CRT vs 60 in group S+CRT), HPV status (54% vs 60% positive, 16% vs 20% negative, and 30% vs 20% not available). However, the number of patients with T1/2 was higher in group S+CRT (80% vs 54%) and more patients received concurrent chemotherapy in group CRT (89% vs 60%). The radiation therapy regime was 63- 65 Gy in 30 daily fractions ± weekly cisplatin (40mg/m^2) chemotherapy or cetuximab (loading dose 400mg/m^2 followed by weekly 250mg/m^2) biotherapy.

Results: In group CRT, complete response (CR) was achieved in 97% patients (in 1 patient, CR was not achieved). Out of 36 patients with response, 2 patients (6%) developed locoregional recurrences (LRR) and 3 patients (8%) developed distant metastases (DM). This was comparable to group S+CRT (7% LRR and 7% DM). With a median follow-up of 51 months, 29 patients in CRT group were alive (5 out of the total of 8 deaths were disease related). In S+CRT group, 14 patients were alive and 1 died of disease. Five-year disease specific survival (DSS) was 88% in CRT group versus 93% in S+CRT group (HR 0.60; 95% CI 0.09-4.0). The difference in overall survival was not statistically significant. Addition of chemo(bio)therapy influenced the outcome ($P = .02$). HPV status ($P = .83$), age ($P = .41$) and number of cycles of chemotherapy received ($P = .16$) were not significant variables. There was a trend of less acute toxicities (grade 3 mucositis was 27% vs 54%, $P = .068$), and hospital admission rate (27% vs 49%, $P = .21$) in group S+CRT, but it was not statistically significant. There was no statistically significant difference in incidence of late effects in two groups (we assessed esophageal, soft tissue, bone, salivary gland and laryngeal toxicity).

Conclusion: This retrospective analysis has not confirmed any significant difference in the outcome of definitive (chemo)radiation therapy versus combined modality treatment in patients with locoregionally advanced carcinoma of the tonsil. Although the TNM 8th edition has been updated based on HPV status, our analysis did not show HPV status as a significant variable.

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Endoscopic Resection Followed by Proton Beam Therapy With Pencil Beam Scanning: A Multidisciplinary Approach to Tumors of the Skull Base

J.E. Leeman,[1] N. Lee,[1] Y. Zhou,[2] K. Sine,[3] V.S. Tabar,[2] and M. Cohen[4]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]ProCure Proton Therapy Center, Somerset, NJ, [4]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Endoscopic resection of anterior skull base tumors offers the ability to perform resection of locally advanced disease with a minimally invasive technique. For patients who require postoperative radiation therapy after endoscopic resection, proton therapy may provide substantial sparing of surrounding normal tissue and superior dosimetry to photon techniques. Herein, we assess the combined approach of endoscopic surgery followed by proton therapy with pencil beam scanning (PBS).

Materials/Methods: We performed a radiation dosimetry comparison between an intensity modulated photon radiation therapy (IMRT) plan and a PBS proton plan in the postoperative setting following endoscopic resection using an illustrative case. An 80-year-old man presented with locally advanced intestinal-type adenocarcinoma of the ethmoid sinus with extensive involvement of the anterior skull base and paranasal sinuses. He underwent endoscopic surgical resection with gross total resection achieved. IMRT and PBS plans were generated for comparison of adjuvant radiation therapy treatment techniques, prescribed to a dose of 66 Gy or 66 Gy (RBE) to the planning treatment volume.

Results: Compared to the IMRT plan, the PBS plan demonstrated a reduction in maximum temporal lobe dose (72.6 Gy vs 69.2 Gy), reduction in mean temporal lobe dose (8.1 Gy vs 5.7 Gy), reduction in mean brain dose (12.82 Gy vs 4.61 Gy), and reduction in mean brainstem dose (24.9 Gy vs 13.6 Gy). Similar maximum doses were delivered to the optic nerves (right, 54.3 Gy vs 54.0 Gy, Left, 54.1 Gy vs 54.6 Gy) as well as optic chiasm (52.7 Gy vs 53.4 Gy), which were directly abutting or encompassed within the target volume. The differences in radiation dose to organs at risk were achieved despite similar metrics of planning target volume coverage (D95, 63.7 Gy vs 62.4 Gy, V100, 97.4 Gy vs 96.9 Gy). The PBS plan delivered dose more homogeneously with a lower Dmax (75.9 Gy vs 69.3 Gy).

Conclusion: A multidisciplinary approach involving endoscopic resection followed by postoperative proton beam therapy with PBS for anterior skull base tumors represents a treatment paradigm with potential for improvements in neurological sparing and toxicity reduction. Proton therapy with PBS offers a particular benefit in terms of dose reduction to organs at risk outside of the planning target volume. Formal comparative studies and clinical trials evaluating this combined approach are needed.

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Treatment of Postoperative Chyle Fistulas With Octreotide: A Systematic Review

J. Waxman, Y. Dundar, P. Svider, and S.N. Raza; *Wayne State University School of Medicine, Department of Otolaryngology - Head and Neck Surgery, Detroit, MI*

Purpose/Objective(s): To systematically summarize and compare published data on the safety and efficacy of somatostatin or octreotide for the treatment of postsurgical chyle fistulas, with special attention paid to head and neck surgery.

Materials/Methods: A literature search of MEDLINE databases was conducted. Studies that reported outcomes of the use of somatostatin/octreotide for postsurgical chyle fistulas were reviewed. The references sections of all studies and review articles were screened for additional studies. No restrictions were placed on the publication year or study design. Exclusion criteria included non-English language studies, reviews, case reports, studies with five or fewer individuals, and studies that involved octreotide for uses other than for chyle leaks.

Results: The initial search yielded 349 articles, of which 21 were included in this review. Fourteen studies investigated the effects of octreotide on postoperative chylothorax in adults and pediatric patients. Three studies investigated the effects of octreotide on postoperative chylous ascites. Four

studies investigated the effects of octreotide on chyle leaks after neck dissections. Most were retrospective studies; no randomized controlled trials were identified. The resolution rate among adults with postoperative chylothorax treated with octreotide ranged from 87% to 89%, and among children ranged from 29% to 100%. The resolution rate of postoperative chylous ascites ranged from 67% to 100%. The resolution rate of chyle leaks after neck dissections ranged from 80% to 100%. Data from case-control studies showed decreased drain volumes, shorter times until drain removal, shorter resolution times, and increased resolution rates for patients treated with octreotide compared to patients treated without. Significant side effects from octreotide were uncommon and rarely serious.

Conclusion: Due to significant heterogeneity in study design, population characteristics, and treatment protocols, as well as significant variability in outcomes, it is difficult at this time to make definitive conclusions about the efficacy of octreotide for treating postoperative chyle fistulas. However, the data generally support its use and suggest quicker resolution times compared to conservative management without octreotide. To reliably assess the impact of octreotide on postoperative chyle fistulas, carefully constructed randomized controlled trials should be conducted.

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Endogenic Erythropoietin Levels are Fluctuated and Consequently Elevated Over Induction, Platinum-Based Chemotherapy in Patients With Advanced HNSCC

D. Leś,[1] J.J. Mrochem-Kwarciak,[2] A. Wygoda,[2] T. Rutkowski,[2] and K. Skladowski[3]; *[1]Institute of Oncology - Maria Sklodowska-Curie Cancer Center, Gliwice, Poland, [2]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [3]Institute of Oncology MSC Cancer Center, Gliwice, Poland*

Purpose/Objective(s): The role of erythropoietin (EPO) in anticancer treatment remains unclear. Clinical trials concerning erythropoietic agents used to augment tumor oxygenation in radiation treatment of head and neck cancer (HNC) patients showed impaired outcomes. Overcorrection of hemoglobin levels together with increased thromboembolic events is one explanation of these results, but it is also postulated that HNC cells which expressed EPO receptors can stimulate of downstream signaling pathways and promote a resistant tumor phenotype over the treatment. The present report concerns the behavior of the endogenic EPO over neoadjuvant, platinum-based chemotherapy in patients with advanced HNSCC.

Materials/Methods: The cohort of 27 patients with HNSCC entered the EPO-monitoring prospective trial between January and July 2017. The HNC characteristics in the 18 patients who completed EPO monitoring at the time of this analysis are as follows: according to primary site—7 OPC (4 HPV positive), 4 NPC, 2 OCC, 2 LXC, 1 HPC, 1 nasal cavity and 1 with CUP; according to T stage—1 T_0, 4 T_1, 1 T_2, 6 T_3 and 6 T_4; according to N stage—2 N_0, 10 N_2 and 6 N_3. All patients had received 2 or 3 cycles of PF induction chemotherapy (cisplatin of 100mg/m^2 at day 1 plus 5-Fluorouracil 1000mg/m^2 at day 1-4). Endogenic EPO was measured in blood serum by enzyme-labeled chemiluminescent immunometric assay, using analyzer Immulite 2000*XPi* and commercial kit reagent before the administration and at day 11±2 of each chemotherapy cycle. The reference range of EPO level of 4.3-29.0 mIU/ml was accepted.

Results: Induction, platinum-based chemotherapy (IPBChT) was realized in 3 or 2 cycles in 14 and 4 patients, respectively. In 10 patients, there was delay of 2nd or/and 3rd ChT cycle delivery (mean delay: 10 days) due to neutropenia. Initial (i.e. before ChT) EPO levels were in the lower half of or even below reference range (minimum 3.3 mIU/ml, maximum 12.3, mean: 7.2±4.1 SD). Then, over IPBChT, EPO levels fluctuated and were consequently elevated in all patients as expressed by means (P values are for each of the two chronological means): 12±4.5 at the middle of cycle 1 (P =.0008); 11.4±4.3 before the 2nd cycle (P =.25); 17±7.8 at the middle of cycle 2 (P =.007); 11.6±7.7 before the 3rd cycle (P =.046); and 31.7±27.4 at the middle of cycle 3 (P =.034). Over the same time, the HGB level generally lowered about 1 g/dl.

Conclusion: The behavior of endogenic EPO in HNC patients over neoadjuvant, platinum-based chemotherapy is changeable. Fluctuating but consequently elevated EPO levels are observed as the treatment progresses. This behavior is consistent despite being done on a small number of patients. Our clinically intriguing trial, especially in the aspect of possibility of tumor progression via endogenic EPO stimulation of its receptors in HNC cells, is ongoing.

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Reduced Uninsured Rates and Racial Disparities in Insurance Coverage for Head and Neck Cancer Patients After Medicaid Expansion

Y.M. Mowery, D.M. Brizel, J.P. Chino, and H. Moss; *Duke University Medical Center, Durham, NC*

Purpose/Objective(s): To evaluate the effect of Medicaid expansion on trends in insurance coverage for patients with head and neck cancer in the United States.

Materials/Methods: Patients aged 18 to 64 with head and neck cancer diagnosed between 2008 and 2014 were identified in the SEER database. Insurance status (insured, Medicaid, or uninsured) at diagnosis was determined. Insurance coverage was compared between states that adopted Medicaid expansion in 2014 ("expansion states") versus states without Medicaid expansion ("non-expansion states"). Categorical and continuous data were compared by chi-square test and Mann-Whitney U test, respectively.

Results: A total of 37,429 patients met inclusion criteria (72.9% in expansion states; 27.1% in non-expansion states). Between 2008 and 2014, 8% were uninsured. Non-expansion states had significantly higher uninsured rates than expansion states (12.9% vs 6.8%, P<.0001; OR 2.0, 95% CI 1.9-2.2). Racial and socioeconomic differences were notable, with non-expansion states having a higher percentage of black patients (21.8% vs 9% in expansion states, P<.00001) and subjects in these states living in regions with a higher percentage of poverty (17.3% vs 14.7% below poverty line, P<.00001). Uninsured rates were relatively stable between 2008 and 2013, followed by a 3% absolute reduction in 2014. A significant decrease in uninsured patients occurred in expansion states (7.2% in 2011-2013 vs. 2.5% in 2014, P<.0001), but not in non-expansion states (12.4% in 2011-2013 vs 12.3% in 2014, P=.99). Similarly, uninsured rates declined across all races and socioeconomic levels in expansion states, but no significant decrease occurred in non-expansion states. Prior to expansion (2011-2013), 7% of white patients, 10.6% of black patients, and 6.2% of other patients were uninsured in expansion states. Uninsured rates were more similar after Medicaid expansion: 2.3% of white patients, 2.2% of black patients, and 3.2% of other patients. Uninsured rates non-significantly rose among black patients living in non-expansion states (14.3% in 2011-2013 vs. 17% in 2014).

Conclusion: Medicaid expansion in 2014 was associated with a significant reduction in uninsured status for patients with head and neck cancer, with the benefit limited to expansion states. Racial disparities in insurance coverage also decreased after Medicaid expansion in expansion states, but not in non-expansion states. Longer follow-up is essential to determine whether increased insurance coverage will translate into improved outcomes for head and neck cancer patients.

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Comparative Analysis of New Staging Systems for HPV-associated Oropharyngeal Squamous Cell Carcinoma in a Population-Based Cohort

A.M. Tanner,[1] A. Mazul,[1] D. Farquhar,[1] J. Taylor,[2] P. Brennan,[3] D. Anantharaman,[4] B. Abedi-Ardekani,[3] N.N. Hayes,[5] M. Weissler,[6] S. Patel,[6] B.S. Chera,[7] A. Olshan,[1] and J.P. Zevallos[6]; *[1]University of North Carolina, Chapel Hill, NC, [2]Wake Forest University School of Medicine, Winston-Salem, NC, [3]International Agency for Research on Cancer, Lyon, France, [4]University of Chapel Hill, Lyon, France, [5]University of North Carolina School of Medicine, Chapel Hill, NC, [6]University of North Carolina Hospitals, Chapel Hill, NC, [7]Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC*

Purpose/Objective(s): The increase in human papillomavirus (HPV)–related oropharyngeal squamous cell carcinoma (OPSCC) has resulted in drastically improved oncologic outcomes. To better prognosticate this cancer, the 8th edition American Joint Committee on Cancer (AJCC) recently created a staging system specifically for HPV-related OPSCC. This system has not yet been validated in a population-based cohort. We sought to compare the prognostic ability of the new 8th edition AJCC staging system to the 7th edition system in a population-based cohort. Our hypothesis is that the 8thedition AJCC staging system will provide better prognostication of HPV-related OPSCC.

Materials/Methods: This retrospective cohort study used patients selected from the Carolina Head and Neck Cancer Study (CHANCE) database. The database contains head and neck cancer patients diagnosed between January 1, 2002 and February 28, 2006 who reside in a 46-county region in central North Carolina and were followed for over 5 years. Patients with OPSCC tumors positive for p16 expression by immunohistochemistry were selected for this study. One hundred and sixty-one HPV-associated OPSCC patients met inclusion criteria out of 1381 study patients. The outcome was 5-year overall survival.

Results: The HPV-related OPSCC cohort was predominantly male (81.9%), white (92.9%), and between 51-65 years of age at time of diagnosis (53.5%). Approximately one-third of cases reported no previous tobacco use. Nearly the entire study population underwent radiation, while 66% underwent chemotherapy and 56% underwent surgery. AJCC 7th edition stage I through stage IVA all had similar 5-year overall survival rates (85.71%-87.50%) and stage IVB had the worst survival (64.52%). AJCC 8th edition stage I (85.0%) patients had a favorable 5-year overall survival compared with stage II (69.2%) and stage III (54.3%), respectively. Hazard ratios were calculated accounting for age, sex, insurance status, tobacco use, and treatment type. (Table) Only the 8th edition stage III showed any statistical significance in risk stratification. Prognostic value was compared by C-index, which was 0.73 (95% CI: 0.63, 0.84) for the AJCC 7th edition and 0.76 (95% CI: 0.65, 0.87) for the AJCC 8th edition.

Conclusion: When compared to the AJCC 7th edition staging system, the 8th edition system improved tumor distribution and risk stratification but did not significantly improve prognostication. While the limitations of the 7th edition still exist, caution may be warranted as we transition to this new approach in staging.

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Abstract 176; Table Adjusted hazard ratios for AJCC 7th and 8th edition

7th Edition			8th Edition		
	HR* (95% CI)	p-value		HR* (95% CI)	p-value
I	1		I	1	
II	0.67 (0.06, 7.98)	0.750	II	1.41 (0.43, 4.68)	0.572
III	1.35 (0.15, 11.83)	0.787	III	3.49 (1.52, 8.00)	0.003
IVA	0.63 (0.07, 5.24)	0.665			
IVB	2.21 (0.27, 18.34)	0.461			

HR: Hazard Ratio; CI: Confidence Interval

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The Current Portfolio of Head and Neck Cancer Trials on ClinicalTrials.gov

N.J. Giacalone,[1,2] N. Milani,[2] B. Rawal,[3] J.D. Schoenfeld,[2] R.B. Tishler,[2] G. Rabinowits,[4] R.I. Haddad,[4] R. Uppaluri,[5] P.S. Catalano,[3] and D.N. Margalit[2]; *[1]Harvard Radiation Oncology Program, Boston, MA, [2]Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [3]Department of Biostatistics & Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [5]Department of Otolaryngology, Division of Head and Neck Surgery, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Purpose/Objective(s): To describe the current distribution of active head and neck cancer (HNC) clinical trials across the spectrum of definitive, recurrent and metastatic (R/M), and quality of life (QOL)/survivorship care, and to describe funding sources and principal-investigator (PI) leadership of HNC trials.

Materials/Methods: We identified all active, interventional HNC trials on ClinicalTrials.gov as of June 26, 2017, using the search terms "head and neck cancer" and all specific HNC subsites, excluding skin cancers. Logistic regression was used to identify associations between trial characteristics and funding type.

Results: We identified 841 active HNC trials on ClinicalTrials.gov, of which 48% are United States (US)-based, 43% international, and 8% both. Fifty percent of trials enrolled curative-intent patients, 44% enrolled R/M patients, and 6% enrolled both. Most trials (76%) included systemic therapy (ST) in the prescribed treatment, 41% included RT, and 12% included surgery; 9% evaluated a QOL/survivorship question. Among trials using ST, 51% were in R/M patients, 46% definitive, and 3% in either. In 2017, immune-oncology (IO) agents were used in 38% of trials including ST, equal in frequency to chemotherapy use, and far surpassing non-IO antibody-based ST (9% ST trials). Most trials enrolled multiple HNC subsites (47%), with specific subsite trials being less common (12% nasopharynx, 10% thyroid, 5% oropharynx, 3% oral cavity, 3% other, 2% larynx/hypopharynx; 18% open to HNC + non-HNC sites, eg esophageal, breast, etc.) Regarding PI leadership, medical oncologists led 34% of trials, radiation oncologists 23%, surgeons 16%, and other specialties 27%. Trials enrolling R/M patients were more likely to have industry funding (54%) relative to trials enrolling definitive patients (18%) (odds ratio [OR] = 5.43; $P < .001$). Trials that included ST (41%) were more likely to have industry funding compared to trials including RT (16%) (OR = 3.70; $P < .001$) or surgery (9%) (OR = 7.42; $P < .001$). Among US trials, a greater proportion of definitive trials are NIH-funded (39%) compared to R/M trials (28%) (OR = 1.41; $P = .13$). There was no association between RT, ST, or surgery use and NIH funding (ST vs. RT, OR = 0.83; $P = .37$; ST vs. surgery, OR 1.05; $P = .88$).

Conclusion: Although most patients with HNC have localized/non-metastatic disease, nearly half of HNC trials are focused on the R/M setting and there are few QOL/survivorship trials especially considering the growing population of HNC survivors. Definitive trials, particularly those not incorporating novel ST agents, are less likely to receive industry funding and are more dependent on NIH funding or other sources of funding. This may have implications for trials that involve de-intensification via minimizing use of ST.

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Relationships Between Serum IL-6, Tobacco Consumption, and the Occurrence of Second Primary Cancers in Head and Neck Cancer Patients

I. Bairati,[1,2] S. Carrondo Cottin,[1] D. Talbot,[1,2] P. Douville,[1,2] and F. Meyer[1,2]; *[1]Cancer Research Center, Laval University and CHU de Québec, Quebec City, QC, Canada, [2]Laval University, Quebec City, QC, Canada*

Purpose/Objective(s): In a previous work, we showed that IL-6 serum levels and tobacco consumption were two independent predictors of second primary cancers (SPC) in head and neck cancer (HNC) patients. The objectives of this study were to assess 1) whether tobacco exposure was a determinant of IL-6 serum levels, and 2) whether the effect of tobacco on the occurrence of SPC was partly mediated by IL-6.

Materials/Methods: This study was conducted as part of a multicenter, randomized, controlled trial evaluating the effect of antioxidants in the prevention of SPC in 540 HNC patients with stages I-II. IL-6 was measured in 527 pretreatment serum samples using chemiluminescent immunometric assays. Current and lifetime exposure to tobacco products were assessed using a structured questionnaire. Tobacco consumption during the year preceding the randomization was used for the main analyses. For objective 1, IL-6 was log-transformed and multivariate linear regressions were used. In addition, tests for linear trend were done to verify that IL-6 levels increased with cumulative past exposures of cigarette consumption. For objective 2, the excess relative risks (ERR= relative risk-1) were calculated using a particular case of the parametric g-formula for estimating the direct effect and the indirect effect via the IL-6 pathway of tobacco consumption on the 5-year risk of SPC.

Results: In the 527 HNC patients, the 5-year risk of SPC was 21.0% (95% CI=17.0%-24.8%). The median of IL-6 serum level was 3.1 ng/L (interquartile range: 2.2-4.4 ng/L) and 63.4% of the HNC patients consumed tobacco during the previous year. Compared to non-users, those who consumed tobacco during the previous year had a relative increase of 73% of their risk of SPC (95% CI: 15.1-172.5%). Tobacco users in the previous year had higher IL-6 serum levels than those who did not consumed tobacco (adjusted β (SE): 0.19 (0.06), *P*-value=.002). In addition, analyses conducted among cigarette smokers showed that IL-6 serum levels increased with longer durations of cigarette smoking (*P*-value for trend=.03) and with the number of pack-years consumed (*P*-value for trend=.04). ERRs associated with the direct and indirect effects of tobacco use on SPC were respectively 59.8% (95% CI: 6.8%; 151.9%) and 13.1% (95%CI: 3.8%, 31.5%). The indirect effect of tobacco consumption via the IL-6 pathway contributed to 18% of the total effect of tobacco on the occurrence of SPC.

Conclusion: Tobacco is a determinant of serum IL-6 levels, a strong predictor of SPC in HNC patients. Although modest, a statistically significant part of the effect of tobacco on the occurrence of SPC appears to be mediated by IL-6. This suggests that the effect of tobacco on the occurrence of SPC is also mediated by an inflammatory process.

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Comparison of the 7th and 8th Editions of the AJCC/UICC Staging for Human Papillomavirus–Related Oropharynx Carcinoma

K. Casper,[1] P.G. Hawkins,[2] M. Mierzwa,[2] E. Bellile,[3] K. Malloy,[3] S.B. Chinn,[4] M.E. Spector,[1] A. Shuman,[1] C.L. Stucken,[4] S. Mclean,[4] F. Worden,[5] P.L. Swiecicki,[5] J. Taylor,[6] C.R. Bradford,[3] M.E. Prince,[4] G.T. Wolf,[4] and A. Eisbruch[2]; *[1]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [2]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [3]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [4]University of Michigan, Ann Arbor, MI, [5]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [6]university of Michigan, Ann Arbor, MI*

Purpose/Objective(s): The current 7th edition AJCC/UICC staging system for oropharyngeal cancer fails to adequately reflect outcomes for human papillomavirus–associated oropharynx cancer given the more favorable prognosis compared to non-HPV–related oropharynx cancer. The upcoming 8th edition AJCC/UICC staging system incorporated concepts developed from the ICON-S classification system for HPV-related oropharynx cancer. The purpose of this study is to compare the validity between the 7th edition and upcoming 8th edition clinical staging systems in a large prospectively collected single-institution cohort.

Materials/Methods: Data from 486 patients treated for HPV-related oropharyngeal cancer with definitive intent at a single academic cancer center were analyzed. Disease, demographic, smoking, and treatment data were collected prospectively. Patients were initially classified according to AJCC 7th edition and retrospectively restaged according the upcoming 8th edition clinical staging systems. Kaplan-Meier was used to compare rates of overall survival. Multivariate Cox regression was used to correlate stage, age, and smoking status with overall survival.

Results: Utilizing the 7th edition staging system, 422/486 (87%) patients were classified as stage IV; 47/486 (9.6%) were stage III; 12/486 (2.5%) were stage II; 5/486 (1%) were stage I. Utilizing the 8th edition clinical staging system, 137/486 (28.2%) were stage III; 98/486 (20%) were stage II; 250 (51.4%) were stage I. Fifty percent (211/422) of the 7th edition stage IV patients were reclassified as a stage I in the 8th edition; 17% (73/422) were reclassified as a stage II; and 33% (138/422) were reclassified as a stage III in the 8th edition system. There was no significant difference in the survival curves of stage III and stage IV in the 7th edition, and there were too few of stage I/II to analyze in the 7th edition. The 8th edition clinical staging demonstrated statistically significant differences in survival curves across each stage ($P<.0001$). The 2-year and 5-year overall survival was 95%/90% for stage I; 93%/79% for stage II; and 86%/61% for stage III. In multivariable analysis, controlling for age and 8th edition staging, smoking was significantly associated with OS ($P=.03$). Conclusion: This analysis is the largest series to date to validate the findings of the ICON-S staging system and apply the 8th edition AJCC/IUCC clinical staging system in a large single-institution cohort. Clinical restaging of the cohort from the 7th edition to the 8th edition provides an improved balance between stages and provides prognostic information that is missing from the 7th edition system.

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Changing Demographics of HPV-Associated Oropharyngeal Squamous Cell Carcinoma

J.D. Thompson,[1] A. Wieland,[2] T. Glazer,[3] T.M. McCulloch,[4] P.M. Harari,[5] M.E. Witek,[5] R.J. Kimple,[5] J.Y. Bruce,[6] R. Hu,[7] and G.K. Hartig[1]; *[1]University of Wisconsin, Madison, WI, [2]Department of Surgery, Division of Otolaryngology and Head and Neck Surgery,*

University of Wisconsin, Madison, WI, [3]University of Wisconsin, Madison, WI, [4]Department of Surgery, University of Wisconsin, Madison, WI, [5]Department of Human Oncology, University of Wisconsin, Madison, WI, [6]University of Wisconsin - Madison, Section of Hematology/Oncology, Madison, WI, [7]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI

Purpose/Objective(s): To evaluate demographic changes over the past 15 years for patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: Using p16-positive immunohistochemistry as a surrogate for HPV-associated OPSCC, we conducted a retrospective chart review of patients identified with p16-positive OPSCC at our institution over the past 15 years. Patients were grouped by year of diagnosis 2002-2010 versus 2011-2016, and both mean age and proportion of patients over 65 were statistically evaluated and compared. A two-sample F-test confirmed equal variance between groups, mean age was compared with a two-sample T-test assuming equal variances, and proportion of patients over 65 was compared with a two-sample Z-test for proportions.

Results: From 2002-2010, 100 patients were identified with p16-positive OPSCC, mean age at diagnosis was 55.17 ± 8.28, and the proportion of patients over 65 was 10.0%. From 2011-2016, 188 patients were identified with p16-positive OPSCC, mean age was 58.54 ± 8.59, and the proportion of patients over 65 was 19.6%. Both the mean age difference and the difference in proportion of patients over 65 were statistically significant ($P = .001$ and $P = .034$, respectively). This trend of increasing age was also observed when patients were further divided into 3 groups as demonstrated in the table below.

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Year of diagnosis	Number of Patients	Mean age at time of diagnosis	Percent of patients > 65 yo
Pre-2009	64	54.98	9.4%
2009-2012	99	56.47	16.2%
2013-2016	125	59.30	20.0%

Conclusion: It appears that mean age at diagnosis and proportion of patients over 65 have increased over the past 15 years at our institution. This initial data suggests a shift in the age demographic of HPV-associated OPSCC, although confirmation of this trend with larger patient numbers on a national level will be important. This study highlights the importance of maintaining a high clinical concern for HPV status for patients regardless of age.

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Second Primary Malignancies in Head and Neck Cancer Patients Treated With Definitive Radiation Therapy

S.P. Ng,[1] M. Kamal,[1] C. Pollard, III,[1] J. Berends,[2] Z. Ayoub,[1] A.S.R. Mohamed,[1] G.B. Gunn,[1] S.J. Frank,[1] H.D. Skinner,[1] J. Phan,[1] W.H. Morrison,[1] A.S. Garden,[1] J.M. Johnson,[1] R. Ferrarotto,[1] S. Lai,[1] E.M. Sturgis,[1] C.D. Fuller,[1] and D.I. Rosenthal[1]; [1]*The University of Texas MD Anderson Cancer Center, Houston, TX,* [2]*The University of Texas Health Science Center San Antonio, San Antonio, TX*

Purpose/Objective(s): Second primary malignancy (SPM) may occur after initial primary head and neck cancer treatment. The risk of SPM in head and neck cancer patients treated with definitive radiation therapy has not been well documented. This study evaluated the prevalence and outcome of SPM in patients with head and neck cancer treated with definitive radiation therapy.

Materials/Methods: Eligible patients include those with histologically confirmed mucosal head and neck cancer treated with definitive radiation therapy between 2000 and 2010, with at least 6 months of follow-up. Age, tobacco smoking status (dichotomized by < or ≥10−pack-year cigarettes), primary site, and mode of detection of SPM were recorded. p16 data was not routinely collected until after 2010. SPM was defined as an invasive solid cancer at a non-contiguous site diagnosed at least 6 months after completion of radiation therapy. Clinical data was collected and the Kaplan-Meier method was used to estimate overall survival.

Results: This study included 1583 patients. Median age was 55 years. The median overall survival was 98 (range: 6-199) months. The majority of patients had primary oropharyngeal cancer (82.1%), followed by nasopharyngeal cancer (5.5%). A total of 133 (8.4%) patients developed an SPM, with 116 patients diagnosed with SPM at least 2 years posttreatment. The median time to develop an SPM was 72 months. 49.6% of SPMs were within the head and neck or thoracic region − 37 mucosal head and neck carcinomas, 2 head and neck sarcomas and 27 esophageal/ lung carcinomas. Patients with SPM were dichotomized into 2 groups: <10-pack-year smoking (23 non- and 17 former smokers) and ≥10-pack-year smoking (44 current and 49 former smokers). In those with SPM, 70% of patients had ≥10-pack-year smoking comprising 93% of thoracic and 64% of head and neck SPMs. The risk of SPM increased exponentially with time with overall rates at 2, 5, 10, and 15 years were 0.2%, 1.2%, 8.5% and 35.1%. SPM rates were higher in patients with ≥10-pack-year smoking than those with <10-pack-year: 2 years (0.4% vs 0%), 5 years (1.5% vs 0.9%), and 10 years (12.4% vs 4.8%). A total of 105 patients (79%) had subsequent curative intent therapy. Five-year overall survival from diagnosis of SPM was 46%.

Conclusion: The majority of SPMs in head and neck cancer patients treated with radiation therapy were in those with a smoking history of ≥10-pack-years, reflecting the same risk factors for mucosal head and neck cancer. Nearly 1 in 2 patients with SPMs were salvaged successfully underscoring the importance of regular clinical surveillance for SPMs, especially of head and neck and thoracic regions.

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The Role of Human Papillomavirus and Epstein-Barr Virus Co-infection in Oropharyngeal Squamous Cell Tumor Differentiation

T. Moore-Medlin,[1] A. Asarkar,[1] X. Ma,[1] J. Flores,[2] X. Gu,[1] and C.A.O. Nathan[1]; [1]*Louisiana State University Health, Shreveport, LA,* [2]*Yale University School of Medicine, New Haven, CT*

Purpose/Objective(s): The recent epidemic of human papillomavirus (HPV)−related oropharyngeal squamous cell carcinoma (OPSCC) has resulted in the identification of a patient subpopulation with distinct

clinical features and outcomes. Viral-related cancers of the head and neck typically have a better prognosis and response to current standard treatment. As both Epstein-Barr virus (EBV) and HPV are most associated with the lymphoid-rich sites of the head and neck, albeit different sites, we aimed to determine if co-infection of these two viruses plays a role in OPSCC. Histologically, HPV-associated tumors are consistently poorly differentiated. We have previously shown that HPV/EBV co-infection contributes to tumorigenicity by increasing cell invasiveness in vitro. Here, we further investigate this finding by analyzing co-infection status and the pathological characteristics of tumors from OPSCC patients.

Materials/Methods: An IRB-approved retrospective chart and specimen analysis of 134 patients diagnosed with OPSCC at our institution was performed. Pathology reports were reviewed to obtain tumor grade and cell differentiation status at the time of diagnosis. The corresponding FFPE specimens were tested for the presence of HPV and EBV using immunohistochemistry and in-situ hybridization. Other clinical data collected included age, gender, race, primary site, smoking pack-years, staging, recurrence, disease-free interval and disease-free survival.

Results: Of 134 patients, 18 were HPV+/EBV+ (13%), 34 were HPV-/EBV- (25%), 76 were HPV+/EBV- (57%), and 6 were HPV-/EBV+ (5%). In HPV+ specimens, the presence of EBV was significantly associated with poor tumor differentiation ($P = .04$). No significant histological difference was seen for any other combination of the two viruses.

Conclusion: Co-infection with EBV and HPV appears to contribute to OPSCC tumorigenicity, as seen in our previous in vitro work and now in clinical specimens. The presence of both viruses seems to be a factor in differentiation, hence corresponding to the level of tumor invasiveness and aggression. Although HPV+ OPSCC patients have a more favorable outcome than HPV-, the oncogenic potential as well as aggressiveness in the presence of both EBV and HPV warrants further exploration, as appropriate classifications may be important in the clinical management of co-infected patients.

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Pediatric Head and Neck Squamous Cell Carcinoma: Patient Demographics, Treatment Trends, and Outcomes

A. Modh,[1] O.H. Gayar, Jr,[1] M.A. Elshaikh,[1] A.C. Paulino,[2] and F. Siddiqui[1]; [1]*Henry Ford Health System, Detroit, MI,* [2]*Texas Children's Hospital, Houston, TX*

Purpose/Objective(s): Head and neck squamous cell carcinomas (HNSCC) are common in adults but considered rare in the pediatric population. However, there is evidence of a rising incidence of pediatric head and neck cancer, which is of concern considering little is known about pediatric HNSCC. There are few standards regarding appropriate management and care of these patients, and most approaches have been extrapolated from adult HNSCC management. The purpose of this study was to examine patient demographics, temporal and treatment trends, and survival outcomes of pediatric non-nasopharyngeal HNSCC using the National Cancer Database

Materials/Methods: The NCDB was queried for pediatric patients (age 0-19 years) diagnosed with non-nasopharyngeal HNSCC (including oral cavity, oropharynx, nasal cavity, larynx, hypopharynx, and salivary glands) from 2004 to 2013. Patients with incomplete or missing follow-up were excluded. Patient demographics and treatment characteristics were evaluated. Linear regression was used to evaluate the trends in the number of cases by year of diagnosis. Kaplan-Meier plots for overall survival (OS) were generated and log-rank tests were used to evaluate outcomes across the cohort and stratified by subsite.

Results: Of 159 patients identified, there was a male predominance (61%) with a median age of 17 years. The majority of patients had disease in the oral cavity (55%). Stage IV was the most common (33%). There was no discernable change in incidence trends over the study period with the number of cases per year ranging from 10-20 ($R^2 = 0.174$). The 5-year OS for the entire cohort was 74% and by subsite: oral cavity (66%), oropharynx (68%), nasal cavity (75%), and larynx/hypopharnx (95%). Laryngeal/hyphopharyngeal disease had statistically significant longer survival when compared to the oral cavity ($p = 0.031$) or oropharynx ($p = 0.029$). The predominant treatment regimen for the oral cavity and nasal cavity was trimodality (surgery, radiation, and chemotherapy) treatment (33% and 29%, respectively), chemotherapy and radiation for the oropharynx (40%), surgery alone for salivary gland (47%) and larynx/ hypopharynx (22%).

Conclusion: We present one of the largest series of pediatric non-nasopharyngeal HNSCC. The number of cases remained steady over the 10-year study period. While treatment patterns were comparable to those of their adult counterparts, survival outcomes were better in the pediatric population when considering historical controls.

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Survival in Asian-Americans With Nasopharyngeal Cancer Undergoing Definitive Radiation Therapy

E. Anderson, E.J. Yoshida, A. Mita, K. Scher, S.L. Shiao, J. Mallen-St.Clair, A.S. Ho, and Z.S. Zumsteg; *Cedars-Sinai Medical Center, Los Angeles, CA*

Purpose/Objective(s): Biologic and clinical differences have been observed in nasopharyngeal carcinomas (NPC) arising in Asian and North American populations. However, it is unclear if these differences are also present within Asian and non-Asian NPC patients living in the United States.

Materials/Methods: Patients with locally advanced NPC undergoing definitive radiation in the National Cancer Database (NCDB) were identified. Overall survival (OS) was estimated using the Kaplan-Meier method and compared with the log-rank test with and without propensity score matching. Univariate and multivariable survival analyses were performed using Cox regression. To compare the effect of race in NPC to its effect in other head and neck cancers, similar analyses were performed in patients with locally advanced oropharyngeal, laryngeal, or hypopharyngeal squamous cell carcinoma (SCC) undergoing definitive radiation. High volume facilities were defined as the top 5% of centers.

Results: Median follow-up was 59.4 months. Of 3941 patients with NPC, 718 were Asian and 3228 were other races. Analysis of baseline characteristics in this cohort revealed Asian race was associated with higher nodal stage, younger age, lower comorbidity scores, higher rates of private medical insurance, higher income, residence in an urban area, and treatment at higher volume facilities (all P-values$<.001$). Asian race was associated with marginally increased frequency of receiving concomitant chemotherapy ($P = .016$). In propensity score-matched cohorts, Asian Americans with NPC undergoing definitive radiation therapy had significantly longer OS than white patients (74.2% vs. 66.0%, log-rank $P < .001$). Similarly, in multivariable analysis adjusting for clinical-, demographic-, facility-, and treatment-related factors, NPC patients of Asian race had improved OS in comparison to white patients (HR 0.66, 95% CI 0.55-0.78, P-value $< .001$). No difference in survival was observed when comparing white patients to other races. In contrast to what was observed for NPC, a multivariable analysis of 46,567 patients with locally advanced SCC of the oropharynx, hypopharynx, and larynx undergoing definitive radiation therapy showed no impact of Asian race on survival (HR 0.93, 95% CI 0.80-1.07, P-value $= .30$) after adjusting for other covariates.

Conclusion: Asian-American patients with NPC undergoing curative radiation in the United States have significantly better OS in comparison to non-Asian patients, even after adjusting for differences in the baseline characteristics of these populations. This effect was not observed in patients with cancers of other head and neck subsites undergoing radiation therapy. The racial differences observed in NPC may be mediated, in part, by a higher incidence of EBV-driven malignancies in Asian Americans.

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Geographic Distance from Patient to Biopsy Site Associated With Advanced Stage at Presentation in Head and Neck Squamous Cell Carcinoma

D. Farquhar,[1] M. Masood,[2] N. Lenze,[2] P. McDaniel,[3] S. Sheth,[4] A. Mazul,[3] and J.P. Zevallos[5]; *[1]University of North Carolina Hospitals, Chapel Hill, NC, [2]University of North Carolina School of Medicine, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill, NC, [4]University of North Carolina Hospitals, Chapel Hill, NC, [5]Washington University School of Medicine, St. Louis, MO*

Purpose/Objective(s): Advanced stage at presentation is associated with poor outcomes in head and neck squamous cell carcinoma (HNSCC). While associations with socioeconomic status have been examined previously, the effect of access to care, including geographic factors, on stage at presentation has not been examined in HNSCC. We sought to determine whether linear distance or travel time to diagnosing provider is associated with HNSCC stage at presentation, using data from a large population-based patient cohort. We hypothesize that increased distance and travel time are associated with increased stage at presentation.

Materials/Methods: Data for analysis was obtained from the Carolina Head and Neck Cancer Epidemiology Study (CHANCE), a population-based case-control study in 46 counties in North Carolina (NC). Cases were identified through rapid case ascertainment with the North Carolina Central Cancer Registry. An in-person interview obtained a complete residence history and other factors, and medical records were used to ascertain stage at diagnosis. Addresses for biopsy sites were obtained from the diagnostic pathology reports. Case residence at the time of diagnosis and biopsy address were geocoded. Linear (Euclidean) distances and driving times (network travel times) were calculated with ArcMap 10.5 (ESRI, 2017). Cases were divided into quartiles based on the distance and the driving time between the case's home address and the biopsy site. Addresses greater than two hours away from the biopsy site were excluded. Outcomes were early (T1-T2) and late (T3-T4) T stage, and the presence or absence of nodal metastasis, at presentation. Logistic regression was used to estimate odds ratios and 95% confidence intervals after adjustment for multiple factors including age, sex, race, income, insurance status, alcohol, and tobacco use.

Results: A total of 1052 HNSCC cases were included in this study. Median distances by quartile were 2.5, 6.8, 16.0, and 30.1 mi. Median driving times were 7.17, 16.3, 31.9, and 61.5 min respectively. Increased distance from case to diagnosing provider was associated with advanced T-stage at presentation (adjusted OR = 2.23, 95% CI 1.50 - 3.23, quartile 4 vs quartile 1). A similar association was noted for driving time (OR = 2.30; 95% CI 1.52 − 3.46). There was no association between distance and the presence of nodal metastasis at presentation (OR = 1.03; 95% CI 0.70 - 1.51).

Conclusion: We identified distance and travel time to diagnosing provider as significant contributors to advanced stage at presentation in HNSCC. Our findings suggest that distance to healthcare provider is a major barrier to early diagnosis of HNSCC with substantial impact on oncologic outcomes.

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Prognostic Value of Hematologic Markers in Head and Neck Squamous Cell Carcinoma

T.C.D. Padua,[1,2] H. Tadokoro,[1] and O.C.C.G. Baiocchi[1]; *[1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]Hospital Paulistano, Sao Paulo, Brazil*

Purpose/Objective(s): The purpose of our study was to investigate the potential prognostic role of pretreatment hematologic markers, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), in patients with head and neck squamous cell carcinoma (HNSCC) treated with chemoradiation therapy in our institution.

Materials/Methods: We retrospectively analyzed medical records of 52 patients diagnosed with HNSCC and treated with definitive chemoradiation therapy between 2010 and 2015 at our institution. Demographic data, clinical stage, tumor characteristics and location, date of diagnosis, date of death, and baseline complete count blood were all collected. Pretreatment NLR and PLR were retrospectively calculated and investigated for correlation with overall survival (OS) using the Kaplan-Meier method. Univariate analysis for categorical and descriptive variables was also performed.

Results: A total of 52 patients with oral cavity (n=3, 5.8%), oropharyngeal (n=25, 48.1%), laryngeal (n=23, 44.2%), and hypopharingeal (n=1, 1.9%) cancer were included in this study. The mean age was 61.5 ± 9.1 years and the population was predominately male (82.7%). In the overall population, median OS (mOS) were 28 months. In univariate analysis, tumor stage (T2 vs T4a- T4b), nodal stage (N0 vs N2 or N3) and PLR were associated with improved OS (HR 1.003; 95% CI 1.001-1.005; $P=.009$). The median value of NLR was 3.239 (0.92-23.51) and PLR was 129.56 (51.42-817.93). Using median value as cutoff, NLR and PLR were significantly associated with OS. Patient with NLR > 3.239 had an mOS of 16 months, whereas the mOS for NLR ≤ 3.239 was 84 months (Log-rank $P=.050$). Patient with PLR > 129.56 had an mOS of 13 months, whereas the mOS for PLR ≤ 129.56 was 84 months (Log-rank $P=.050$). Using ROC curves, NLR and PLR were also associated with OS. PLR had the greatest area under the curve (AUC) of 0.739 (0.595-0.883; $P=.004$), and NLR had the AUC of 0.672 (0.506-0.838; $P=.039$).

Conclusion: Our results indicate that pretreatment hematologic markers (NLR and PLR) are associated with prognosis in HNSCC patients treated with chemoradiation therapy, and represent a cost effective and easily measured marker for patient stratification. Further validation in prospective studies is needed, especially in context of immunotherapy.

Author Disclosure: **T.C. Padua**: None. **H. Tadokoro**: None. **O.C. Baiocchi**: None.

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Defining the Young Oral Cavity Cancer Patient

E.J. Marchiano,[1] A.C. Birkeland,[1] K.J. Kovatch,[1] M.E. Prince,[1] C.R. Bradford,[2] J.C. Brenner,[1] D.B. Chepeha,[3] M.E. Spector,[4] and S.B. Chinn[1]; *[1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [3]University of Toronto, Toronto, ON, Canada, [4]Department of Otolaryngology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Emerging data have suggested an increased incidence of oral cavity squamous cell (OCSCC) in young patients without traditional risk factors. However, the cause remains unclear. Here we seek to further characterize the young OCSCC patient population and better define the transition from young to traditional oral cancer patients.

Materials/Methods: The Surveillance, Epidemiology, and End Results (SEER) database (2004-2011) and the University of Michigan Head and

Neck Cancer Epidemiology Database (UMHNC) (1998-2016) were queried for cases of OCSCC (excluding stage IVb and Lip) resulting in 9,766 and 232 patients respectively. Additional clinical and histopathologic variables were collected. Data were extracted from the electronic medical record and research databases, with institutional IRB approval. Descriptive statistics and Kaplan-Meier survival analyses were performed using SPSS Statistics Version 24 (IBM Corp, NY).

Results: Using the SEER database, we identified two significant demographic shifts in OCSCC that described 40 years of age as a transition point defining the young cohort. There is a transition in the male to female ratio from near equivalence (1.2:1) in young patients to a greater male predominance (1.6:1) in patients over 40 ($P = .002$). The second shift is seen in anatomic subsite, where the vast majority of tumors arise in the oral tongue among young patients compared to a more even distribution of subsites in traditional patients (90.3% vs 58.5% oral tongue primary; $P < .001$). These demographic trends were validated in the UMHNC cohort, where patients in the young (<40) group showed a male: female ratio of 0.8:1.0 (compared to 1.3:1.0) and 84.1% (compared to 35.6%) of tumors arising from the oral tongue ($P = .183$ and $<.001$, respectively). Traditional patients were significantly more likely to have exposure to known risk factors for OCSCC (tobacco use 81.0% vs 43.2%, $P<.001$; alcohol use 52.1% vs 9/1%, $P<.001$). In the SEER cohort, the 5-year disease-specific (DSS) of young and traditional patients did not differ significantly among stage III and IV patients, although both remained poor for stage IV disease at 49% and 37%, respectively.

Conclusion: We have objectively identified 40 years of age as a transition point for two distinct features for young, low-risk OCSCC patients, including a higher proportion of female patients and tumors airing from the oral tongue, using national cohort data validated with our institutional data. DSS does not differ between young and traditional patients for advanced disease and remains very poor. These patients comprise an interesting and important cohort given their lack of traditional risk factors yet similarly poor outcomes. By defining an objective measure of age, further investigation into the biologic mechanisms for tumorigenesis in this group is essential for characterizing disease in these patients.

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Trends and Patterns of Proton Therapy Utilization Among Patients With Head and Neck Cancer: Analysis from the National Cancer Database (2005-2014)

A. Lee,[1,2] S. McBride,[1] D. Schreiber,[2,3] N. Riaz,[1] J.E. Leeman,[1] P. Xie,[1] X. Li,[1] V.W. Osborn,[1,2] T. Waldenberg,[1] C. Sabol,[1] D. Spielsinger,[1] T. Brinkman,[1] J.K. Kim,[1,2] N. Lee,[1] and C.J. Tsai[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Radiation Oncology, SUNY Downstate Medical Center, Brooklyn, NY, [3]Summit Medical Group MD Anderson Cancer Center, Berkeley Heights, NJ*

Purpose/Objective(s): To analyze national trends and patterns of proton therapy use among patients with head and neck cancer.

Materials/Methods: Using the National Cancer Database, we identified patients diagnosed with any head and neck primary malignancy of all stages between 2005 and 2014. Patients treated with radiation therapy and proton therapy directed specifically to the primary site were selected. Distribution of patient/clinical factors, socioeconomic status, demographic factors, and treatment facility type were evaluated. Univariable and multivariable logistic regression was used to correlate factors associated with proton therapy use compared to other modalities of radiation therapy.

Results: There were 245,859 who received any radiation therapy as part of their initial treatment course and 468 (0.2%) who received proton therapy. The use of protons underwent a small increase in utilization from 0.1% in 2005 to 0.4% by 2014 (OR 3.041, $P<.001$). The most common primary sites treated with proton therapy were the nasal cavity/nasopharynx (n=174, 37.2%) and the oral cavity (n=107, 22.9%). On multivariate logistic regression, treatment at an academic facility (OR 2.345, $P<.001$), income >$63,000 (OR 1.606, $P<.001$) and most recent years of diagnosis (2013-2014, OR 3.050, $P<.001$) were associated with increased likelihood of receiving proton therapy. In addition, patients who received proton therapy were more likely to travel a longer distance for treatment (OR 1.918, $P<.001$) compared to those receiving other modalities of radiation. Higher Charlson/Deyo comorbidity score (OR 0.729, $P=.033$), non-white race (OR 0.605, $P=.004$), geographic regions in the south (OR 0.320, $P<.001$) or mid-west (OR 0.488, $P<.001$), and urban locations (OR 0.447, $P=.001$) compared to metropolitan areas were associated with decreased likelihood of receiving proton therapy. There were no differences in utilization with age or with history of second primary cancers.

Conclusion: Protons have undergone an incremental increase in utilization in the United States, but remains an uncommon modality for treatment of head and neck cancer. As the indications and benefits of proton therapy in head and neck cancer continue to emerge, decreasing the cost of its use and increasing its availability is necessary to reduce disparities in the provision of proton therapy.

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Conducting a Free Head and Neck Cancer Screening Clinic at a Major Academic Center

S.A. Rosenberg,[1] G.C. Blitzer,[1] H.C. Ko,[1] B.M. Anderson,[1] H.M. Geye,[1] J. Kiltz,[1] A. Neumann,[2] S.H. Dailey,[2] T.M. McCulloch,[2] A. Wieland,[2] G.K. Hartig,[2] J.Y. Bruce,[3] M.E. Witek,[1] R.J. Kimple,[1] and P.M. Harari[1]; *[1]Department of Human Oncology, University of Wisconsin, Madison, WI, [2]Department of Surgery, Division of Otolaryngology and Head and Neck Surgery, University of Wisconsin, Madison, WI, [3]Section of Hematology Oncology, Department of Medicine, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Our institution conducts a free head and neck cancer screening clinic annually. The goal of this report is to analyze clinical outcomes related to our cancer screening program.

Materials/Methods: Each spring, our institution conducts a three-hour free head and neck cancer screening clinic during head and neck cancer awareness week. The goals of the program are to raise awareness of head and neck cancer, caution about the hazards of tobacco use, and identify abnormalities in the oral cavity and oropharynx. The program is advertised in the hospital and the community on television, flyers, online, and through social media. During a screening visit, each person completes a short questionnaire regarding risk factors and symptoms related to the head and neck. They then undergo a brief examination by an experienced head and neck practitioner (otolaryngologist, radiation oncologist, physician assistant) without the use of special equipment or laryngoscopy. We analyzed the number of patients screened each year, population demographics, tobacco and alcohol use history, cancers detected, and counseling provided to patients from 2009 to 2017.

Results: An average of 144 people (range 77-183) underwent free head and neck cancer screening each year of the program. The majority of those screened were women (61%) and were approximately 54 years old (mean age range 44-58). Although only 14% (range 8%-19%) of those screened indicated active tobacco use, almost half of the population (48%) noted some prior tobacco use. The mean number of pack-years was 17.6 (range 15-21). Tobacco cessation counseling was given to 5% (average range 2%-10%) of those screened each year. Abnormal findings were identified on screening examinations in 11% of participants each year of the program (range 3%-16%). In total 7 malignancies were found within the population: 1 oral cavity, 1 salivary gland, 1 larynx, 2 skin, and 2 thyroid malignancies.

These were subsequently treated with surgery, radiation, or chemoradiation, as appropriate.

Conclusion: This free cancer screening program raises awareness of important issues surrounding the risk of head and neck cancer in the community. On average, we identify approximately 1 new malignancy each year and reinforce the value of tobacco cessation. We will work to increase the rate of tobacco cessation counseling provided given the rate of tobacco use in our community. This type of screening program can raise cancer awareness and favorably engage the community with local health care providers.

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Head and Neck Cancers Associated With Exposure to the September 11, 2001, World Trade Center Terrorist Attacks

J.E. Leeman,[1] S. McBride,[2] D. Spielsinger,[1] E. Sherman,[3] R.J. Wong,[4] N. Riaz,[1] N. Lee,[1] and C.J. Tsai[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [4]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Following the World Trade Center (WTC) terrorist attacks on September 11, 2001, over 100,000 people were exposed to respirable toxins, resulting in numerous adverse health consequences. The dust cloud that formed following the building collapse contained many known carcinogens and exposure at the collapse site has been linked to an increase in overall cancer risk. Herein, we describe the oncologic characteristics and disease outcomes of WTC-exposed patients with HNC who have presented to our institution.

Materials/Methods: We queried the medical records of our institutional tumor registry for all patients diagnosed with HNC from January 1, 2002, to March 1, 2017 (excluding melanoma, lymphoma, and thyroid cancers), who reported exposure at the WTC site on or after September 11, 2001, or involvement in the rescue/cleanup effort. Outcomes for patients with human papillomavirus (HPV) positive oropharyngeal carcinoma and WTC exposure were compared to cohorts of HPV+ and HPV- OPC without WTC exposure who were treated at our institution with definitive chemoradiation from 2002-2013. The Kaplan-Meier method, log-rank testing, and Cox regression analysis were utilized for statistical analyses.

Results: A total of 87 patients were identified with HNC diagnosed from 2002-2017 who reported WTC exposure. The annual number and proportion of WTC-exposed HNC patients has been steadily increasing since 2002 (2002-2004: 3 patients, 2008-2010: 17 patients, 2014-2016: 29 patients). The median time from September 11, 2001, to HNC diagnosis was 10.5 years. WTC-exposed patients with HPV+ OPC experienced significantly inferior locoregional control (LRC) and disease-free survival (DFS) compared to non-WTC exposed patients with HPV+ OPC (WTC Exposed: 48-month LRC 80.3%, DFS 65.6%; non-WTC exposed: LRC 94.0%, DFS 80.1%, $P=.03$ and $P=.04$. Multivariate analysis accounting for age, T-stage and N-stage revealed hazard ratios of 2.63 (95%CI 1.00-6.91, $P=.05$) and 1.9 (95%CI 1.02-3.70, $P=.04$) associated with WTC exposure for the endpoints of LRC and DFS, respectively.

Conclusion: The number of patients presenting to our institution with HNC following exposure at the WTC site has been steadily increasing, with most cancers developing >10 years following the event. This single-institution study cannot establish evidence of exposure-mediated causation but higher recurrence rates in the WTC-exposed HPV+ OPC population suggest a treatment refractory tumor biology and possible exposure synergism with HPV-mediated oncogenesis. Genomic studies as well as updated epidemiological studies with follow-up extending beyond 10 years are needed to better characterize this unique and growing population.

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Impact of HPV-Status on Prognostic Potential of the AJCC Staging System for Larynx Cancer

S.M. Davidson,[1] H.C. Ko,[2] P.M. Harari,[2] A. Wieland,[3] S. Chen,[4] A.M. Baschnagel,[2] R.J. Kimple,[2] and M.E. Witek[2]; *[1]Department of Oncology, Division of Radiation Oncology, Western University, London, ON, Canada, [2]Department of Human Oncology, University of Wisconsin, Madison, WI, [3]Department of Surgery, Division of Otolaryngology and Head and Neck Surgery, University of Wisconsin, Madison, WI, [4]Department of Statistics, University of Wisconsin School of Medicine and Public Health, Madison, WI*

Purpose/Objective(s): We evaluated the ability of the American Joint Committee on Cancer 7th edition (AJCC) staging system to prognosticate the overall survival of patients with human papillomavirus (HPV)−positive laryngeal squamous cell carcinoma.

Materials/Methods: Patients diagnosed with laryngeal squamous cell carcinoma treated with curative intent were identified in the National Cancer Database (NCDB) for this retrospective analysis. Multivariate analysis was utilized to determine factors correlated with overall survival in the HPV-negative and HPV-positive cohorts. Unadjusted and propensity-score weighted Kaplan-Meier estimation was used to determine overall survival of HPV-negative and HPV-positive patients across AJCC stage groupings.

Results: We identified 3,238 patients with laryngeal squamous cell carcinoma of which 2,812 were HPV-negative and 426 were HPV-positive. Overall survival adjusted for age, sex, and co-morbidity status confirmed significant differences between all consecutive stage groupings in the HPV-negative cohort (I vs. II, $P<.001$; II vs. III, $P<.05$; III vs. IVA, $P<.001$; IVA vs. IVB, $P<.05$) whereas only stage IVA and IVB ($P<.01$) exhibited a significant difference in overall survival for HPV-positive patients.

Conclusion: The current AJCC staging system does not accurately distinguish risk of mortality for patients with HPV-positive disease. These data support the consideration of HPV status in estimating prognosis as well as clinical trial design and clinical decision making for patients with laryngeal squamous cell carcinoma.

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Oral Squamous Cell Carcinoma in Young Patients—A Case-Control Analysis

M. Stewart,[1] M.C. Topf,[1] J.M. Curry,[2] D. Cognetti,[3] and A. Luginbuhl[1]; *[1]Thomas Jefferson University Hospital, Philadelphia, PA, [2]Sidney Kimmel Cancer Center at Thomas Jefferson University Hospital, Philadelphia, PA, [3]Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Purpose/Objective(s): A subgroup of younger patients develop squamous cell carcinoma (SCC) of the oral cavity without identifiable risk factors. Controversy exists in the literature regarding the tumor biology and pathogenesis in this group of patients and its effects on prognosis and survival.

Materials/Methods: A retrospective matched control study describing the outcome of 21 previously untreated oral cavity SCC patients less than 45

years old treated at a single institution from 2008 to 2016 was performed. The young patient group was compared with a control group of previously untreated patients greater than 45 years old matched for oral cavity subsite, pathologic TNM staging, and year of treatment.

Results: There was an equal distribution of T stages in the younger patient group with 7 T1, 8 T2, and 6 T3/T4. Younger patients were more likely to be never smokers ($P = .017$). There was no difference between younger and older patients with regards to overall survival ($P = .771$) and disease-free survival ($P = .970$). There was no statistical difference in adjuvant treatment modalities received between the two cohorts. The patterns of failure were similar between the two groups. All 9 young patients that recurred are deceased, including 2 patients who committed suicide.

Conclusion: Young patients with oral cavity SCC do not have a worse prognosis than a matched older patient group in this case-controlled study. Further research is necessary to determine the pathogenesis of oral cavity SCC in young patients without identifiable risk factors and identify the subset of young oral cavity SCC patients with aggressive disease. Further support and clinical interventions are necessary to identify and prevent psychosocial distress in young head and neck cancer patients.

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Oral Cancer in the Non-Smoker, Non-Drinker Population - Is Dental Hardware a Possible Risk Factor?

J. Yesensky,[1] R. Hasina,[2] K. Wroblewski,[1] J. Bellairs,[1] Z. Gooi,[1] V. Saloura,[1] N. Cipriani,[1] E.E. Vokes,[1] L. Portugal,[1] T. Seiwert,[1] E.A. Blair,[1] and N. Agrawal[1]; [1]*University of Chicago, Chicago, IL,* [2]*University of Chicago, Chicago, IL, United States*

Purpose/Objective(s): Oral cavity squamous cell carcinoma (OCSCC) arising in patients without history of tobacco or alcohol use remains poorly characterized. We hypothesized that non-smokers and non-drinkers with OCSCC had prior exposure to metallic dental hardware and devised a study to investigate this

Materials/Methods: We utilized a questionnaire querying the lifetime oral health status of patients. Of 204 eligible patients, 54 agreed to participate and completed the survey. Demographics and extensive oral health history were collected.

Results: The cohort was divided into three age ranges, 18-45, 46-65, and 66+ years. Tongue cancer was the most prevalent in all three age groups. The majority of patients had metallic dental hardware in the years prior to diagnosis. The type of hardware was unique in each group. The younger population with almost exclusively oral tongue cancer had a high prevalence of metallic orthodontic braces (31%) within 15 years prior to diagnosis. In the 45-66+ age groups, 86% had crowns, dental implants, and/or dentures with metallic elements.

Conclusion: In the non-smoker, non-drinker OCSCC patients, there is a high proportion of metallic dental hardware use. Given the increase in use of orthodontic braces in the USA among young people, and older adults retaining teeth longer (better restoration, longevity), exposure to metallic dental hardware has increased in the last few decades. Although this study does not prove a causal relationship between OCSCC and dental hardware, this is a step towards raising awareness, identifying, and investigating their role. We advocate obtaining a thorough dental history in OCSCC patients.

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Nodal Radiographic Prognostic Factors in the New Stage I p16-Positive Oropharyngeal Cancer of the AJCC 8th Edition: Are All N1 Disease the Same?

O. Bhattasali,[1] L.D. Thompson,[2] A. Schumacher,[1] and S. Iganej[1]; [1]*Southern California Permanente Medical Group, Los Angeles, CA,* [2]*Southern California Permanente Medical Group, Woodland Hills, CA*

Purpose/Objective(s): The AJCC 8th edition cancer staging manual consolidates all patients with p16+ oropharyngeal cancer with unilateral nodal disease no larger than 6 cm in size within the new clinical N1 group. The new classification system comprises a heterogeneous group of disease with varying radiographic findings. Our objective was to identify the radiographic characteristics which may portend a poor prognosis.

Materials/Methods: We conducted a central radiological review of the staging imaging studies of patients who underwent upfront definitive concurrent chemoradiation for p16+ oropharyngeal cancer from May 2006 to September 2015. Pathology review was performed of all cases with standardized p16 reporting. All patients had at least an MRI or CT scan for review; 52% also had PET scans. Nodal stage was determined through central radiographic investigation. A total of 230 patients had AJCC 8th edition stage I (cT1-2N1) disease and were included for analysis. Image findings analyzed included the largest node size, location/level of involved node(s), overt radiographic extracapsular extension (ORECE), presence or absence of matted lymphadenopathy, and predominant appearance of involved nodes (solid, cystic, or both).

Results: Median follow-up for surviving patients was 40 [12-115] months. Median age was 61 [35-81] years. For the entire cohort, 3-year progression-free survival (PFS) and overall survival (OS) were 86% and 89%, respectively. On multivariate analysis, ORECE (HR = 2.73 [1.13-6.60], $P = .03$), retropharyngeal (RP) involvement (HR = 3.19 [1.30-7.86], $P = .01$), and low-neck involvement (level IV and/or Vb) (HR = 4.15 [1.58-10.93], $P = .004$) were predictors for poorer PFS. Of note, no recurrences were observed in patients with predominantly cystic nodes (n = 37). Low-neck involvement was also a poor prognostic factor for OS (HR = 4.72 [1.53-14.61], $P = .007$), whereas RP involvement trended toward poorer OS but did not reach significance (HR = 2.82 [0.98-8.13], $P = .06$).

Conclusion: This analysis involving central assessment of nodal radiographic prognostic factors for stage I p16+ oropharyngeal carcinoma validates the new clinical N1 classification system by confirming no prognostic impact for size; however, additional image findings within this cohort negatively impacted outcomes. The presence of low-neck disease, RP adenopathy, and ORECE were associated with statistically significantly worse PFS. Low-neck involvement was also a statistically significant predictor for inferior OS in these patients. We believe caution is advised against de-intensification efforts in stage I patients with these factors. Interestingly, no treatment failures were observed in patients with predominantly cystic nodes; however, intercurrent disease death may have precluded a significant prognostic impact of this factor on multivariate analysis.

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Early Response Assessment on Mid-Treatment CT Predicts Locoregional Recurrence in Oropharyngeal Cancer Patients Treated With Definitive Radiation Therapy

R. Kabarriti,[1] P. Brodin,[1] G.L. Lundgren,[2] W.A. Tome,[3] S. Kalnicki,[3] and M.K. Garg[1]; [1]*Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY,* [2]*IRWAM, Recife 51130020, Brazil,* [3]*Albert Einstein College of Medicine, Bronx, NY*

Purpose/Objective(s): To evaluate if response assessment based on midtreatment computed tomography (CT) scans can predict locoregional recurrence (LRR) for patients receiving definitive IMRT for oropharyngeal head and neck (H&N) cancer.

Materials/Methods: H&N patients treated at our institution undergo CT rescans at 15th RT fraction and are replanned in case of inadequate dose to gross disease or increased dose to organs at risk. A retrospective cohort analysis was performed on 95 consecutive patients with oropharyngeal cancer treated in 2007-2015. The volumes of primary GTV and involved lymph nodes were delineated on pre- and midtreatment CT by an investigator blinded to treatment outcomes. Pre- and midtreatment volumes were compared to compute this volumetric change as an early response assessment. We used Cox proportional hazards regression analysis to

evaluate the efficacy of midtreatment reduction in tumor volume (TV) as a predictor of LRR, while adjusting for total TV, Charlson comorbidity score, HPV status as p16 expression, clinical stage, smoking, total treatment time, and time from planning CT to midtreatment scan.

Results: Out of the 95 patients, 73 had complete data for inclusion in the Cox regression. Of these, 69% had stage IVa and 65% were HPV positive. With a median follow-up of 2.6 years, 14 patients experienced LRR. Twenty patients were excluded due to missing HPV status since they were treated before routine testing of p16 expression. Table 1 shows that the reduction in total TV is an independent predictor of LRR (HR 0.27, 95% CI: 0.08-0.92, $P=.037$), and the reduction in primary GTV volume is an even stronger predictor (HR 0.16, 95% CI: 0.04-0.62, $P=.008$), along with Charlson comorbidity score and total TV prior to RT. Stratifying patients into a high-risk group with reduction in total TV at midtreatment ≤median and/or total TV prior to RT >median, compared to a low-risk group with neither, showed a clear separation in Kaplan-Meier curves with actuarial 3-year locoregional control of 79% for the high-risk and 92% for the low-risk patients.

Conclusion: Our study shows that early response assessment based on midtreatment CT is an independent predictor of LRR and can be used to effectively distinguish high-risk and low-risk patients, allowing for risk-adaptive treatment stratification at the midway point.

Abstract 195; Table Significant predictors of LRR in Cox regression analysis

	Hazard ratio (95% CI)	*P*-value
Model 1		
Reduction in total TV at midtreatment (≤median vs. >median)	0.27 (0.08−0.92)	0.037
Charlson comorbidity score	1.25 (1.04−1.50)	0.018
Total TV prior to RT (per 10 cc change in TV)	1.12 (1.02−1.24)	0.022
Model 2		
Reduction in primary GTV volume at mid-treatment (≤median vs. >median)	0.16 (0.04−0.62)	0.008
Charlson comorbidity score	1.31 (1.09−1.58)	0.005
Total TV prior to RT (per 10 cc change in TV)	1.14 (1.03−1.27)	0.012

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MRI-Based Radiation Therapy: Intrafraction Motion Quantification of Head and Neck Tumors Using Cine Magnetic Resonance Imaging

T. Bruijnen, B. Stemkens, C. Terhaard, J.J.W. Lagendijk, C.P. Raaijmakers, and R.H. Tijssen; *University Medical Center Utrecht, Utrecht, Netherlands*

Purpose/Objective(s): Recently, our department showed that in a first-in-man study high field guided radiation therapy using the Unity (Elekta) is feasible. This opens the ability for the near future to see while you treat. For head and neck cases, intrafraction motion, based on breathing and tongue movement, may be visualized, and the treatment adapted. We quantified this motion using cine Magnetic Resonance Imaging

Materials/Methods: MR imaging on a 3T scanner was performed in 84 head and neck cancer patients selected for radiation therapy treatment with immobilization mask. Approximately 5 minutes after the start of the examination, 2D sagittal cine scans were acquired for 1 minute (7 Hz) in the center of the tumor. Pixel-wise deformable vector fields were computed using non-rigid image registration to quantify respiratory-induced tumor displacements and tumor drifts for the anterior-posterior and superior-inferior directions. Population-based PTV margins were computed to account for the internal motion.

Results: Intrafraction motion was analyzed in 84 patients (43 oropharynx/ 29 larynx/ 12 nasopharynx). Mean maximum respiratory−induced tumor displacements for the combined subsites were 2.4 mm (range: 0.3-13.3) in the superior, 2.4 mm (0.3−8.0) in the inferior, 1.8 mm (0.2−5.9) in the anterior, and 1.8 mm (0.3−5.2) in the posterior directions. The mean tumor drifts for the combined anatomical positions were 0.6 mm (range: 0.0-3.6) in the superior, 0.6 mm (0.0−2.2) in the inferior, 0.5 mm (0.0−1.7) in the anterior, and 0.5 mm (0.0−1.7) in the posterior directions. Nasopharyngeal tumors required no PTV expansion, oropharyngeal tumors 0.5 mm isotropic expansion, and the laryngeal tumors 2 mm in the superior direction.

Conclusion: Intrafraction tumor displacements were quantified and population-based PTV margins were calculated for head and neck tumors. Incorporating the motion information in the margin recipe primarily expanded the PTV for laryngeal tumors approximately 2 mm. Although the mean tumor displacements were small, there were some subjects that exhibited respiration-induced tumor displacements larger than 10 mm. These cases will be traced by the use of the MRI-linac and treatment might be adapted.

Abstract 196; Table PTV margins generated with the motion information for each anatomical position and in-plane direction

PTV margin Anatomical position	superior [mm]	Inferior [mm]	Anterior [mm]	Posterior [mm]
Nasopharynx (n= 8)	2.7	2.6	2.9	2.9
Oropharynx (n=43)	3.0	3.1	3.2	3.1
Larynx (n=33)	4.2	3.5	3.2	3.2
All combined (n=84)	3.7	3.3	3.2	3.2

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Adaptive Replanning for HPV-Associated N2b Oropharyngeal Squamous Cell Carcinoma in Response to Anatomic Changes During Radiation Therapy

H.J. Zhu,[1] R.J. Amdur,[1] B. Lu,[1] C. Liu,[1] and W.M. Mendenhall[2]; [1]*Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL,* [2]*Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL*

Purpose/Objective(s): Repeat CT simulation and dosimetric planning in response to weight loss or tumor response takes substantial resources. All published studies are compromised by heterogeneity of the study population, timing of replanning, and dosimetric endpoints. We report the first prospective evaluation of dosimetric changes from replanning at a uniform timepoint in a uniform patient population.

Materials/Methods: We prospectively studied 10 consecutive patients treated with primary radiation therapy and concurrent weekly chemotherapy for p16-positive oropharyngeal carcinoma with neck stage N2b. Repeat CT simulation was performed on treatment day 21. The target volumes and normal tissue constraints were defined per recent RTOG protocols. High-risk and standard-risk planning target volumes (PTV) were given 70 Gy and 56 Gy in 35 treatment days using simultaneously integrated boost intensity-modulated radiation therapy. Normal structures included: spinal cord, brainstem, parotids, larynx, pharyngeal constrictors, and oral cavity. We compared PTV and normal structure doses in 3 scenarios: no replan, replan for the final 4 weeks of treatment, and replan for the final 2 weeks. The effect of replanning was determined by creating a new dose plan with the second simulation CT. The new dose map was scaled proportionally to its actual respective days of use, then deformably registered with the initial plan to create an accumulated dose map

accounting for the anatomy change. The impact of tumor response and weight change were analyzed in multivariate linear regression models.

Results: No replanning resulted in underdosage of the target volumes: both PTV70 and PTV56 coverage reduced by 4% on average, and maximally 9% and 12%, respectively; no case met the main coverage requirement (D95% = prescription dose) for both PTVs. Replanning for the final 4 or 2 weeks improved PTV coverage by 4% and 2% on average, therefore meeting the coverage requirement in 90% and 60% cases, respectively. Failure to meet PTV coverage goals without replanning was associated with volume shrinkage of adenopathy ($P < .001$), but not weight loss. For all normal structures, the dose change was small (<1 Gy) without replanning. Specifically, the dose change to the contralateral parotid without replanning was ≤1% despite average volume shrinkage of 21%.

Conclusion: This is the first prospective study of adaptive replanning with a uniform treatment program, uniform replanning times, and a homogeneous study population where replanning is expected to be important. Our findings were dramatically different from most prior publications. The primary risk without replanning was underdosing the PTV, not an increased dose to normal structures. Replanning in this setting should be considered.

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A Novel Radiographic Grading System to Evaluate Extranodal Extension in Regional Nodal Metastases from Head and Neck Squamous Cell Carcinoma

M.R. Corby, S. Mukherjee, K. Fedder, and M.J. Jameson; *University of Virginia, Charlottesville, VA*

Purpose/Objective(s): The American Joint Committee on Cancer (AJCC) has introduced the use of clinical extranodal extension (ENE) in its updated staging of head and neck cancers. Under this new classification system, evidence of ENE determined by physical exam and supported by radiological evidence upstages a patient to N3 disease. Several studies have explored the correlation of radiographic ENE with pathological ENE using a variety of imaging classification criteria. Although clearly necessary due to these revisions in staging, there is no currently accepted standard for grading radiographic ENE. We are therefore presenting a novel radiographic grading system of ENE and its correlation with histopathologic results.

Materials/Methods: Two neuroradiologists developed a grading system based on identifiable radiologic characteristics where ENE was rated as absent, possible (irregular margins), probable (infiltration of surrounding fat plane), or present (complete nodal replacement, soft tissue invasion, or nodal conglomerate). Pretreatment contrasted neck CT scans were independently reviewed. Histologic sections of neck dissection specimens from these patients were then reviewed by a surgical pathologist blinded to the radiology results. Histologic ENE was scored as 0 (no ENE), 1 (thickened nodal capsule, no peripheral extension), 2 (ENE <1 mm beyond capsule), 3 (ENE >1 mm beyond capsule), or 4 (obliterated nodal architecture). Sensitivity, specificity, positive and negative predictive value and inter-rater reliability were calculated.

Results: Data from 141 patients with head and neck squamous cell cancer who underwent neck dissection at a tertiary medical center over a 5-year period were included. Patients all had a previously untreated neck and had preoperative CT and surgical pathology available. Scans designated as having probable or present ENE demonstrated 93% specificity for any histologic ENE (grade 2 or higher). However, sensitivity of imaging for detecting ENE ranged from 34%-70%, even when considering high grade histologic ENE. Inter-rater reliability between the two neuroradiologists had a Spearman correlation coefficient of 0.85.

Conclusion: This novel radiographic grading system of cervical lymph node metastases can be used effectively to rule out the presence of ENE. Necks with absent radiologic ENE are extremely unlikely to have any degree of pathologic extension outside the nodal capsule. With high specificity and strong inter-rater reliability, this system can successfully be adopted to avoid overstaging patients based on the new AJCC guidelines for nodal metastasis.

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Stability Analysis of CT Radiomics Features With Respect to the Variation of Manual Segmentation in Oropharyngeal Cancer

R. Liu,[1] H. Elhalawani,[2] C.D. Fuller,[3] and H. Zhu[2]; *[1]Rice University, Houston, TX, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Accurate segmentation of tumors and quantification of tumor features are important for cancer detection, diagnosis, monitoring, and planning therapeutic intervention. Due to inherent noise components in multiparametric imaging and inter-observer variations, it is common that various segmentation methods, including both manual segmentation and computer-aided segmentation methods, may produce large segmentation errors in tumor volumes and their associated radiomics features. Such errors may eventually lead to large prediction errors. The aim of this study is to carry out the stability analysis for various radiomics features with respect to segmentation results based on the contrast-enhanced CT axial images.

Materials/Methods: All the 436 CT images were imported to a commercial software and the gross tumor volumes of primary disease (GTVp) were segmented by two expert radiation oncologists. In order to illustrate the variations of segmentation results, additional two segmentation results were set up via resizing the original segmented regions of interest (ROIs) based on their geometric information on the surface. For the three ROI image groups, we calculated 109 radiomics features, and wavelet-based features. Then, a logistic regression model was built to investigate the correlation between the radiomics features extracted from GTVp and the response to chemoradiation in terms of overall survival (OS). Finally, based on the prediction probabilities, we assessed the inter-rater reliability and reproducibility via calculating the intraclass correlation coefficients (ICC) and concordance correlation coefficients (CCC), respectively.

Results: One of the features, 25percentile, outperforms other features in terms of both ICC and CCC. Its ICC and CCC between the original segmentation group and resized segmentation groups are around 0.27. In terms of the prediction accuracy, top features with high AUC extracted from different segmentation results are different from each other. Another interesting finding is that gray-level co-occurrence matrix (GLCM) based features have low ICC and CCC (<0.3) in comparison between original segmentation group and each resized segmentation group, while have high ICC and CCC (>0.9) in comparison between two resized segmentation groups. Considering the prediction performance, these GLCM based features derived from original segmentation group perform well with the area under the curve (AUC) above 0.7, which means these traditional features are sensitive to segmentation results.

Conclusion: The segmentation variability affects both the radiomics features and prediction accuracy. Moreover, it is of great meaning to discover radiomics features with robustness of segmentation variability in oropharyngeal cancer, which can be warranted for treatment monitoring and prognosis prediction.

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Significance of Negative Posttreatment 18-FDG PET/CT Imaging in Patients With p16/HPV-positive Oropharyngeal Cancer

S.P. Ng, J.M. Johnson, G.B. Gunn, D.I. Rosenthal, H.D. Skinner, J. Phan, S.J. Frank, W.H. Morrison, E.M. Sturgis, F. Mott, C.D. Fuller, and A.S. Garden; *The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Patients with p16/HPV-associated oropharyngeal squamous cell carcinoma have a favorable outcome after treatment. In this group of patients who potentially have a long life expectancy, the optimal surveillance strategy and modality is not well established. We aim to determine the ability of a negative postradiation PET/CT scan in predicting the risk of subsequent relapse in these patients.

Materials/Methods: A retrospective analysis of patients with p16/HPV-associated oropharyngeal squamous cell carcinoma who completed definitive radiation therapy and had a posttreatment PET/CT scan from 2006 to 2013 was performed. Patient, tumor and treatment characteristics, and clinical outcomes were recorded. Tumors were considered HPV/p16 positive if either HPV (by in-situ hybridisation) or p16 (by immunohistochemistry) was positive. Disease-free (DFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method.

Results: A total of 327 patients were evaluated. The median age was 57 years. The most common primary sites were base of tongue (50%) and tonsil (48%). 291 (89%) had a negative posttreatment PET scan. For these 291 patients who had a complete metabolic response after treatment, the 5-year DFS and OS were 91% and 89% respectively. The median time to develop recurrence was 16 months. Of the 291 patients, 24 patients (8%) had disease recurrence (Table); 11 (4%) patients had further surgery and/or radiation, and 8 (3%) were without disease on last follow-up. The majority of patients with recurrences had distant metastatic disease (54%). Less than 5% of patients who had a negative PET result after definitive radiation therapy developed local and/or regional recurrence.

Abstract 200; Table Summary of site of recurrences, subsequent management, and outcomes

Site of recurrence	No of patients (n=24)	Salvage treatment	Successful salvage
Local	1	1	1
Regional	9	6	5
Local & Regional	1	1	0
Distant	11	3*	2
Regional & Distant	1	0	
Local, Regional & Distant	1	0	

*Solitary lung metastasis salvaged with surgery and/or radiation therapy.

Conclusion: Patients who achieve a complete metabolic response on posttreatment PET imaging have excellent prognosis and the risk of developing a recurrence in the future is very low. Therefore, a more cost-effective surveillance program should be considered for this subgroup of patients.

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CT-Based Nodal Radiomic Biomarkers Predictive of Patient Outcome in Head and Neck Squamous Cell Carcinoma

A. Rishi,[1] K. Latifi,[1] G.G. Zhang,[2] A.O. Naghavi,[1] H. Enderling,[1] E.G. Moros,[1] J. Heukelom,[3] A.S.R. Mohamed,[4] C.D. Fuller,[5] L.B. Harrison,[6] and J.J. Caudell[1]; *[1]H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology, Tampa, FL, [2]Moffitt Cancer Center, Tampa, FL, [3]Netherlands Cancer Institute, Department of Radiation Oncology., Amsterdam, Netherlands, [4]The University of Texas MD Anderson Cancer Center, Houston, TX, [5]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [6]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Purpose/Objective(s): Non-invasive radiomic biomarkers involve high-throughput extraction of imaging data and may provide important complementary information. We investigated the association between pretreatment nodal radiomic features and clinical outcome for head neck cancer (HNC).

Materials/Methods: After institutional review board approval, patients with lymph node−positive head and neck squamous cell carcinoma treated with definitive radiation therapy were retrospectively reviewed. Lymph node delineation for radiation planning was based on computed tomography (CT), and 39 intensity- and shape-based first-order radiomics features were extracted from nodal volumes. Locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) were estimated by a Cox proportional hazard regression univariate analysis (UVA). Association between radiomic features and known p16 status were also analyzed by Wilcoxon rank-sum test.

Results: A total of 44 patients were identified with a median follow-up of 12 months. Primary sites consisted of the oropharynx (n=41) and oral cavity (n=3). Of the oropharyngeal primaries, 27 patients (66%) were p16 positive. Median radiation dose was 68 Gy (range 54-70 Gy). The majority of patients received concurrent chemotherapy (n=36, 73%). No radiomic features were associated with p16 status (all $P>.1$). The 2-year actuarial LRC, DFS, and OS were 84%, 84%, and 94%, respectively. On UVA, radiomic features with a trending association to LRC included sphericity ($P=.055$), eccentricity ($P=.07$), spherical disproportion ($P=.068$), convexity ($P=.072$), and long-axis dimension ($P=.091$), of which sphericity ($P=.082$), and convexity ($P=.072$) also showed a trending association with DFS. The radiomics features significantly associated with DFS were surface area [HR 1.02 (95% CI: 1-1.04); $P=.02$], long-axis [HR 1.02 (95% CI: 1-1.04); $P=.03$], and short-axis dimension [HR 1.09 (95% CI: 1.01-1.18); $P=.04$]. Other features with a trending association with DFS were volume ($P=.057$), kurtosis ($P=.09$), and TGV ($P=.09$). No radiomic features predicted for OS on UVA.

Conclusion: This study identified certain lymph node radiomic features that may be prognostic for DFS in HNC. Further work is required to improve the power and resolution of these features, with the goal towards identifying novel predictive tools to aid in personalized radiation therapy.

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Evaluation of Pre- and Post-IMRT FDG-PET SUV Values for the Prediction of Tumor Control In HPV-Positive Oropharyngeal Cancer Patients

C.E. Cardenas,[1] A.S.R. Mohamed,[2] S.P. Ng,[3] S. Westergaard,[4] M. Aristophanous,[2] J.M. Johnson,[1] E.M. Sturgis,[5] A.S. Garden,[2] and C.D. Fuller[6]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]MD Anderson Head and Neck Cancer Symptom Working Group, The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Peter MacCallum Cancer Centre, Melbourne 8006, Australia, [4]University of Texas Medical Branch, Galveston, TX, United States, [5]MD Anderson Cancer Center, Houston, TX, [6]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): To evaluate the predictive value of pre- and post-IMRT FDG-PET SUV for human papillomavirus (HPV)−positive oropharyngeal squamous cell carcinoma (OPSCC) patients.

Materials/Methods: A dataset of HPV+ OPSCC patients treated between 2006 and 2012 at MD Anderson Cancer Center was retrospectively analyzed under an IRB-approved protocol. The following inclusion criteria were used: P16 positivity, locally advanced disease with measurable primary and nodal tumor, and availability of pretreatment PET/CT prior to start of chemo/radiation therapy and posttreatment PET at the first follow-up and before any salvage attempt. Both the pre- and post-IMRT PET/CT scans were deformably registered to the IMRT planning CT using the ADMIRE image registration software (Elekta, Sweden). The gross tumor volume (GTV) on the planning CT was then projected to both the pre- and post-IMRT PET/CT scans. Using the mapped GTVs on the pre- and post-IMRT PET/CT scans, we extracted the mean and maximum SUV at each time point and calculated the changes ($\Delta SUV_{mean,max}$) to correlate these uptake values with outcomes. Univariate analysis was done using Cox proportional hazard models. Recursive partition analysis was used to identify significant threshold values for each examine endpoint. Lastly, nuclear oncology reports for post-IMRT FDG-PET were reviewed to correlate the qualitative expert-reviewed reports with outcomes.

Results: One hundred and sixty-one patients were eligible for this study. Median follow-up was 48 months and the median prescribed dose was 70 Gy in 33 fractions. Seventy-seven patients (48%) received induction chemotherapy and 123 (76%) received concurrent chemotherapy. Four-year local and regional control (LC, RC) were 94% and 93%, respectively. The recurrence-free survival (RFS) and the overall survival (OS) at 4-year were 83% and 86%, respectively. On univariate analysis, post-IMRT GTV mean and maximum SUV were significantly correlated with LC ($P = .004$ and .0001, respectively) and RFS ($P = .005$ and .0007, respectively). Post-IMRT maximum SUV was also correlated with OS ($P = .004$). The pre-IMRT and $\Delta SUV_{mean,max}$ were not significantly associated with any of the examined endpoints. For post-IMRT PET/CT, a SUV_{max} of 5.78 was found as the most significant threshold value for worse LC ($P = .0050$), with 4-year LC of 61% and 97% for $SUV_{max} \geq 5.78$ vs $SUV_{max} < 5.78$, respectively. Using the expert-reviewed reports, the positive predictive values of post-IMRT PET for LC and RC were 33% and 50%, respectively, while the negative predictive values of post-IMRT PET for LC and RC were 96.6% and 95.4%, respectively.

Conclusion: Post-IMRT FDG-PET quantitative metrics provide additional predictive value for LC, RFS, and OS for HPV+ OPSCC. In particular, post-IMRT SUV_{max} provided an improvement in sensitivity and specificity over expert-reviewed reports when predicting local control.

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Discrimination of Epstein-Barr Virus Status in NPC Using CT-Derived Radiomics Features: Linking Imaging Phenotypes to Tumor Biology

P. Yang,[1,2] D. Mackin,[3] C. Chen,[1] A.S.R. Mohamed,[4] H. Elhalawani,[2] Y. Shi,[1] J. Yao,[1] S. Volpe,[2] L.E. Court,[5] H. Jin,[1] and C.D. Fuller[6]; *[1]Hunan Cancer Hospital, Changsha, China, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]University of Texas M.D. Anderson Cancer Center, Houston, TX, [4]MD Anderson Head and Neck Cancer Symptom Working Group, The University of Texas MD Anderson Cancer Center, Houston, TX, [5]Department of Radiation Physics, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [6]MD Anderson, Houston, TX*

Purpose/Objective(s): This study aims at employing computed tomography (CT)−based radiomics analysis within the primary tumor among NPC patients for the selection of candidate features, which can be correlated to EBV status.

Materials/Methods: Data for biopsy-proven NPC patients dispositioned to definitive (chemo)radiation therapy at a single Chinese institution between 2005-2012 were scanned (n = 202). Pretreatment contrast-enhanced CT (CECT) images and contours of the gross primary tumor were extracted in DICOM-RT format for patients with known EBV status. Serum EBV antibody levels were determined by titration using an Immunoenzymatic assay with 400 set as a cutoff value for the test (less than 400 denotes a negative test and vice versa). A total of 60 radiomics features were selected from the categories intensity direct (n = 11), neighborhood intensity difference (NID; n = 5), gray-level co-occurrence matrix (GLCM; n = 22), gray-level run length (GLRL; n = 9), and shape (n = 13). The features were tested for correlation with volume, mean image intensity, and image intensity standard deviation, and they were removed if the absolute value of the Spearman correlation was greater than 0.8. After features with the highest average redundancy were excluded, 26 radiomics features remained. Potential candidate features for a multivariate logistic regression model were determined using the least absolute shrinkage and selection operator (LASSO); the optimal value of the regularization parameter lambda was determined to be 0.03. To measure the performance of the model and correct for optimism, Hosmer-Lemeshow test and bootstraping method (n = 1000) were applied. False discovery rate (FDR) was evaluated using permutation test. The final area under the curve (AUC) was determined to assess the model performance.

Results: The final cohort included a total of 202 NPC patients with known EBV status. Median age was 47 (IQR: 39-52) and 72.8% were males. The disease was staged as II, III, or IV in 5.5%, 43.8%, and 50.7% of the patients, respectively. Based on EBV serological testing, patients were categorized into EBV-positive (56.9%) and EBV-negative (43.1%). After calibration, the LASSO fit selected four features. The most discriminative feature was Sphericity (0.00585). Other candidate features were the neighborhood gray tone difference based feature Texture Strength (0.01384), GLCM feature Correlation (0.01390), and statistical feature Kurtosis (0.04222). The apparent AUC and confidence intervals (CI) for the prediction of EBV status of the primary tumor was 0.73 [95% C.I.: 0.66-0.80].

Conclusion: This study represents the first attempt to use high-throughput imaging analytics to correlate imaging features to NPC biology in terms of EBV status. Our data shows that CECT-based radiomics features, specifically shape and intensity features, can discriminate between EBV-positive and EBV-negative tumors.

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Interobserver Variation in the International MRI Linear Accelerator Oropharyngeal Carcinoma Delineation Study

S. Blinde,[1] A.S.R. Mohamed,[2] A. Al-Mamgani,[3] K. Newbold,[4] I. Karam,[5] J.R. Robbins,[6] D. Thomson,[7] N. Raaijmakers,[8] C.D. Fuller,[9] and C. Terhaard[10]; [1]*Universitätsklinikum Heidelberg, Marburger Iohnenstrahl-Therapiezentrum, Marburg, Germany,* [2]*MD Anderson Head and Neck Cancer Symptom Working Group, The University of Texas MD Anderson Cancer Center, Houston, TX,* [3]*The Netherlands Cancer Institute (NKI-AVL), department of radiation oncology, Amsterdam, Netherlands,* [4]*The Royal Marsden NHS Foundation Trust, London, United Kingdom,* [5]*Princess Margaret Cancer Centre, Toronto, ON, Canada,* [6]*Medical College of Wisconsin, Milwaukee, WI,* [7]*Christie NHS Foundation Trust, Manchester, United Kingdom,* [8]*UMC Utrecht, Utrecht, Netherlands,* [9]*MD Anderson, Houston, TX,* [10]*University Medical Center Utrecht, Utrecht, Netherlands*

Purpose/Objective(s): Nowadays, a (contrast-enhanced) CT is used for delineation of oropharyngeal carcinomas (OPCs). MRI, however, has better soft tissue contrast. MR-guided radiation therapy has just started, but will be standard in the near future. Therefore, we want to determine the variation in target delineation for oropharyngeal cancer (OPC) by international experts using MR as a single delineation modality and determine the variation in target delineation for OPC after adding PET and CT to MRI.

Materials/Methods: Twenty-four radiation oncologists from 7 centers affiliated with the MRI linear accelerator (MRL) Consortium were asked to delineate the gross tumor volume (GTV) and the clinical target volume (CTV) of the primary tumor of 4 OPC cases. In the first phase, observers were given a brief clinical history, physical examination, and the T1, T1 plus Gadolinium and T2 weighted MRI sequences. Target contours were delineated according to experts' institutional guidelines. The absolute and encompassing volumes, the generalized conformity index and median surface distances were then calculated from the voxel count maps of each case. The data were also analyzed with the Simultaneous Truth and Performance Level Estimation (STAPLE) algorithm. In the second phase, PET and CT data were sent to the observers and they were asked to contour the same cases again using MRI, PET, and CT. Then, the data were analyzed as in phase 1.

Results: Median years of experience for the participating radiation oncologists was 5 years (range 0-15 years). The mean absolute volumes of the GTV's of case 1, case 2, case 3, and case 4 in phase 1 were 6.5 ml (range: 3.9-9.9 ml), 8.6 ml (range 1.9-22.1 ml), 32.6 ml (range: 17.3-64.4 ml), and 20.3 ml (range 7.8-33.6 ml), respectively. The conformity indices for the GTV of the primary tumor in phase 1 were 0.6, 0.38, 0.5, and 0.59 for case 1, case 2, case 3, and case 4, respectively. The mean absolute volumes of the GTV' of case 1, case 2, case 3, and case 4 in phase 2 were 5.6 ml (range: 1.1-10.7 ml), 7.6 ml (range 1.3-16.5 ml), 21.0 ml (range: 5.8-44.5 ml), and 16.6 ml (range 5.4-30.2 ml), respectively. The conformity indices for the GTV of the primary tumor in phase 2 were 0.53, 0.38, 0.44, and 0.48 for case 1, case 2, case 3, and case 4 respectively. The STAPLE algorithm covers the median GTV voxel density.

Conclusion: The interobserver variation of target volumes delineation of OPC patient based on MR is high. Adding PET and CT to MRI does not seem improve the interobserver variability in target delineation for OPC.

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Impact of Routine Surveillance Imaging on Detecting Recurrence in Human Papillomavirus–Associated Oropharyngeal Cancer

B.A. Harr,[1] J. Bodmann,[2] C.A. Reddy,[1] J. Ferrini,[2] J. Heney,[3] D. Ives,[2] J. Hamker,[3] N.M. Woody,[1] J.L. Geiger,[2] N.P. Joshi,[1] S. Koyfman,[1] and D.J. Adelstein[2]; [1]*Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH,* [2]*Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH,* [3]*Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): The utility of routine surveillance neck and chest imaging after definitive (chemo)radiation therapy (CRT) for oropharyngeal cancer (OPC) in patients (pts) with human papillomavirus (HPV)–associated disease—with their excellent outcomes, unique patterns of failure and lower risk of second aerodigestive primary tumors (SPT)—is unknown. This study examines the utility of surveillance imaging in detecting locoregional (LRF) and distant failures (DF) as well as SPT.

Materials/Methods: From an IRB-approved database, we identified all HPV+ OPC pts who received definitive CRT between 2004 and 2015 whose initial posttreatment imaging was not suspicious for disease recurrence (DR). CT Neck and either CXR or CT chest were obtained variably in follow up (f/u) based on provider preference and clinical concern. Each image interpretation was coded: 0 (negative), 1 (likely reactive), 2 (suspicious for disease) or 3 (recurrent disease). DR included the first event of biopsy proven LRF and/or DF and were back dated to the first date of image interpretation $\geq$2. The Mann-Whitney test/Chi-square was used to determine differences in baseline characteristics between G1 and G2. Fine & Gray regression was used to determine if there was an association between imaging frequency and DR and imaging frequency and diagnosis of a SPT.

Results: 225 pts were eligible for this study; 30% had T3-T4 disease and 90% had $\geq$ N2 disease. All received CRT with most receiving IMRT (80%) and concurrent cisplatin (63%). Median age was 58.5, median f/u was 40.8 m (range [R]: 5.7 – 108.7). 64% met annual chest screening criteria for lung cancer. A median of 6 scans were obtained in f/u (R: 2-22) with a mean of 1.94 s/y (R: 0.5-6.5). Two groups were defined based on image frequency: pts with <2 scans/year (s/y) (123; 55% - Group 1 [G1]) and pts with $\geq$ 2 s/y (102; 45% - Group 2 [G2]). Pts in G2 were more likely to have $\geq$ N2b disease (85% vs. 72%; p=0.04), be current/recent smokers (46% vs 29%; p=0.04), and had a higher mean pack-year history (23 vs. 15; p=0.03). A total of 21 failures were observed, 7 LRF and 15 DF. 6 of the 7 LRF occurred within 24 m of treatment completion; 14 of 15 DF occurred within 36 m of treatment completion. Regression analysis showed G2 pts had a significantly increased risk of DR compared to G1 pts (HR 10.3; p=0.002). Five SPT were found (2 lung, 2 esophagus, and 1 oropharynx) between 4.5 to 159 m post-CRT.

Conclusion: HPV+ OPC pts have low overall failure rates minimizing the utility of surveillance imaging. Most LRF were found within 2 years post-CRT and DF found within 3 years post-CRT. The frequency of imaging during this time should be modified based on known risks of DR. After these time points, surveillance imaging should be continued only in pts who fit lung cancer screening guidelines.

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Prospective In Silico Study of A Novel MRI-Guided Dose Adaptation Technique For Human Papillomavirus–Positive Oropharyngeal Cancer Patients

A.S.R. Mohamed,[1] M. Aristophanous,[1] P. Blanchard,[2] M. Kamal,[3] Y. Ding,[4] A.S. Garden,[1] D.I. Rosenthal,[1] G.B. Gunn,[5] and C.D. Fuller[6]; [1]*MD Anderson Head and Neck Cancer Symptom Working Group, The University of Texas MD Anderson Cancer Center, Houston, TX,* [2]*The University of Texas MD Anderson Cancer Center, Division of Radiation*

Oncology, Houston, TX, [3]Clinical Oncology and Nuclear Medicine Department, Ain Shams University, Cairo, Egypt, [4]The University of Texas MD Anderson Cancer Center, Department of Radiation Physics, Houston, TX, [5]The University of Texas MD Anderson Cancer Center, Houston, TX, [6]MD Anderson, Houston, TX

Purpose/Objective(s): To determine the feasibility and dosimetric benefits of a novel MRI-guided IMRT dose-adaption strategy for HPV+ oropharyngeal cancer.

Materials/Methods: Pretreatment and biweekly intreatment serial MRIs was done using RT immobilization setup. The initial gross tumor volume ($GTV_{initial}$) was manually segmented using T2- and T1+contrast MR images then propagated to the registered simulation CT. The initial clinical target volume ($CTV_{initial}$) was defined as the $GTV_{initial}$+6-8mm expansion to incorporate high-risk subclinical disease. For each patient, 2 IMRT plans were created (i.e. standard and adaptive). The prescription dose for the standard plans was 2.12 Gy/fx for 33 fractions to the $PTV_{initial}$ ($CTV_{initial}$+3mm). For the adaptive plan, a new $GTV_{adaptive}$ was segmented on serial MRIs in case of a detectable tumor shrinkage, then a new $CTV_{adaptive}$ was generated to cover the $GTV_{adaptive}$+5mm margin. The prescription dose to $PTV_{adaptive}$ ($CTV_{adaptive}$+3mm) was 2.12 Gy/fx to allow for maximum dose to the residual disease, resulting in a cumulative dose, should disease persist through therapy, of up to 70 Gy. Prescription dose for any previously involved volumes was 1.52 Gy/fx to ensure a floor dose of 50.16 Gy to any region ever deemed to have been directly involved with tumor. All uninvolved upper-neck elective nodal volumes outside the $CTV_{initial}$/$CTV_{adaptive}$ was encompassed in $CTV_{elective}$ and prescribed 1.52 Gy/fx for a total of 50.16 Gy. All plans were optimized to achieve 99% CTV coverage. Dosimetric parameters of OARs were recorded for standard vs adaptive plans then the normal tissue complication probability (NTCP) for toxicity endpoints were calculated using literature-derived models.

Results: Five patients were included in this pilot study, 3 men and 2 women. Median age was 58 years. Three tumors originated at the tonsillar fossa and two at the base of tongue. The average dose to 95% of $PTV_{initial}$ volume was 70.6 Gy (SD, 0.5) for standard plans versus 59.5 Gy (SD, 2.0) for adaptive plans. The majority of OARs showed a decrease in dosimetric parameters using adaptive plans compared with the standard plan, particularly for swallowing related structures. The average reduction of the probability of developing dysphagia $\geq$ grade 2 and feeding tube persistence at 6-month posttreatment was 11% and 4%, respectively. The probability of developing hypothyroidism at 2-year posttreatment was also reduced by average 5% while the probability of xerostomia at 1-year was only reduced by average 1% for adaptive plans compared with standard IMRT.

Conclusion: This *in silico* results showed the suggested adaptive approach is technically feasible, safe (with no normal tissue exceeding modeled dose constraints), and advantageous in reducing dose to OARs specially swallowing musculature, thus reducing the NTCP of dysphagia $\geq$ grade 2 and feeding tube persistence at 6-month posttreatment.

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Exploration of an Early Imaging Biomarker of Osteoradionecrosis in Oropharyngeal Cancer Patients: Case-Control Study of the Temporal Changes of Mandibular Radiomics Features

H. Elhalawani,[1] S. Volpe,[1,2] S. Barua,[3] A. Mohamed,[1,4] P. Yang,[1,5] S.P. Ng,[1,6] S. Lai,[7] K.A. Hutcheson,[8] G.B. Gunn,[1] L.E. Court,[9,10] A. Rao,[11] and C.D. Fuller[1,10]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]University of Milan, Department of Hemato-Oncology, Milan, Italy, [3]Rice University, Houston, TX, [4]University of Alexandria, Clinical Oncology and Nuclear Medicine Department, Alexandria, Egypt, [5]Hunan Cancer Hospital, Changsha, China, [6]Peter MacCallum Cancer Centre, Melbourne 8006, Australia, [7]The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX, [8]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, [9]Department of Radiation Physics, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [10]University of Texas Graduate School of Biomedical Sciences, Houston, TX, [11]The University of Texas MD Anderson Cancer Center, Department of Bioinformatics and Computational Biology, Houston, TX*

Purpose/Objective(s): We aim to characterize the kinetics of radiomics features of various mandibular subvolumes after IMRT and identify subvolumes at high risk for developing osteoradionecrosis (ORN).

Materials/Methods: We included oropharyngeal cancer patients treated by IMRT with subsequent radiographically proven $\geq$G2 ORN. Mandibular subvolumes showing ORN as well as a neighboring radiographically intact mandibular subvolume receiving the same dose (Control) were manually segmented. For each patient, pre-IMRT, 2-, and 6-month post-IMRT scans were co-registered. ORN and Control ROIs were propagated to all time points. A total of 145 radiomics features were extracted from each ROI using automated software. A histogram approach and Spearman correlation test were used to exclude features according to extreme degrees of variability and high level of correlation, respectively. This resulted in 50 features from the following categories: shape, gray-level co-occurrence matrix (GLCM) 3D, GLCM 2.5D, neighbor intensity difference (NID) 3D, NID 2.5D, and intensity histogram. We computed the underlying temporal trajectory signatures using Functional Principal Component Analysis. Random Forest classification was used to build a predictive model.

Results: Seventeen patients, with the majority having base of tongue primary. Ten patients had G2, 7 G3 ORN, which were ipsilateral to the tumor subsite of origin in 82.4% of cases. Median time to ORN diagnosis was 15.4 months. The ORN ROI mean dose was 63 Gy ($\pm$6.5). The corresponding AUCs and 95% confidence intervals (C.I.) for the prediction of ORN, according to the 5 models, are illustrated in the Table. A combination of baseline features and temporal trajectories proved to be the best classifier. Conversely, delta changes at intermediate time points (model 2 and 3) held were the least predictive of ORN incidence. This suggests that the functional approach yields a superior predictive power in the correlation of radiomics features to normal tissue toxicity over time.

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	Predictive Model	AUC	95% Low C.I.- High C.I.
1	Baseline features only	0.74	0.58-0.92
2	Baseline/2-month post-IMRT Delta	0.59	0.38-0.80
3	Baseline/6-month post-IMRT Delta	0.67	0.47-0.86
4	All time points temporal trajectories	0.72	0.54-0.93
5	Combination of baseline features and temporal trajectories	0.84	0.71-0.98

Conclusion: Temporal trajectories of radiomics features derived from sequential pre- and post-RT CT scans can provide markers that are correlates of mandibular injury. Radiomics may convey additional clinical information from routine imaging studies in radiation oncology towards antecedently preemptive management of ORN.

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Prognostic Value of Reticulocyte, Immature Reticulocyte, and Osteopontin in HNSCC Patients Treated by Radiation And Chemotherapy

J.J. Mrochem-Kwarciak, T. Rutkowski, A. Wygoda, A. Chmura, R. Deja, Ł. Boguszewicz, P. Widlak, A. Brewczyński, and K.A. Skladowski; *Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland*

Purpose/Objective(s): Anemia is associated with poor outcome in patients treated with radiation therapy (RT), probably because it leads to low oxygen level in tumors. Plasma osteopontin and hemoglobin (Hb) may be putative parameters associated with tumor hypoxia in HNSCC patients. The number of reticulocytes (Ret) and immature reticulocyte fraction (IRF)—a new routine parameter in hematology analysis—can be used to ensure a more accurate monitoring of changes of the function of erythropoiesis. The aim of this study was to test the clinical utility of parameters of the red blood cell system and the concentration of OPN as a marker of tumor hypoxia.

Materials/Methods: Between 01/2009 and 08/2013, 251 patients with squamous cell carcinoma of the oropharynx (39%), hypopharynx (13%), larynx (44%), and oral cavity (4%) were treated with RT alone (48%) or combined with chemotherapy (52%). There were 15 (6%), 112 (45%), 74 (29%), and 50 (20%) patients with T1, T2, T3, and T4 tumor stage, respectively, and 99 (40%), 26 (10%), 105 (42%), and 21 (8%) patients with N0, N1, N2 and N3 nodal stage of disease, respectively (no patients with distant metastases were included). OPN and parameters of the red blood cell system were estimated in plasma or blood before treatment and immediately after treatment completion.

Results: Pretreatment OPN level was generally higher in patients with advanced T stage (T3-4) compare to early (T1-2) stage ($p = .024$), but was not correlated with N stage ($P = .58$). Strong negative correlation was found between patients with anemia (Hb< 11 g/ml) before treatment and OPN ($P = .008$), IRF ($P = .0007$), and the hemoglobin content of reticulocytes ($P = .05$); additionally, a negative correlation was found between patients with anemia after treatment and IRF ($P = .002$). Significantly longer overall survival (OS) was found for patients with lower OPN ($p = .0001$) and higher Ret ($P = .03$) before treatment and lower posttreatment Ret ($P = .04$). Also, in the multivariate analysis, pretreatment OPN and pre- and posttreatment Ret levels were independent prognostics factors for shorter OS ($P = .03$; $P = .01$; $P = .02$, respectively)

Conclusion: Anemia in HNSCC patients before treatment has the nature of chronic disease with stimulated erythropoiesis. Immediately after treatment, ineffective erythropoiesis increases the risk of death. Pre- and posttreatment Ret and pretreatment OPN are independent prognostic determinants of survival.

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Role of 18F-FDG PET/CT in Evaluating Posttreatment Nasopharyngeal Carcinoma With Inconclusive Results on Conventional Modalities: A Single Institution Experience

H.H. Lu, M.H. Tsai, and N.T. Chiu; *National Cheng Kung University Hospital, Tainan, Taiwan*

Purpose/Objective(s): Nasopharyngeal carcinoma (NPC) is an endemic malignancy in Southeast Asia treated with primary chemoradiation therapy. In follow-up of this disease, it is often difficult to distinguish residual or recurrent disease from posttreatment inflammation with conventional imaging such as magnetic resonance imaging (MRI). 18F-FDG PET/CT may play an important role in evaluating residual/recurrent NPC, as well as distant metastasis. The aim of this retrospective analysis is to review our institutional experience and report the performance of 18F-FDG PET/CT in this setting.

Materials/Methods: We reviewed the records of NPC patients with complete radiation therapy treatment from June 2005 to January 2015 who underwent 18F-FDG PET/CT because of suspicious residual/recurrent or metastatic NPC on conventional modalities. The final diagnosis was determined by histopathology if available, or otherwise by clinical consensus or follow-up.

Results: The records of 54 consecutive patients were reviewed. Overall sensitivity and specificity of 18F-FDG PET/CT in evaluating residual/recurrent or metastatic NPC were 92.0% and 62.7% on a patient-based analysis. The positive predictive value and negative predictive value (PPV/NPV) for primary, nodal, and distant sites were 65.2%/96.7%, 86.7%/100.0%, and 84.6%/97.6%, respectively. For patients with initial T-stage of T4 (20 of 54 patients), the positive predictive value and negative predictive value in detecting residual/recurrence at the primary site were 45.5% and 100.0%. Among the 12 patients with distant metastasis, PET/CT was true positive in 11, including three clinically occult distant metastases (5.6%), and there was one PET false negative due to brain metastasis. A significant lower overall survival was found for the patients with positive posttreatment PET/CT compared with negative findings ($P = .035$).

Conclusion: In patients with suspicious residual/recurrent tumor or metastasis on conventional modalities, 18F-FDG PET/CT demonstrated a high negative predictive value and is especially useful to exclude primary site recurrence in T4 patients. Furthermore, a positive posttreatment PET/CT is associated with lower overall survival.

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Dosimetric Impact of Metal Artifacts From Dental Implants and Clinical Implications for Head And Neck IMRT Treatment Planning

M. Mallory, S.S. Sood, M.J. Tennapel, A.M. Chen, and C.E. Lominska; *University of Kansas School of Medicine, Department of Radiation Oncology, Kansas City, KS*

Purpose/Objective(s): Dental implants are increasingly prevalent in the head and neck cancer patient population and result in the creation of artifacts on CT imaging for treatment planning. In our practice, we have noticed more mucosal toxicity adjacent to dental implants and hypothesized that this observation may be due to errors in dose calculation. The purpose of this study was to retrospectively evaluate dosimetric differences in target coverage and organ at risk (OAR) sparing when adjusting for spurious CT measurements attributed to dental metal artifact.

Materials/Methods: Nine patients with dental implants who were previously treated at our institution with definitive radiation for oropharyngeal cancer were selected for this retrospective study. All patients were treated with 6 MV photons using intensity modulated radiation therapy (IMRT). Dose calculation was performed using an algorithm with heterogeneity corrections. Dental implant and streak artifact volumes were contoured and new IMRT plans were generated with identical beam geometry and monitor units using the uncorrected reference CT data set and a corrected CT data set. Artifacts were assigned a soft tissue electron density value with a Hounsfield unit (HU) of zero. Using descriptive statistics, target volumes and OAR dosimetry were reported and compared between the clinical treatment plans and re-calculated plans. Target volumes analyzed were GTV (D95, D98, D99), intermediate-risk PTV (D95, D98, D99), and high-risk PTV (D95, D98, D99, D2cc). The maximum dose, Dmax, was also collected for each plan. OARs analyzed included the bilateral parotids (mean), oral uninvolved (mean), OAR pharynx (mean), mandible (max), and cord (max).

Results: The median artifact volume was 41.6 cc (range, 22.5 to 56.8 cc). When accounting for artifact error, there were small but statistically significant relative increases in Dmax (0.24%, $P = .0273$), mean oral uninvolved dose (0.24%, $P = .0234$), and mean left parotid dose (0.20%, $P = .0469$). On average, the hot spot (Dmax) increased by 181 cGy when accounting for artifact. There were no significant dosimetric differences between plans in terms of GTV, intermediate-risk PTV, and high-risk PTV

coverage. There were no significant differences for the mandible max dose, cord max dose, OAR pharynx mean dose, or the right parotid mean dose.
Conclusion: In this retrospective study, there was minimal dose variation to target volumes and OAR structures when substituting artifact with soft tissue density HUs. There were significant differences in terms of maximum dose and dose to the uninvolved oral cavity, which suggests that ignoring artifacts in CT images during planning may result in greater hot spots. While small, these differences are worthy of further study as they may at least partially contribute to increased rates of empirically observed mucosal toxicity in the vicinity of dental artifacts.
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Neoadjuvant Pembrolizumab is Active in Surgically Resected Head and Neck Cancer

S. Palackdharry,[1] M. Gillison,[2] F. Worden,[3] M. Old,[4] P. O'brien,[5] N.E. Dunlap,[6] E. Cohen,[7] K. Casper,[8] M.L. Mierzwa,[9] J.C. Morris,[1] N. Hashemi Sadraei,[1] B. Huth,[1] V. Takiar,[1] R. Butler,[1] J. Mark,[1] Y. Patil,[10] K. Wilson,[1] E. Janssen,[11] L. Conforti,[1] B. Yaniv,[1] and T. Wise-Draper[1]; *[1]University of Cincinnati, Cincinnati, OH, [2]MD Anderson Cancer Center, Houston, TX, [3]University of Michigan, Ann Arbor, MI, [4]The James Cancer Hospital and Solove Research Institute, Wexner Medical Center at The Ohio State University, Department of Otolaryngology-Head and Neck Surgery, Columbus, OH, [5]Medical University of South Carolina, Charleston, SC, [6]University of Louisville, Louisville, KY, [7]UC San Diego, Moores Cancer Center, Department of Hematology/Oncology, La Jolla, CA, [8]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [9]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [10]University of Cincinnati Medical Center/University of Cincinnati College of Medicine, Cincinnati, OH, [11]Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Purpose/Objective(s): Approximately 60% of head and neck squamous cell carcinoma (HNSCC) patients present with locally advanced disease. Surgical candidates often receive postoperative radiation and cisplatin if they have high-risk pathological features. Despite intensive therapy, up to 50% of patients will suffer relapse. Therefore, improved treatment modalities are desperately needed. The checkpoint inhibitor, programmed death-ligand 1 (PD-L1), is upregulated in HNSCC and treatment with anti-PD-1 inhibitor (pembrolizumab) was shown to decrease tumor burden in patients with recurrent/metastatic HNSCC. Additionally, PD-L1 expression is increased in response to radiation treatment both in vitro and in vivo. Importantly, pretreatment with anti-PD-L1 antibody prior to radiation resulted in increased survival of mice with implanted HNSCC tumors compared to radiation alone. Therefore, we hypothesized that neoadjuvant pembrolizumab is active in previously untreated HNSCC and concurrent adjuvant treatment with pembrolizumab combined with standard of care would result in decreased relapse. To test this hypothesis, a multisite "Phase 2 Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02641093) funded by Merck was initiated.
Materials/Methods: Eligible patients with high-risk (Stage III/IV) locally advanced HNSCC were consented to receive pembrolizumab 200 mg I.V. 1-3 weeks before planned surgical resection. Pretreatment biopsies and postoperative specimens were archived for H&E and immunohistochemistry. Peripheral blood was collected for ELISA. Following resection, patients were stratified based on pathological risk to receive adjuvant standard of care (SOC) combined with pembrolizumab every three weeks for a total of seven doses. Patients are followed for disease-free and overall survival. Safety was determined by delays in SOC treatment.
Results: Sixteen of 80 planned patients have been enrolled. To date, 3 patients were replaced due to pre-surgical infection, discovery of a secondary medullary thyroid cancer, and withdrawal of consent. Preliminary results show 8 of 10 patients demonstrated a pathological tumor response after a single dose of pembrolizumab. Tumor immune cell infiltration was not significantly changed, however, there was an increase in plasma proinflammatory cytokines with treatment. Interestingly, only the 2 patients without a pathological tumor response after pembrolizumab recurred (8 month [range 2-21 months] median time to follow-up). No delays in SOC treatment have occurred.
Conclusion: Preliminary results demonstrated tumor responses after just one dose of pembrolizumab in previously untreated HNSCC patients that may predict patient outcome.
Author Disclosure: **S. Palackdharry**: None. **M. Gillison**: Consultant; Bristol-Myers Squibb, Merck, Celgene, Astra Zeneca, Amgen. **F. Worden**: Advisory Board; Merck. **M. Old**: Facilitate meetings; encourage and implement solutions; OSU Physician Faculty Engagement Steering Committee. Facilitate meetings and encourage & implement solutions; OSU Ambulatory Space & Environment Subcommittee. **P. O'brien**: None. **N.E. Dunlap**: Honoraria; Osler Institute. **E. Cohen**: Consultant; AstraZeneca, Merck. **K. Casper**: None. **M.L. Mierzwa**: None. **J.C. Morris**: Speaker's Bureau; Merck. **N. Hashemi Sadraei**: Speaker's Bureau; Genentech. **B. Huth**: None. **V. Takiar**: None. **R. Butler**: None. **J. Mark**: None. **Y. Patil**: None. **K. Wilson**: None. **E. Janssen**: None. **L. Conforti**: None. **B. Yaniv**: None. **T. Wise-Draper**: Research Grant; Merck. Consultant; Bristol-Myers Squibb.

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Towards a Tumor Specific De-Intensification Strategy in Oropharyngeal Squamous Cell Carcinomas: Using Tumor Immunophenotypes to Predict Patient Outcomes

W.H. Stepp,[1] A. Mazul,[1] S. Patel,[2] and J.P. Zevallos[2,3]; *[1]University of North Carolina, Chapel Hill, NC, [2]University of North Carolina Hospitals, Chapel Hill, NC, [3]Washington University School of Medicine, St. Louis, MO*

Purpose/Objective(s): Many of the clinical trials that de-intensify treatment for patients with suspected HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) use p16 expression alone to positively identify HPV-mediated tumors. While p16 immunohistochemistry is widely available and has a strong correlation with HPV-positive OPSCC, approximately 12% of p16-positive cases have non-HPV16-positive and HPV-negative tumors. In these patients, treatment de-intensification based on p16 immunohistochemistry alone could adversely affect this patient population who have more frequent recurrent disease and may not receive treatment consistent with standard of care if included in trials with de-intensified radiation therapy. In this study, we show that OPSCC that are HPV-positive have a unique genetic signature with respect to gene expression and tumor specific mutations, even in the context of p16-positive immunohistochemistry.
Materials/Methods: Formalin-fixed, paraffin-embedded p16-positive or p16-negative OPSCC samples were obtained from the university pathology core facility. Samples were sectioned onto slides and examined by a university pathologist who marked tumor boundaries. Tumor tissue was microdissected and RNA from tumor tissue was harvested. RNA was either hybridized directly to a Nanostring PanCancer Immune molecular RNA array or reverse-transcribed into cDNA and assayed for HPV16 mRNA targets (E1, E2, E5, E6/E7, and E1E4) using quantitative, real-time PCR.
Results: Using NanoString molecular array technology, we have identified a pattern of immunoregulatory and cancer-associated gene expression in HPV-positive OPSCCs that clusters patients into HPV-positive, low-risk and HPV-positive, high-risk patients. Further, when stratified by clinical characteristics such as smoking status, we find that HPV-positive, never smokers have a distinct gene expression profile from those patients who are HPV-positive and have ever smoked. Additionally, we find that HPV-mediated OPSCC tumors susceptible to recurrent disease may be identified with increased accuracy by combining viral mRNA qPCR and DNA-seq reads in combination with a tumor-derived genetic signature.
Conclusion: The use of p16-IHC alone to identify OPSCC candidates eligible for radiation therapy de-intensification may be insufficient. Using a combination of host, tumor and viral genetics, we may be able to limit the number of cases where radiation therapy is de-intensified in the setting of p16-positive immunohistochemistry. This could prevent recurrence of

more aggressive subtypes of HPV-positive, p16-positive OPSCC. Further, the use of molecular profiling of tumors from multiple angles (e.g. host and onco-virus transcription) may aid in the clinical typing of OPSCCs, promote the discovery of drug targets, and improve our ability to safely de-intensify radiation therapy of HPV-positive OPSCCs.

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HNSCC Gene Expression Subtypes, Including a HPV Subtype, Demonstrate Differential Immune Cell and Biomarker Associations

H. Faruki,[1] G.M. Mayhew,[1] D.N. Hayes,[2] C. Perou,[3] and M. Lai-Goldman[1]; *[1]GeneCentric, Research Triangle Park, NC, [2]Lineberger Cancer Center, Chapel Hill, NC, [3]Lineberger Cancer Center, University of North Carolina, Chapel Hill, NC*

Purpose/Objective(s): Human papilloma virus (HPV) RNA expression in combination with a gene expression signature of 144 genes was used to classify head and neck squamous cell carcinoma (HNSCC) into 5 distinct subtypes. The subtypes are investigated for differential associations with clinical features, immune infiltration, and immune marker expression.

Materials/Methods: Using previously published Bindea et al. immune cell gene signatures (24 in total) and the TCGA Head & Neck cancer gene expression dataset (HNSCC n=520), we examined immune cell expression in relation to 5 HNSCC gene expression subtypes (atypical, classical, basal, mesenchymal, and HPV subtype). The HPV tumor subtype was determined by alignment of RNAseq with HPV sequences and by evaluation of its gene expression profile. Signatures of multiple immune cells as well as single immune-biomarkers, (*CTLA4, PDCD1*(PD-1), and *CD274*(PD-L1) were examined across the 5 subtypes. Differential gene expression was examined using the Kruskal-Wallis test. Immune cell signature associations with tumor subtype and with *CD274* expression were evaluated using linear regression. Survival-based associations were evaluated with cox proportional hazard models.

Results: Immune cell expression was significantly different across the subtypes (Tcells KW $P=1.7e\text{-}17$) and in general was highest in HPV positive tumors. The classical expression subtype demonstrated lower Tcell immune expression. *CD274* (PD-L1) expression was less variable across the subtypes but lowest expression was again seen in the classical subtype (KW $P=3.7e\text{-}06$). Mutation burden varied across the subtypes with the highest mutation burden observed in the atypical subtype and the lowest mutation burden in the HPV tumors (KW $P=1.7e\text{-}10$). Subtype and HPV status were more strongly associated with immune expression than *CD274* (PD-L1) expression (median F-test *P*-value and adjusted R-squared were 2.0e-16 and 0.14 for subtype versus 6.7e-07 and 0.04 for *CD274*). Cox models with adjustment for stage suggested higher immune cell expression is associated with better survival, and most strongly in the HPV tumor subtype including T gamma delta cells HR 0.2 (95% CI 0.06-0.68) and T cells HR 0.33 (95% CI 0.14-0.79).

Conclusion: Biologic subtypes of HNSCC reveal key differences in immune cell expression, which were not always correlated with *CD274* (PD-L1) expression. Evaluation of subtypes as potential biomarkers for immunotherapy response in HNSCC should be investigated.

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A Novel Immunotherapy: LYC-55716, a Small-molecule RORγ Agonist, in Clinical Trials for Head and Neck Squamous Cell Carcinoma

X. Hu,[1] X. Liu,[1] H. Li,[1] M. Bogdan,[1] Y. Gao,[1] B. Fox,[2] G. Weems,[3] H.J. Wilkins,[3] and L. Carter[1]; *[1]Lycera Corp., Ann Arbor, MI, [2]Celgene Corp., Seattle, WA, [3]Lycera Corp., Plymouth Meeting, PA*

Purpose/Objective(s): Retinoic acid receptor–related orphan receptor γ-t (RORγ) is the master transcription factor for Type 17 effector T cell differentiation and function. Synthetic RORγ agonists augment the activity of this transcriptional regulator by modulating a gene expression program in immune cells, resulting in enhanced effector functions and decreased regulatory T cell (Treg) activity. LYC-55716 and other RORγ agonists have shown promise as monotherapy and combination therapy in preclinical syngeneic tumor models. In parallel with Phase 1 clinical testing (NCT02929862), preclinical and bioinformatics assessments were performed to evaluate the potential for head and neck squamous cell carcinoma (HNC) tumors to respond to RORγ agonist therapy, for possible inclusion in a Phase 2a trial.

Materials/Methods: A RORγ agonist signature was derived from transcriptional profiling of primary murine and human T cells treated ±RORγ agonists. Using a panel of murine syngeneic models, The Cancer Genome Atlas (TCGA) dataset, and other public datasets, a series of bioinformatic analyses were conducted to provide information on HNC tumors with regard to (a) expression of RORγ and RORγ-inducing cytokines; (b) RORγ biology and surrogate indicators of endogenous RORγ ligands correlated with prognosis; (c) immune profiles within the tumor microenvironment. Tumor-infiltrating lymphocytes (TILs) and PBMCs from HNC patients were assessed for RORγ expression and the effects of a RORγ agonist.

Results: Target expression: Analysis of TCGA RNAseq data determined that HNC was one of 15 tumors types for which >20% of samples expressed the highest levels of RORγ. TCGA analysis also showed that RORγ-inducing cytokines IL-6, IL-23α, and IL-1β were highly expressed in HNC tumors. In a small cohort of HNC patients, a significant fraction of $CD4^+$ TILs expressed RORγ. Target biology: TCGA analysis indicated low expression of sterol synthesis and efflux genes in HNC. Analyses of TCGA and public datasets found high expression of RORγ and agonist signature genes in HNC tumors was associated with improved survival. Immune profiles: In TCGA, HNC tumors are associated with high mutational burden and infiltration of immune cells.

Conclusion: Preclinical data from syngeneic tumor models, bioinformatic analyses of TCGA dataset, and the expression of RORγ and its correlation with improved survival support the selection of HNC for inclusion in a Phase 2a clinical trial.

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Withdrawn

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Utilization of Immunotherapy in Head and Neck Cancers Pre-Food and Drug Administration Approval of Immune Checkpoint Inhibitors

S.P.P. Wu,[1] M. Tam,[2] N.K. Gerber,[1] Z. Li,[3] B. Schmidt,[4] M. Persky,[5] N.J. Sanfilippo,[6] T. Tran,[7] A. Jacobson,[7] M. DeLacure,[7] K.S. Hu,[2] M. Persky,[8] D.P. Schreiber,[9] and B. Givi[7]; *[1]New York University School of Medicine, New York, NY, [2]NYU Langone Health, Department of Radiation Oncology, New York, NY, [3]NYU Langone Health, Department of Medical Oncology, New York, NY, [4]New York University School of Dentistry, New York (and vicinity), NY, [5]New York University Langone Health Medical Center, New York (and vicinity), NY, [6]NYU Langone Medical Center, Department of Radiation Oncology, New York, NY, [7]NYU Langone Health, Department of Otolaryngology, New York, NY, [8]New York University School of Medicine, New York (and vicinity), NY, [9]Front Range Radiation Oncology PC, Littleton, CO, United States*

Purpose/Objective(s): Two novel immune checkpoint inhibitors were approved by Food & Drug Administration (FDA) in 2016 for head and neck cancer squamous cell carcinoma (HNSCC) patients who have

progressed on standard chemotherapy. However, immunotherapy agents have been used in HNSCC before the approval of these new agents. We investigated the patterns of immunotherapy utilization in the pre-FDA approval era using the National Cancer Database (NCDB) as a benchmark in anticipation of paradigm changes in the coming years.

Materials/Methods: We selected all patients with HNSCC in NCDB from 2004 to 2014. Patients were categorized into those who were recommended for immunotherapy and those who were not. The recommended group was further divided into patients who received immunotherapy and those who did not. Temporal patterns of immunotherapy recommendation, primary site of the tumor, stage of the disease and place of treatments were analyzed among others.

Results: We identified 366,662 patients with HNSCC during the study period. Only a small minority were recommended for immunotherapy (4788, 1.3%). Majority of patients who were recommended for immunotherapy, received treatment (4223, 88%). Majority of recommendations were from the academic centers and comprehensive cancer programs and made during 2013-2014 (76.3%). Majority of patients were stage IV (2585, 61.2%) The most common sites were tongue (1154, 27.3%) and tonsil (915, 21.7%). Patients with eye and orbit cancers (5032, 1.4% of total cohort) were more likely to be recommended and receive immunotherapy (198, 4.7% of all who received immunotherapy $P<.0001$).

Conclusion: Only a small minority of HNSCC patients are considered and received immunotherapy until 2014. Most patients were treated at academic and comprehensive cancer programs and diagnosed with advanced disease. This data could serve as a benchmark to monitor changes in the patterns of immunotherapy utilization after the FDA approval of the novel agents in 2016.

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Preliminary Results From a Phase 2 Trial of Tipifarnib in HRAS-Mutant Head and Neck Squamous Cell Carcinomas

A. Ho,[1] N. Chau,[2] I. Brana Garcia,[3] C. Ferte,[4] C. Even,[4] F. Burrows,[5] L. Kessler,[5] V. Mishra,[5] K. Magnuson,[5] C. Scholz,[5] and A. Gualberto[5]; [1]*Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Dana-Farber Cancer Institute, Boston, MA,* [3]*Vall D'Hebron Institute of Oncology, Barcelona, Spain,* [4]*Institut Gustave Roussy, Villejuif, France,* [5]*Kura Oncology, San Diego, CA*

Purpose/Objective(s): HRAS is a proto-oncogene that is overexpressed and mutated in head and neck, bladder, thyroid, and salivary gland tumors, among others. While discovered over 40 years ago, no specific therapies have yet been developed targeting mutant HRAS. Tipifarnib is a potent and highly selective inhibitor of farnesyltransferase, a critical enzyme requisite for HRAS activation. Over 5,000 patients (pts) have been treated with tipifarnib; although responses have been documented in several tumor indications, the mechanisms of response are still poorly understood. Tipifarnib has demonstrated robust activity in HRAS-mutant patient-derived xenograft (PDX) models of head and neck squamous cell carcinoma (HNSCC) and squamous non-small cell lung cancer that are resistant to standard therapies. This Phase 2 study (NCT02383927) was conducted to test the hypothesis that inhibition of mutant HRAS oncogenic activity with tipifarnib could translate to objective responses in HNSCC pts driven by the HRAS oncogene.

Materials/Methods: The study was originally designed to enroll pts into 2 single-arm study cohorts: Cohort 1 (thyroid cancer) and Cohort 2 (other solid tumors), each one with a 2-stage design (11+7 evaluable pts). Two objective responses needed to be observed in the first stage for each cohort to proceed to stage 2. The prespecified activity goal for the first stage of accrual in Cohort 2 was met. Based on data observed in the first stage of this Cohort, enrollment to the second stage of Cohort 2 has been limited to HRAS-mutant HNSCC since August 2016. For enrollment, pts must have an HRAS-mutant, locally advanced/unresectable and/or metastatic solid tumor malignancy and RECIST v1.1 measurable disease. Tipifarnib is given at 900 mg orally twice daily on days 1-7 and 15-21 of 28-day cycles. Response assessments are conducted every 8 weeks.

Results: As of August 30, 2017, 7 pts with HNSCC have been enrolled. Tipifarnib was generally well-tolerated with fatigue, myelosuppression, nausea, and vomiting constituting the most common adverse events (all grades). Six pts are currently evaluable for efficacy. Four (67%, 3 confirmed, 1 unconfirmed) pts achieved a partial response, 3 of whom remain on treatment currently in cycle 3, cycle 5, and cycle 19. One subject discontinued in Cycle 21. Two (33%) pts had disease stabilization as best response (4 cycles, ongoing and 7 cycles). Four of these pts were refractory to prior therapies, including immunotherapy and cetuximab +/- chemotherapy regimens.

Conclusion: Encouraging activity of tipifarnib was observed in pts with HRAS-mutant HNSCC. Trial enrollment continues.

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Routine Surveillance Scanning in Patients With Squamous Cell Carcinoma of the Head and Neck: Lung Screening CT Scans Have Value but Head and Neck Scans Do Not Identify Patients Who Achieve Long-Term Disease Control

A.J. Iovoli,[1] A. Platek,[1] L.H. DeGraaff,[1] M.E. Platek,[2] A. Hassan,[2] V. Gupta,[2] K.E. Wooten,[2] W.L. Hicks,[2] and A.K. Singh[2]; [1]*Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY,* [2]*Roswell Park Cancer Institute, Buffalo, NY*

Purpose/Objective(s): To examine the utility of computed tomography (CT) imaging as a routine surveillance tool for the detection of recurrent head and neck squamous cell carcinoma (HNSCC).

Materials/Methods: Clinical characteristics of HNSCC patients treated between 2008-2017 with radiation therapy (RT) or concurrent chemoradiation (CCRT) were abstracted from medical records. In patients who achieved a complete clinical response (CCR) to treatment by positron emission tomography (PET) scan, surveillance CT scans were conducted to the maxillofacial area, neck, and chest every 3 months in year 1, every 6 months in year 2, and every 12 months in years 3 and beyond. Overall survival (OS) curves and multivariate cox proportional hazard ratios (HR) were examined.

Results: At this single institution, 588 patients were treated for HNSCC. Median follow up duration for the entire cohort was 30.9 months (range = 6-88 months). Of the 449 (76%) evaluable patients who achieved a CCR, 85 (19%) patients had a recurrence. Among the 85 patients with disease recurrence, 25 (29%) patients remained alive, of which 15 (18%) underwent successful salvage treatment and became free of disease. Lung screening CT scans detected failure in 8 of these successfully salvaged patients. Among the 8 patients successfully salvaged for locoregional recurrence, 3 failures were asymptomatic at onset and detected by laryngoscope or dental exam. The remaining 5 failures were symptomatic and detected upon work up. One patient was successfully salvaged for both local and distant failure. Maxillofacial and neck screening CT imaging failed to detect any successfully salvaged patients.

Conclusion: Routine surveillance for HNSCC patients with lung CT imaging had value but head and neck CT scans failed to identify any successfully salvaged patients. Given this finding, routine CT imaging surveillance in HNSCC patients should be restricted to annual lung screenings. Surveillance head and neck CT imaging is not recommended until better salvage treatment is available to treat locoregional recurrence.

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A Phase 2a, Multicenter, Open-Label Study of RM-1929 Photoimmunotherapy in Patients With Recurrent Head And Neck Cancer

D. Cognetti,[1] J.M. Curry,[2] A.M. Gillenwater,[3] W.N. William,[4] S.T. Kochuparambil,[5] D. McDonald,[5] M. Fidler,[6] K.M. Stenson,[6] N.R. Vasan,[7] M.A. Razaq,[8] J. Campana,[9] and J. Johnson[10]; *[1]Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA, [2]Sidney Kimmel Cancer Center at Thomas Jefferson University Hospital, Philadelphia, PA, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]The University of Texas MD Anderson Cancer Center, Division of Cancer Medicine, Houston, TX, [5]Allina Health, Virginia Piper Center Institute, Minneapolis, MN, [6]Rush University Medical Center, Chicago, IL, [7]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [8]University of Oklahoma, Oklahoma City, OK, [9]Colorado Head and Neck Specialists, Denver, CO, [10]SIdney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Purpose/Objective(s): Patients with recurrent head and neck squamous cell cancer (rHNSCC) have poor prognoses and limited treatment options after they have failed standard therapies. We are investigating photoimmunotherapy (PIT) for the treatment of rHNSCC using a novel targeted light-activated drug conjugate RM1929, consisting of the EGFR-directed monoclonal antibody cetuximab conjugated to the phthalocyanine dye, IRDye 700DX.

Materials/Methods: This is a multi-institutional open-label Phase 2a study of rHNSCC patients who cannot be satisfactorily treated with surgery, radiation, or platinum chemotherapy. PIT, using a previously determined optimal drug dose and light treatment dose, was performed to evaluate the safety and efficacy associated with repeat dosing of up to 4 treatment cycles, 4-8 weeks apart, in patients with persistence of disease. For each treatment, nonthermal red light was applied to the tumors 24 hours after intravenous infusion of the photoactivated conjugate. The light was applied on the surface for superficial mucosal/cutaneous disease or within the tumor (via fiber optic diffusers placed by ultrasound guidance) for submucosal/subcutaneous or nodal disease. Responses and Progression-Free Survival (PFS) were calculated using CT RECIST 1.1. All CT RECIST 1.1 measurements were determined by an independent blinded radiologist.

Results: Nineteen patients with rHNSCC who were treated with RM-1929 PIT and have been followed for at least 3 months were included in the outcome analysis. There were no dose-limiting toxicities or skin photosensitivity reactions observed. No toxicity was noted for normal tissues exposed to therapeutic light treatment. Two reported SAEs, tumor hemorrhage and tumor pain, were assessed as possibly or probably related to treatment. CT RECIST 1.1 demonstrated a PFS of 153 days (5.1 months). Objective response rate (ORR), complete response (CR) and disease control rate (DCR) by CT RECIST 1.1 were 42% (8/19), 26% (5/19) and 84% (16/19) respectively.

Conclusion: Photoimmunotherapy with RM1929 in patients with rHNSCC is safe and well-tolerated. CT RECIST 1.1 PFS, ORR, and CR response rates are improved over those of standard of care therapies and encouraging in these patients who have failed standard therapies and have typically recalcitrant disease. Further investigation of this novel therapeutic strategy is warranted and a Phase 3 clinical trial is planned.

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Risk of Severe Laryngeal Toxicity Following Re-Irradiation With Head and Neck Stereotactic Body Radiation Therapy

B.J. Gebhardt,[1] J.A. Vargo,[2] D.C. Ling,[3] B. Jones,[4] D.A. Clump II,[3] J. Ohr,[5] R.L. Ferris,[6] and D.E. Heron[3]; *[1]Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, [2]West Virginia University Cancer Institute, Morgantown, WV, [3]Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [4]Geisinger Commonwealth School of Medicine, Scranton, PA, [5]Department of Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [6]Department of Otolaryngology, Eye & Ear Institute, University of Pittsburgh Medical Center, Pittsburgh, PA*

Purpose/Objective(s): Survival rates are poor following recurrent head and neck cancers (rHNC) after prior radiation therapy. SBRT is an increasingly utilized technique for re-irradiation of rHNC. Prior studies have demonstrated late grade 3+ toxicity rates <20% overall, though this rate increased to 50% with larynx/hypopharynx recurrences. We sought to evaluate the association between laryngeal dose and the risk of severe toxicity in patients undergoing SBRT as re-irradiation for rHNC, as no validated dose-volume constraints exist to guide SBRT in this setting.

Materials/Methods: We retrospectively reviewed patients with previously-irradiated rHNC treated from 2008-2013. Patients treated early in our experience with incomplete dosimetry were excluded. Patients were treated with linear accelerator-based SBRT to a median of 44 Gy in 5 fractions delivered on a twice-weekly basis with concurrent Cetuximab. SBRT plans were retrospectively reviewed, and the larynx was contoured. The maximum dose to 0.1cc ($D_{0.1cc}$), 1cc (D_{1cc}), 2cc (D_{2cc}), and 5cc (D_{5cc}) of the larynx and the mean larynx dose were recorded and analyzed for association with laryngeal toxicity, including dysphagia and airway compromise, using binary logistic regression.

Results: A total of 75 patients were identified, and 12 patients were excluded due to prior laryngectomy. Median follow-up was 8 months (range: 1-91) for all patients, and 37 months for surviving patients (range: 31-91]. Five patients (8%) received more than 1 course of SBRT, and cumulative larynx doses from fused summary plans were recorded. The median $D_{0.1cc}$, D_{1cc}, D_{2cc}, D_{5cc}, and mean larynx doses were 17.1 Gy [interquartile range (IQR) 0.6-45.4 Gy], 8.8 Gy [IQR 0.5-36.5 Gy], 6.3 Gy [IQR 0.5-30.0 Gy], 3.8 Gy [IQR 0.4-18.5 Gy], and 3.0 Gy [0.3-13.2 Gy], respectively. The overall rates of severe acute and late toxicity were 15.9% and 20.0%, respectively. The rate of severe laryngeal toxicity was 12.7%. There was no association between severe laryngeal toxicity and prior RT dose, time from RT to SBRT, SBRT dose, or planning target volume size. Laryngeal toxicity was associated with $D_{0.1cc}$ [Odds ratio (OR) 1.10, 95% CI 1.01-1.19, $P=.031$], D_{1cc} (OR 1.11, 95% CI 1.02-1.20, $P=.013$) D_{2cc} (OR 1.11, 95% CI 1.03-1.20, $P=.006$), D_{5cc} (OR 1.10, 95% CI 1.04-1.17, $P=.002$), and mean larynx dose (OR 1.09, 95% CI 1.03-1.15, $P=.004$). On multivariable analysis (MVA), only D_{5cc} was associated with laryngeal toxicity. The rate of severe laryngeal toxicity was 50.0% at a D_{5cc} >30 Gy vs. 2.3% for <30 Gy.

Conclusion: The results demonstrate a low risk of severe laryngeal toxicity with SBRT for re-irradiation of rHNC, which was associated with all dosimetric parameters on univariate analyses. Only D_{5cc} remained significant on MVA, and the risk of toxicity was 50% with D_{5cc} >30 Gy, which represents a potentially validated constraint to guide application of SBRT for future clinical trial design.

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A Modular Polymer Platform that Delivers Recombinant Cytokines and Cisplatin Allows for De-Escalation of Radiation Therapy in an Animal Model of Head and Neck Squamous Cell Carcinoma

P. Pellionisz,[2] K. Badran,[1] Y. Lin,[2] J. Mallen-St.Claire,[2] D. Schaue,[3] D.A. Elashoff,[2] S. Dubinett,[4] S. Sharma,[5] B. Wu,[2] and M. St.John[6,7]; *[1]University of California Los Angeles, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA, [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, [4]UCLA, Los Angeles, CA, [5]university of California, Los Angeles, Los Angeles, CA, [6]UCLA David Geffen School of Medicine, Department of Head and Neck Surgery, Los Angeles, CA, [7]Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Purpose/Objective(s): To evaluate the safety and efficacy of a novel modular polymer platform for head and neck squamous cell carcinoma (HNSCC). 50% of HNSCC patients fail primary management, and salvage of patients with recurrent disease is of paramount importance. We had previously shown the antitumor efficiency of this novel polymer in delivering chemokines (CCl21) and cisplatin in an animal model of SCCHN. Here we evaluate the safety and efficacy of this polymer in combination with radiation therapy (RT) in an effort to see if this combination allows for a de-escalation of RT.

Materials/Methods: SCCVII/SF tumors were established in in C3H/HeJ mice. Tumors were then treated with either (1) no polymer, (2) plain polymer, (3) CCl21-polymer, (4) cisplatin polymer, and (5) combination CCl21 and cisplatin secreting polymer. The mice were then treated with three different doses of RT. Tumor size was measured every day until the mice were euthanized. Four weeks later, necropsy was performed to evaluate for vascular or nerve damage and to assess tumor size and weight.

Results: Cisplatin-polymer, CCL21-polymer, and the combination CCl21-cisplatin polymer effectively reduced SCCVII/SF tumors in the C3H/HeJ mice by over 16-fold ($P<.01$) as compared to control and plain polymer groups. Additionally, treatment with Cisplatin-polymer, CCL21-polymer and the combination CCl21-cisplatin polymer allowed for a 4-fold reduction in the dose of RT required. Histopathology revealed no adverse tissue effects when the cisplatin polymer was inserted in direct contact with the carotid artery, jugular vein or vagus nerve.

Conclusion: Our promising results indicate that this polymer may represent a new therapeutic modality for patients with HNSCC that is safe and efficacious. Our data provides a strong rationale for further evaluation of this polymer in de-intensification of radiation therapy. Once this polymer platform is further optimized we will plan for the ultimate validation in the context of a prospective trial in patients with unresectable advanced or recurrent HNSCC.

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Metformin Induces Pro-Tumorigenic Cytokines And Natural Killer Cells In Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma

B. Yaniv, N. Hashemi Sadraei, S. Palackdharry, V. Takiar, and T. Wise-Draper; *University of Cincinnati, Cincinnati, OH*

Purpose/Objective(s): Concurrent chemotherapy and radiation (CRT) continues to be standard of care for unresectable locally advanced head and neck squamous cell carcinoma (LAHNSCC). In the HPV (human papillomavirus) positive non-smoker population the cure rate approaches greater than 90%. However, the cure rate can be as low as 50% in HPV negative smokers necessitating newer and more effective treatments. Interestingly, diabetic HNSCC patients taking the biguanide, metformin, have been shown to have superior survival outcomes. However, the mechanism by which metformin results in superior outcomes for these patients is unclear. In vivo, metformin was shown to prevent HNSCC tumor formation in mouse models via activation of AMPK and inhibition of the mTOR pathway. Metformin has also been shown to activate CD8+ T cells and activation of AMPK has been shown to activate NKT cells. Therefore, we hypothesized that the addition of metformin to CRT would be safe and would result in enhanced tumor responses through activation of AMPK and activation of the innate immune system. Here we report our findings on the effect of metformin on the immune system utilizing our phase 1 open label clinical trial (NCT02325401) entitled "Dose-finding Study of Metformin With Chemoradiation in Locally Advanced Head and Neck Squamous Cell Carcinoma".

Materials/Methods: Trial eligibility criteria included newly diagnosed, non-diabetic, LAHNSCC patients eligible for definitive CRT. Patients received a 14-day lead-in of metformin in escalating dose cohorts (1000, 2550, or 3000 mg daily in divided doses) followed by a combination of metformin and standard of care CRT (cisplatin 100mg/m2 days 1, 22, and 43, 70 Gy radiation in 35 fractions) using a modified toxicity probability interval design. Blood was collected before and after metformin treatment and was processed for serum and separation of peripheral blood mononuclear cells (PBMCs). PBMCs were analyzed by flow cytometry to determine immune cell subsets and serum was analyzed by Luminex (Human 10-plex) for cytokine release.

Results: Eighteen patients have been enrolled out of 18 planned patients for dose escalation. Median time to follow-up is 21 months (range 3-29 months). Patient serum ELISA examination revealed overall increases in the pro-tumor immune cytokines TNF-a, IL-2, and decrease in the anti-tumor immune cytokine IL-4 in response to metformin. Metformin treatment also resulted in increased populations of cytotoxic T cells, NK and NKT cells and overall activation of innate immunity. Clinically, median overall survival has not been reached, and in fact, no patients on study have relapsed.

Conclusion: Metformin administration in LAHNSCC results in activation of pro-tumorigenic immunity which may result in enhanced tumor responses and decreased tumor relapse.

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Hypothyroidism and Wound Healing After Salvage Laryngectomy

A. Rosko,[1] A.C. Birkeland,[1] E. Bellile,[2] K.J. Kovatch,[1] A.L. Miller,[3] C.C. Jaffe,[1] A. Shuman,[4] S.B. Chinn,[1] C.L. Stucken,[1] K. Malloy,[2] J.S. Moyer,[1] K. Casper,[4] M.E. Prince,[1] C.R. Bradford,[2] G.T. Wolf,[1] D.B. Chepeha,[5] and M.E. Spector[4]; *[1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [3]Massachusetts Eye and Ear Infirmary, Boston, MA, [4]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [5]University of Toronto, Toronto, ON, Canada*

Purpose/Objective(s): Patients undergoing salvage laryngectomy are predisposed to impaired wound healing secondary to the tissue effects of XRT and CRT, which often results in a pharyngocutaneous fistula. The effects of hypothyroidism on fistula formation and wound healing is not established.

Materials/Methods: A single-institution retrospective case series was performed. Inclusion criteria included preoperatively euthyroid adults who underwent salvage laryngectomy with concurrent neck dissection between 1997-2015 for persistent or recurrent laryngeal squamous cell carcinoma after radiation or chemoradiation therapy (n = 182). The principle explanatory variable was postoperative hypothyroidism (defined as TSH > 5.5 mIU/L). The primary endpoints were pharyngocutaneous fistulae and wounds requiring re-operation. Multivariate analysis was performed.

Results: The fistula rate was 46.7% in hypothyroid patients compared a 22.8% fistula rate in euthyroid patients. In the multivariate analysis, patients who developed hypothyroidism in the postoperative period had a 3.6 times higher risk of fistula (95% CI: 1.8 - 7.1, $P = .0002$). Similarly, hypothyroid patients had an 11.4 times greater risk of developing a fistula severe enough to require reoperation (24.4% versus 5.4%) when compared to euthyroid

patients (95% CI: 2.6 − 49.9, $P = .001$). Additionally, when analyzing TSH as a continuous variable, the risk of fistula ($P = .003$) and fistula requiring reoperation ($P = .001$) steadily increased with increasing TSH. This corresponds to an approximately 12.5% incremental increase in the absolute risk of fistula with each doubling of the TSH and a 10% increase in the absolute risk of fistula requiring reoperation with each doubling of the TSH. While advanced stage, flap reconstruction, and postoperative hypocalcemia were associated with hypothyroidism, no variables aside from hypothyroidism were associated with the formation of a fistula.

Conclusion: Postoperative hypothyroidism independently predicts postoperative wound healing complications. The association of hypothyroidism with fistula formation may yield opportunities to modulate wound healing with thyroid supplementation, or provide a biomarker of wound progression.

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Efficacy and Safety of Three or More Courses of Radiation for Head and Neck Malignancies

A.J. Xu,[1] L. Luo,[2] J.E. Leeman,[3] P.B. Romesser,[1] D. Spielsinger,[4] C. Sabol,[3] T. Waldenberg,[1] T. Brinkman,[3] X. Li,[3] P. Xie,[3] N. Riaz,[3] S. McBride,[1] N. Lee,[3] and C.J. Tsai[3]; *[1]Memorial Sloan Kettering Cancer Center, New York, NY, [2]Massachusetts General Hospital, Boston, MA, [3]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [4]Memorial Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Recurrent head and neck cancers are associated with significant morbidity and mortality. Salvage treatments are poorly defined and the outcomes of more than two courses have not yet been described. In this study, we investigate the safety and feasibility of delivering three or more courses of radiation with overlapping fields in patients with recurrent head and neck malignancies.

Materials/Methods: A single-institution database of 3,063 patients who underwent head and neck radiation between 2011 and 2017 was queried for re-irradiation. Treatments plans were reviewed to identify patients who underwent at least three courses of overlapping radiation. Thirty-six patients were identified with three or more courses of head and neck radiation therapy with overlapping fields. Toxicity was assessed using Common Terminology Criteria for Adverse Events version 4.0. Kaplan-Meier survival analysis was performed to calculate median survival times.

Results: Thirty-six patients were identified with three or more courses of overlapping radiation to the head and neck region. Thirty-two patients underwent treatment for multiply recurrent disease and 4 patients were treated for metachronous head and neck primary tumors. Radiation therapy spanned from 1984 to 2017 and included external beam photon radiation, intraoperative brachytherapy, and proton radiation. Primary tumor sites included skin (10), oral cavity (5), nasal cavity/paranasal sinus (6), nasopharynx (4), salivary gland (4), larynx (4), oropharynx (3), and thyroid (2). Median age at the start of the third radiation course was 64 years of age. Median time intervals were 27 months between the 1st and 2nd courses of radiation, and 14 months between the 2nd and 3rd courses of radiation. Median doses for the 1st, 2nd, and 3rd courses of radiation were 64, 57, and 44 Gy, respectively. Spinal cord, brainstem, and optic nerves were the most common organs at risk that exceeded institutional guidelines. 10 patients (28%) experienced long-term toxicities of grade 3 or higher, including PEG placement (4), soft tissue necrosis (2), bleeding (2), osteoradionecrosis (1), and tracheoesophageal fistula (1). Median survival after completing three courses of radiation was 15.6 months (95% confidence interval 9.2-32.4 months).

Conclusion: Multiple courses of re-irradiation to the head and neck region are feasible with an acceptable toxicity profile.

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Patterns of Oropharyngeal Cancer Failure Detection in the HPV Era

W. Su, B. Miles, M. Posner, P. Som, L. Kostakoglu, V. Gupta, and R.L. Bakst; *Icahn School of Medicine at Mount Sinai, New York, NY*

Purpose/Objective(s): Recent studies have suggested that the majority of newly diagnosed oropharyngeal cancer cases are caused by HPV. It is well known that HPV+ disease behaves differently from HPV- disease and is an important favorable prognostic indicator in oropharyngeal cancers. However, patterns of failure along with failure detection methods in HPV+ patients are not well characterized. Current surveillance imaging guidelines are based on a pre-HPV era and it is unclear whether they are applicable in the HPV era.

Materials/Methods: All HPV+ oropharyngeal cancer patients treated at our institution from 2005-2017 with biopsy proven recurrence were identified. Their failure patterns and methods for recurrence detection were analyzed. Detection of recurrence was classified as symptom-based, detected by routine physical examination, or asymptomatic and detected by surveillance imaging.

Results: Eighteen HPV+ oropharyngeal cancer patients experienced disease recurrence with a median follow up of 42.3 months. 13 (72.2%) of which experienced distant recurrence. Three (16.7%) patients experienced symptoms that led to recurrence being discovered. Overall, 14 (77.8%) patients had asymptomatic recurrence detected based on PET-CT surveillance imaging, and 1 (5.6%) patient had asymptomatic recurrence detected with CT with contrast. Fourteen (77.8%) patients experienced distant recurrence, with the lung (10 patients, 71.4%) being the most common site of metastases, and 4 (28.6%) patients experienced metastases outside of the lung. 4 (22.2%) patients experienced local-regional recurrence. The median time to recurrence was 19.7 months and median survival after recurrence was 16.7 months. Three-year overall survival was 94.4% (95% CI, 84.4-100%). Three-year postrecurrence survival was 83.6% (95% CI, 64.9-100%).

Conclusion: In HPV+ patients, most failures are asymptomatic distant metastases detected by PET/CT. These failures most frequently occur greater than 1 year from treatment completion and have favorable survival despite recurrence. Given that the majority of surveillance data is derived from the pre-HPV era with poor survivals following failure, the role and timing of whole body surveillance imaging should be readdressed in this new patient population.

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SBRT of Recurrent HNC Should be Most Effective in Patients With Nasopharyngeal or Small Volume Lesions

M. Kentnowski,[1] M. Stąpór-Fudzińska,[2] A. Wygoda,[2] T. Rutkowski,[2] B. Pilecki,[2] J. Niedziałek,[2] P. Polanowski,[2] A. Zarudzka,[2] A. Brewczyński,[2] U. Dworzecka,[2] K. Dębiec,[2] D. Księżniak-Baran,[3] A. Bieleń,[2] D. Łożyńska-Podhrebelna,[4] D. Leś,[1] and K. Skadowski[5]; *[1]Institute of Oncology - Maria Sklodowska-Curie Cancer Center, Gliwice, Poland, [2]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [3]Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice, Slaskie, Poland, [4]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [5]Institute of Oncology MSC Cancer Center, Gliwice, Poland*

Purpose/Objective(s): Precise beam-delivery techniques like SRT/SBRT have allowed reirradiation as a potentially curative salvage therapy. It is generally agreed that SBRT remains a reasonable choice of salvage for inoperable recurrence of head and neck cancer, because its GTV-limited dose delivery prevents acute radiation toxicity and offers acceptable treatment tolerance.

Materials/Methods: This is a retrospective analysis of reirradiation of 65 patients with recurrent HNC using microbeam SBRT over 2010-2017. The median age of the patients was 58 years (range, 28−91 years), with 38 males and 27 females. All recurrences occurred in the previously radiated with the dose ≥40 Gy. Patients who received SBRT as a planned boost after primary radiation therapy and those who had second primary tumor outside the reirradiation area were excluded from the analysis. Recurrent HNC characteristics were as follows: according to primary site—24 NPC, 17OPC, 15 OCC, 4 HPC, 3 with nasal cavity, and 2 with LXC; according to T stage—9 T0, 10rT_1, 26rT_2, 13rT_3, and 7rT_4; according to N stage—52 rN_0, 9rN_1, and 4 N_2. Patients had received median dose in PTV of 24 Gy (minimum 5 Gy, maximum 52 Gy, mean: 22, 7 Gy ± 8.65 Gy SD in 1-13 fractions). The median BED (for alpha/beta = 3 Gy) from first radiation was 60.48 Gy (range 46.8-72 Gy), from secondary radiation was 66.7 Gy (range 13.3-121 Gy) and sum of both treatments was 127 Gy (range 62-156 Gy).

Results: The median follow-up time for all reradiated patients was 16 months, and the 2-year overall survival rate was 27%. Estimated prognostic factors for overall survival were: primary site (nasopharynx versus other sites), PTV maximal diameter, and PTV volume. Detailed analysis of PTV maximal diameter and PTV volume showed a lower response rate in patients with tumor diameter greater than 4cm (65%) and volume greater than 21cm^3 (34%), compare to <4cm (80%; $P = .045$) and <21cm^3 group (53%; $P = .008$). The 2-year overall survival rates were 16.4% in the >4cm PTV maximal diameter group and 34% ($P = .003$) in the <4cm PTV maximal diameter group and 22% in the >21cm^3 PTV volume group and 32.5% ($P = .002$) in the <21cm^3 PTV volume group. We recorded 2 incidents of haemorrhage during reirradiation in the >4cm PTV maximal diameter group.

Conclusion: For recurrent HNC patients, the "r" tumor site, the amount of PTV volume, and PTV maximal diameter are significant prognostic factors for patient survival after reirradiation using SBRT.

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Platinum-Based Chemotherapy Plus Cetuximab in Patients With Recurrent or Metastatic Nasopharyngeal Cancer

Y. Ueda, M. Tahara, T. Fujisawa, T. Enokida, and S. Okano; *National Cancer Center Hospital East, Kashiwa, Japan*

Purpose/Objective(s): Platinum-containing doublet chemotherapy regimens are generally considered the standard first-line systemic therapy for recurrent or metastatic (R/M) nasopharyngeal caner (NPC). Gemcitabine (GEM)+Cisplatin (CDDP) demonstrated significant improvement of both progression-free survival and overall survival over 5FU+CDDP for R/M NPC in a phase 3 study, leading to standard of care as first-line therapy for R/M NPC. Although the results of a phase 2 study of cetuximab (Cmab) in combination with carboplatin in patients with heavily pretreated NPC was reported, there was no available data for platinum-based chemotherapy plus Cmab as first-line therapy for R/M NPC. The objective of the currents study was to evaluate safety and efficacy of platinum-based chemotherapy plus Cmab in patients with R/M NPC.

Materials/Methods: We conducted a retrospective review of patients with recurrent or metastatic NPC who were treated with platinum-based chemotherapy plus cetuximab during 2013 to 2017 at our institute. Treatment consisted of CDDP or carboplatin+5FU+Cmab(PFE) or paclitaxel+carboplatin+Cmab(PCE).

Results: Eleven patients were identified; patient characteristics were median age, 54.7 years (36-75); male /female 8/3; PS 0/1/2, 6/5/0; histology WHOI/II/III/ unknown, 2/3/3/3; number of prior chemotherapies 0/1/2/3 2/2/1; treatment regimen: PFE/PCE: 3/8.

Of the 10 patients assessable for efficacy, 1 patient (10%) achieved complete response (CR), 3 patients (30%) with partial responses (PR), 5 patients (50%) with stable disease (SD), and 1 patient (10%) with progressive diseases (PD), in best response. Overall response rate (ORR) was 40% in all patients. The median progression-free survival (PFS) were 5.6 overall, 6.5 for patients treated with PFE, 5.4 months for patients treated with PCE, respectively. The median overall survival (OS) were 25.3 overall, 25.3 for patients treated with PFE, 25.8 months for patients treated with PCE, respectively. A patient who achieved CR has continued to receive Cmab maintenance for 42.3 months. Most common adverse events(AEs) were acne-like rash (81.8%), skin cracks (72.7%), and bone marrow suppression (54.5%). Most common grade 3 AEs were acne-like rash (1 patient) and althralgia (1 patient). Grade 4 AEs were infusion reaction (1 patient) and allergy due to carboplatin (1 patient). No treatment-related death was observed.

Conclusion: Platinum-based chemotherapy plus Cmab demonstrated promising efficacy with ORR 40%, median PFS 5.6 months and OS of 25.3 months, with acceptable toxicities. Cmab in combination with gemcitabine plus CDDP, warrants further investigations.

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Immunomodulation in Novel Cancer Therapies: The Role of CC-motif Chemokine Ligand 21 and Programmed Cell Death Protein 1

K. Badran,[1] P. Pellionisz,[2] A.Y. Han,[2] T. Heineman,[1] S. Saggi,[2] A.N. Goel,[2] S. Sharma,[3] S. Dubinett,[4] and M. St. John[5,6]; *[1]University of California Los Angeles, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA, [3]university of California, Los Angeles, Los Angeles, CA, [4]UCLA, Los Angeles, CA, [5]UCLA David Geffen School of Medicine, Department of Head and Neck Surgery, Los Angeles, CA, [6]Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Purpose/Objective(s): Investigations in immunomodulating therapies for cancer treatment over the past 20 years have flourished. Given the complex tumor microenvironment and differential signaling pathways, a wide variety of potential targeting mechanisms have come to attention. Herein, we review the immunomodulating potential of Chemokine 21 (CCL-21) in preclinical and clinical studies, as well as examine the novel multifaceted immune-based treatments in advanced head and neck cancer.

Materials/Methods: A systematic review of the CC-motif Chemokine Ligand 21 in order to identify the inflammatory historical background, role in cancer, preclinical investigations, and novel polymer-based delivery system was undertaken. Additionally, current ongoing clinical trials were evaluated for impact. Finally, the role of CCL-21 in the head and neck cancer population is reviewed and future pathways discussed.

Results: The role of CCL-21 is critical in promoting DC homing and T-lymphocyte activation. Tumor antigen presentation is significantly amplified both locally and peripherally following introduction of CCL-21. The results of the phase 1 studies in lung cancer and melanoma are promising. CCL21 is important in the formation of tertiary lymphoid structures and their presence in tumors is associated with favorable immune responses.

Conclusion: Based on the findings on CCL21, it is anticipated that the rational combination with immune checkpoint blockade therapy will improve the antitumor benefit of this chemokine in a broad range of solid tumors with low tumor infiltrating lymphocyte frequency (TIL). Future studies could assess the combined efficacy of CCL21-based regimens with immune checkpoint blockade therapy in various solid tumors as immune activation by CCL21 leads to upregulation of PD-1 on activated T cells. CCL21-based therapeutic vaccination approaches will prove beneficial for tumors that are not accessible for intratumoral administration of CCL21. Furthermore, material and nanoparticle engineering provides several attractive strategies to design more potent CCL21 immunotherapy.

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Re-Irradiation of Recurrent Buccal Mucosa Cancer Utilizing Customized Intraoral Mold-Based HDR Brachytherapy

C.A. Rountree, M. Ashenafi, J.B. Martin, R. Hymel, and A.K. Sharma; *Medical University of South Carolina, Charleston, SC*

Purpose/Objective(s): Feasibility of re-irradiation in recurrent buccal mucosa squamous cell carcinoma after definitive external beam radiation therapy utilizing customized intraoral mold HDR brachytherapy,

Materials/Methods: An 82-year-old male with a 3-year history of right buccal mucosal lesions, diagnosed as moderate dysplasia with inability to rule out invasion, was referred to radiation oncology as he was not a surgical candidate. Examination demonstrated extensive erythematous lesions involving the right oral commissure, gingivobuccal sulcus, right anterior tonsillar pillar, and soft and hard palate. He received 70 Gy in 35 fractions with a complete treatment response; however, 6 months later, he presented with stomatalgia and oral mucosa bleeding. Physical examination revealed new ulcerations of the right lower vermillion lip and exophytic plaque-like lesions along the posterior right maxillary alveolar ridge extending to the gingivobuccal sulcus and along the buccal mucosa and hard and soft palate. Biopsy of the tumor demonstrated hyperplastic squamous epithelium with mild to moderate dysplasia. Initially, the patient declined surgical treatment but returned as the tumors became more symptomatic. Subsequently, decision was made to treat with intraoral HDR brachytherapy as this was a previously irradiated field. Impressions were made and a customized mold was embedded with UV exposed low-Z shielding, which allowed for kV CT treatment planning. Eight 6-French catheters were inserted into the mold and a CT scan was obtained to determine the mold composition and needle placement. Modifications were made and a fitting test was conducted to assess reproducibility and comfort. A neck brace was constructed to secure the mold placement. Two CT simulations were obtained: one with contrast to delineate the extent of the tumor, and the other without contrast but with addition of radiopaque markers inside catheters to digitally reconstruct the source path. Rigid registration fused the two CT scans and the clinical target volume (CTV) and mandible were delineated. We prescribed 30 Gy in 10 fractions using the following criteria: CTV target, V90% $\geq$90% (28.6 $Gy_{2/2}$) and mandible, $D_{0.1cc} <$ 28.6 $Gy_{2/2}$ was a hard constraint.

Results: HDR plan produced a CTV $V_{90\%} =$ 90.7%, $V_{200\%} =$ 2.4 cc. Mandible $D_{0.1cc}$ received 25.9 $Gy_{2/2}$. Prior to fraction 6 of 10, the plan was modified to address medial soft palate contours as a result of tumor shrinkage. Adaptive planning on new image data sets used the same criteria as the original plan. Soft palate $D_{0.1cc}$ was reduced by 9%. Patient completed treatment without complications or interruptions. Four months after treatment, he had no evidence of disease recurrence.

Conclusion: This report demonstrates the design and use of non-invasive intraoral mold brachytherapy as a promising treatment modality for complex tumor recurrences within the oral cavity.

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Inhibition of MK2 Decreases Inflammatory Cytokine Production and Tumor Volumes in HPV-Positive and HPV-Negative Models of Head and Neck Squamous Cell Carcinoma

K. Berggren,[1] S. Restrepo Cruz,[1] M.D. Hixon,[1] A. Cowan,[2] M.A. Ozbun,[3] S. Keysar,[4] A. Jimeno,[4] S.A. Ness,[5] D.J. McCance,[6] E.J. Beswick,[7] and G.N. Gan[1]; *[1]Department of Internal Medicine, Section of Radiation Oncology, University of New Mexico School of Medicine, Albuquerque, NM, [2]Department of Surgery, University of New Mexico, Albuquerque, NM, [3]University of New Mexico School of Medicine and Comprehensive Cancer Center, Albuquerque, NM, [4]Department of Medical Oncology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, [5]University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, [6]Department of Pathology, University of New Mexico, Albuquerque, NM, [7]Department of Molecular Genetics and Microbiology, University of New Mexico, Albuquerque, NM*

Purpose/Objective(s): The MAP kinase-activated protein kinase (MK2) pathway is involved in cell differentiation, proliferation, epithelial-to-mesenchymal transition (EMT), and the inflammatory responses in various cancers. Increased MK2 expression is associated with poor outcomes in head and neck squamous cell carcinoma (HNSCC), but it remains unknown if MK2 activity promotes tumor growth and radiation resistance in human papillomavirus positive, p16+ (HPV+) or negative, p16- (HPV-) HNSCC. Our overall hypothesis is that inhibition of MK2 pathway increases tumor radiosensitivity and decreases tumor EMT and growth in both HPV-positive and HPV-negative HNSCC. We evaluated the effect of radiation therapy (RT) alone or in combination with an MK2 inhibitor (MK2i) on cytokine production, EMT gene expression, and on in vitro and in vivo tumor cell growth.

Materials/Methods: HPV+ (UM-SCC47) and HPV- (TU167, HN11) cell lines and HNSCC patient-derived tumor xenografts (PDTXs) were treated with an MK2 inhibitor (MK2i, 50μM), RT (10Gy), or MK2i+RT and compared to untreated controls. Inflammatory cytokine and EMT gene expression was determined by qRT-PCR and protein expression by immunoblot or cytokine array. For in vivo experiments, tumors were initiated from cell lines or PDTXs, and were treated with MK2i (50 μM or 50ug/25g mouse), RT (5Gy), or MK2i+RT to examine tumor growth and survival time compared to control. PDTX phospho-MK2 (pMK2) intensity was analyzed by IHC and quantitated using the HALO digital pathology imaging system.

Results: In both HPV+ and HPV- HNSCC cell lines, RT significantly increased expression of inflammatory cytokines (IL-1α, IL-1β, and IL-6) and EMT (SNAI1, ZEB2, VIM) markers compared to control cells, whereas the addition of MK2i prior to RT treatment significantly decreased pMK2 levels and mRNA expression for all cytokine and EMT genes. MK2i treatments decreased pMK2 expression compared to RT alone in cells by immunoblot and by IHC. The preliminary HPV+ or HPV- xenograft tumors treated with RT and MK2i+RT had decreased tumor volumes compared to MK2i-treated and control mice. Tumors obtained from RT-treated animals had increased mRNA levels of IL-1β, IL-6, TNF-α, and EMT genes (SNAI1, ZEB2, VIM) compared to MK2i and MK2i+RT treated mice.

Conclusion: Inhibition of MK2 activity abrogated RT-induced inflammatory cytokine and EMT gene expression *in vitro* and *in vivo*, and dual MK2i and RT treatments reduced tumor growth in mice compared to RT alone. Work remains ongoing but our findings indicate that MK2 may be a

mediator of radiation resistance in HNSCC, and may be a potential therapeutic target in both HPV+ and HPV- HNSCC.

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Intravascular Redox Homeostasis Regulates NETosis and Cancer Metastasis

M. Inoue,[1] M. Enomoto,[1] Y. Koike,[2] M. Di Grappa,[1] X. Zhao,[1] K. Yip,[1] S.H. Huang,[3] J.N. Waldron,[3] M. Ikura,[1] F.F. Liu,[1] and S.V. Bratman[1]; [1]*Princess Margaret Cancer Centre Research Institute, University Health Network, Toronto, ON, Canada,* [2]*Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Mie, Japan,* [3]*Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Purpose/Objective(s): Neutrophil extracellular traps (NETs) entrap circulating tumor cells (CTCs) and promote the initiation of metastasis within distant organs in preclinical models. These models require artificial and exogenous inflammatory stimuli to trigger NETosis. Thus, it remains unknown whether NETs have a major influence on distant metastasis in cancer patients. The objective of this study was to uncover endogenous regulators of NETs and cancer metastasis that could become new targets for therapeutic and biomarker development. We hypothesized that a reservoir of free thiol in plasma provided by non-oxidized albumin counteracts the formation of NETs and decreases cancer metastasis

Materials/Methods: We measured free thiol levels, albumin concentration and oxidation status, and NET marker proteins within plasma from a cohort of HNSCC patients treated with definitive radiation therapy. For mechanistic analyses of NET induction, human neutrophils were cultured in media with various sources of albumin and free thiol content. NETs were detected by immunocytochemistry, extracellular DNA concentration, and DNA immunoprecipitation followed by immunoblotting for NET marker proteins. Albumin thiols were blocked by chloramine-T or iodoacetamide. NET deposition in mouse lungs was detected by Sytox-Orange staining followed by two-photon microscopy. To model lung metastasis, Cal33 HNSCC cells expressing mCherry or *firefly* luciferase were injected via tail vein followed by fluorescence or luminescence imaging.

Results: Of 22 HNSCC patients analyzed, 8 developed lung metastasis (median time-to-metastasis = 489 days [range: 115-786 days]). A reduction in plasma free thiol and non-oxidized albumin levels was associated with elevated risk of subsequent lung metastasis (log-rank $P = .023$ and 0.009, respectively). A significant increase in NET markers was observed in plasma from patients with low levels of non-oxidized albumin ($P = .008$). Oxidation of albumin thiols led to accumulation of intracellular reactive oxygen species within cultured neutrophils, causing NETosis. In mouse models, blocking of albumin free thiols resulted in enhanced NETosis. NETs were deposited in the lungs where they contributed to the colonization of HNSCC CTCs and initiation of lung metastases. Moreover, we found that CTC trapping and metastasis was abrogated by direct inhibition of NETs through multiple mechanisms.

Conclusion: These results indicate that plasma albumin thiol content is an endogenous regulator of intravascular redox homeostasis and NETosis, thereby representing a potentially generalizable biomarker for the prediction of hematogenous metastasis. Strategies that target albumin thiols and NETs could provide new therapeutic and diagnostic opportunities in combatting cancer metastasis.

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Mutational Profiles of Recurrent Laryngeal Squamous Cell Carcinoma

A.C. Birkeland,[1] J.D. Smith,[1] A. Rosko,[1] R.C. Hoesli,[1] S.K. Foltin,[1] S.B. Chinn,[1] A. Shuman,[2] G.T. Wolf,[1] C.R. Bradford,[3] M.E. Prince,[1] M.E. Spector,[2] and J.C. Brenner[1]; [1]*University of Michigan, Ann Arbor, MI,* [2]*Department of Otolaryngology, University of Michigan, Ann Arbor, MI,* [3]*University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

Purpose/Objective(s): Recurrent laryngeal squamous cell carcinoma (LSCC) after radiation (RT) or chemoradiation (CRT) remains a challenging disease to treat. A better understanding of the genetic drivers in this cohort may lead to more successful prognostication and application of targeted therapies and other treatment regimens. To date, there has been little data on the mutational landscape of recurrent LSCC after RT or CRT. Here, we describe our initial efforts in using targeted sequencing panels in this critical cohort.

Materials/Methods: Patients with biopsy-proven primary (n = 15) or recurrent (n = 21) LSCC from with available tissue from 2000-2012 were identified at the University of Michigan. Clinical, pathologic, and survival data were collected. Formalin-fixed, paraffin-embedded tumor blocks were collected, and DNA was isolated. Amplicon-based DNA sequencing was performed using an AmpliSeq Comprehensive Cancer Panel. Single nucleotide and copy number variants were called. Sequencing results were compared with mutational and survival data from primary LSCC samples from The Cancer Genoma Atlas (TCGA; n = 117).

Results: We identified similarly mutated genes in our recurrent LSCC cohort as in primary LSCC in our cohort and in TCGA, including frequent mutations in *TP53* and *NOTCH1*, and copy number variations in *PIK3CA*, *CDKN2A,* and *CCND1*. Amplifications in *CCND1* (19% vs 7%) and *ERBB2* (14% vs 7%) and mutations in *NOTCH1* (19% vs 7%) were more prevalent in our recurrent LSCC cohort than our primary LSCC cohort. Patients with *CCND1* amplifications tended to have a worse prognosis. Individuals with poor survival with recurrent LSCC had specific targetable aberrations (namely in *PIK3CA* and *CCND1* among other targets).

Conclusion: Recurrent LSCC after RT/CRT and surgery is a deadly disease process, with no current treatment options. These tumors have mutational profiles similar to those of primary LSCC, but may have higher rates of mutations in specific targetable genes. Using sequencing panels in recurrent LSCC, individualized targeted therapies may be applied in these cohorts who otherwise would not have any treatment options. Further investigation in larger cohorts will be needed to characterize the mutational landscape of recurrent LSCC.

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Characterization and Radiosensitivity of HPV-Related Oropharyngeal Squamous Cell Carcinoma Patient-Derived Xenografts

J. Lilja-Fischer,[1,2] B. Ulhøi,[3] J. Alsner,[1] M. Stougaard,[3] M. Thomsen,[3] P. Lassen,[4] T. Steiniche,[3] V. Nielsen,[5] and J. Overgaard[1]; [1]*Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus,*

Denmark, [2]Department of Otorhinolaryngology—Head & Neck Surgery, Aarhus University Hospital, Aarhus, Denmark, [3]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark, [4]Department of Oncology and Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [5]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Purpose/Objective(s): The purpose of this study was to create a number of patient-derived xenografts (PDXs) reflecting the heterogeneity of oropharyngeal squamous cell carcinoma (OPSCC) and compare the models with the corresponding human original tumors. Also, we aimed to determine if the PDX model is suitable for radiation therapy research.

Materials/Methods: Fresh tumor biopsies from patients with primary, untreated OPSCC were implanted subcutaneously in immunodeficient mice. PDX tumors were serially transplanted and expanded, producing generations of PDX tumors with identical origin. PDX tumors and their corresponding human original were compared using histology, immunohistochemistry, gene expression profiling and next-generation sequencing (NGS). Radiosensitivity was assayed by subjecting PDX tumors to low-dose irradiation in a growth delay assay (4-8 Gy, single fraction).

Results: Tumor specimens from 34 OPSCC patients were xenografted, resulting in tumor growth in 20 cases (59%). However, 8 PDX models had a lymphoma-like histologic and immunohistochemical appearance and were disregarded. Further studies were conducted on 12 valid PDX models that retained histological and immunohistochemical features, yielding a final take-rate of 35%. No differences were noted between the full patient cohort and patients giving rise to valid PDXs with regard to HPV status, smoking or tumor characteristics. Although NGS revealed that valid PDX tumors had a mean of 22 genetic variants more than the original tumor ($P<.02$), there was a high concordance between PDXs and original tumors, with more than half of genetic variants retained in the PDX, including important driver mutations in *TP53*, *PIK3CA*, *KMT2D*, *KMT2C* and *NOTCH1*. Gene expression analysis revealed high concordance between PDX and original tumors with regard to expression of HPV oncogenes *E6* and *E7*. However, there were notable differences in tumor microenvironment parameters with PDX tumors showing higher expression of hypoxia-related genes and lower expression of genes related to inflammation and low-dose irradiation of PDX tumors resulted in a reproducible growth delay. Radiosensitivity studies revealed that the most radiosensitive PDX models were HPV-positive, although one HPV-positive PDX model was relatively radioresistant.

Conclusion: It is possible to generate PDX models from OPSCC patients that reflect differences in etiology with regard to HPV and smoking. Most PDX models retain histological and immunohistochemical features as well as important driver gene alterations. There are some differences related to tumor microenvironment and immune response. Overall, the PDX model is a promising high-fidelity research tool that may aid in development of personalized medicine. Perspectives include biomarker development, testing of targeted therapies, and improvement of radiation therapy.

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Mutational Landscape of Human Papillomavirus—Associated Oropharynx Squamous Cell Carcinoma in Patients Treated on a Phase 2 De-intensified Chemoradiation Trial

D.H. Moon,[1] Z. Mahbooba,[1] X. Zhao,[1] H. Jo,[1] R.J. Amdur,[2] W.M. Mendenhall,[3] N.C. Sheets,[1] M. Weissler,[1] T. Hackman,[1] A. Zanation,[1] B. Thorp,[1] S. Patel,[1] J. Weiss,[1] J. Grilley-Olson,[1] D.N. Hayes,[1] and B.S. Chera[1]; *[1]University of North Carolina Hospitals, Chapel Hill, NC, [2]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [3]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL*

Purpose/Objective(s): Next-generation sequencing (NGS) technique was used to analyze the mutational landscape of a cohort of patients with favorable risk human papillomavirus (HPV)—associated OPSCC prospectively treated with de-intensified chemoradiation therapy.

Materials/Methods: Patients with confirmed HPV- or p16-positive OPSCC, ≤10 pack-years smoking history or abstinent for the past 5 years, and ECOG performance status 0-1 were enrolled on a phase 2 de-intensification trial (NCT01530997). All patients were treated with intensity-modulated radiation therapy (RT) to a total dose of 60 Gy in 2 Gy fractions + concurrent weekly cisplatin (30 mg/m^2) (patients with T0-T2 N0-N1 received RT only). A separate informed consent was obtained for the use of tumor samples from the initial biopsy specimen pretreatment to identify genetic aberrations of prognostic or therapeutic significance via a NGS assay protocol (NCT01457196). Targeted panel of >200 cancer-associated genes from tumor DNA were sequenced and filtered via an identical pipeline in reference to 20 non-malignant specimens.

Results: Forty-three patients were enrolled for NGS. Median age was 58; 81% of patients were male; and 53%, 35%, and 12% were never smoker, ≤10 pack-year smoker (PYS), and >10 PYS, respectively. Frequency of clinically relevant mutations are shown in the Table. Interestingly, mutations most commonly associated with HPV-negative tumors and tobacco use were present in a subset of tumors including FAT1 (20.9%), AJUBA (9.3%), FGFR1 (9.3%), CDKN2A (2.3%), and TP53 (2.3%). At a median follow-up of 16 months, 2 of the 43 patients had progression of disease. First patient (55 yo white male, T2N2b, ≤10 PYS, right lung recurrence) had paucity of notable mutations while the second patient (37 yo white female, T2N2b, never smoker, left neck recurrence) had multiple significant mutations including PIK3CA, CDKN2A, TP53, RB1, NOTCH3, MYCN, FBXW7, and FAT1.

Conclusion: Our study confirms notable frequently mutated genes including PIK3A, NOTCH1, FGFR3, FBXW7, ZNF750, FAT1, KMT2C, and KMT2D in a cohort of favorable risk HPV-associated OPSCC. Better understanding of relevant genetic aberrations may aid patient selection for de-intensification and the development of predictive biomarkers in this favorable and increasing subset of OPSCC.

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Mechanism/ pathway	Gene	N (%)
Cell cycle	RB1 CDKN2A	3 (7.0) 1 (2.3)
Receptor tyrosine kinases	FGFR3 IGF1R FGFR1 FGFR2	8 (18.6) 4 (9.3) 4 (9.3) 1 (2.3)
Oncogenes	MYCN KRAS	3 (7.0) 2 (4.7)
Differentiation	FBXW7 ZNF750 NOTCH1	11 (25.6) 10 (23.3) 9 (20.9)
PI3K pathway	PIK3CA PIK3R1	13 (30.2) 1 (2.3)
Immune evasion	HLA-A TRAF3 B2M	5 (11.6) 3 (7.0) 2 (4.7)
Tumor suppressor gene	KMT2D (MLL2) KMT2C (MLL3) FAT1 NF1 TP53	16 (37.2) 12 (27.9) 9 (20.9) 3 (7.0) 1 (2.3)

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A Systematic Algorithm for Metabolically Based Sensitization to Cisplatin in Head and Neck Squamous Cell Carcinoma

W. Yu,[1] Y. Chen,[2] N. Putluri,[1] F. Stossi,[1] S. Lai,[3] and V.C. Sandulache[1]; *[1]Baylor College of Medicine, Houston, TX, [2]MD Anderson Cancer Center,*

Houston, TX, [3]The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX

Purpose/Objective(s): Cisplatin is the most commonly utilized systemic agent in the setting of head and neck squamous cell carcinoma (HNSCC). Despite nearly half a century of clinical use, our understanding of cisplatin activity in HNSCC and the primary drivers of its effectiveness or lack thereof, remains limited. Here we undertook a systematic evaluation of cisplatin processing and effects on HNSCC cell death in order to develop a broadly applicable approach for chemo-sensitization.

Materials/Methods: Established HNSCC cell lines were chosen to represent the relative frequency of oncogenic events common to HNSCC (ie, *TP53* mutation, HPV activation, *NOTCH* mutation). In vivo experiments were carried out using a xenograft murine model. Induction coupled plasma mass spectrometry was used to measure cisplatin transport and DNA-binding. DNA damage secondary to oxidative stress was measured using quantitative gammaH2AX phosphorylation and foci formation. Cisplatin effects on cell death were measured using individual assays for senescence, apoptosis, mitotic catastrophe, as well as the clonogenic survival assay. Cisplatin-generated metabolic shifts were measured using both steady-state metabolomics interrogation and ^{13}C kinetic experiments.

Results: HNSCC cells import cisplatin in a dose- and time-dependent fashion but only a small fraction of cisplatin is bound to DNA following acute exposure. Cisplatin generated oxidative stress is a critical driver of cisplatin toxicity in HNSCC across molecular backgrounds. Mechanisms of cell death vary by genomic background and are not predictive of relative cisplatin sensitivity. Cisplatin transport, neutralization by thiol moieties, and DNA-damage repair are dependent on energy (ATP) and reducing equivalents (NADH, NADPH). Cisplatin exposure triggers measurable changes in central carbon flux, particularly in the conversion of pyruvate into lactate due to NADH depletion; compensatory changes in the citric acid cycle and pentose phosphate pathway are insufficient to restore reducing equivalent levels and are not consistent across molecular backgrounds. Direct measurements of intratumoral pyruvate and lactate correlate with relative cisplatin toxicity under in vivo conditions. Targeted inhibition of glycolytic flux potentiates cisplatin toxicity through (1) altered transport, (2) prolonged oxidative stress, and (3) decreased DNA repair (via PARP).

Conclusion: Cisplatin toxicity in HNSCC is largely driven by non-specific oxidative stress across molecular backgrounds. Lactate dehydrogenase (LDH) activity appears to be both a marker of cisplatin toxicity and a potentially suitable target for metabolic targeting in HNSCC resistant to cisplatin. Conversely, metabolic targeting of non-glycolytic metabolic pathways is unlikely to be successful in sensitizing HNSCC cells to cisplatin across molecular backgrounds.

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Targeting Single and Multiple Cell Signaling Pathways in Combination With Radiation in Head and Neck Cancer

G.D. Wilson,[1] S. Galoforo,[2] K.G. Blas, Jr,[3] T.G. Wilson,[4] A. Hana,[4] M. Dabjan,[4] and B. Marples[5]; *[1]Department of Radiation Oncology, Beaumont Health System, Royal Oak, MI, [2]Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI, [3]Beaumont Health, Royal Oak, MI, [4]William Beaumont Hospital, Royal Oak, MI, [5]University of Miami Miller School of Medicine, Department of Radiation Oncology, Miami, FL*

Purpose/Objective(s): The greatest gains for HPV-negative head and neck cancer (HNSCC) are likely to be made by the development of novel therapies based on molecular targeted agents, DNA damage response exploiting drugs and immunotherapeutic approaches combined with chemoradiation. In this pre-clinical study, we report the combination of radiation with 4 different molecular targeted agents.

Materials/Methods: Two low-passage HNSCC cell lines/xenograft models were used, UT-SCC-14) and UT-SCC-15, based on their reproducible growth and their differing mutational landscape and radiation and drug sensitivity. Single and dual inhibition of the EGFR/RAS/RAF/MEK and PI3K/AKT/mTOR pathways in combination with fractionated (3 weeks) radiation (RT) was studied using tumor growth inhibition, overall survival and molecular analysis of pathway inhibition. The drugs used were 1) binimetinib, a potent inhibitor of MEK1/2, 2) buparlisib, a specific oral inhibitor of the PI3K family, 3) gedatosilib, a highly potent dual inhibitor of PI3Kα, PI3Kγ, and mTOR, and 4) dacomitinib, an irreversible pan-ErbB inhibitor.

Results: The table summarizes the growth delay data. Briefly, dacomitinib proved to be the most effective agent alone or in combination with RT in both models. Gedatosilib delayed growth alone but did not enhance RT. Buparlisib was not effective in UT-SCC-14 either alone or in combination with RT but significantly inhibited growth in UT-SSC-15 both alone and with RT. A similar result was found with binimetinib. Combining buparlisib and binimetinib elicited a significant growth delay in both tumor models but combining gedatosilib and dacomitinib was no more effective than dacomitinib alone. Combining two agents with RT did not enhance growth delay compared to one effective agent alone. The growth delay and survival data correlated with the ability of the agents with or without RT to downregulate key signaling proteins.

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	UT-SCC-14	UT-SCC-15		UT-SCC-14	UT-SCC-15
Con	24.9 ± 3.6	29.8 ± 2.3	Con	18.2 ± 3.5	33.3 ± 5.8
RT	63.3 ± 6.8	99.6 ± 5.6	RT	77.0 ± 4.9	132.2 ± 4.3
BUP	28.5 ± 1.4	85.0 ± 4.4	DAC	51.4 ± 3.8	87.7 ± 9.9
BIN	28.4 ± 3.9	82.3 ± 7.1	GED	27.9 ± 3.1	70.4 ± 10.6
BUP/BIN	36.2 ± 2.9	108.0 ± 8.5	DAC/GED	47.0 ± 5.6	96.0 ± 6.5
BUP/RT	64.2 ± 0.6	160.2 ± 9.8	DAC/RT	146.1 ± 10.8	156.0 ± 13.2
BIN/RT	97.0 ± 10.6	123.9 ± 8.1	GED/RT	88.8 ± 7.6	100.3 ± 4.6
BUP/BIN/RT	101.8 ± 11.1	112.6 ± 9.9	DAC/GED/RT	148.2 ± 7.8	176.4 ± 17.4

Conclusion: The data from this study show promising agents in combination with RT but variability of response between different xenografts. The molecular basis for this variability will be discussed but dacomitinib has emerged as a promising agent to be considered for clinical studies.

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Genetic Mutations in KEAP/NFE2L2 Associated With Radiation Resistance in Early-Stage Laryngeal Squamous Cell Carcinoma: A Case Series

D. Farquhar,[1] S. Sheth,[2] A. Mazul,[3] P. Little,[4] D.N. Hayes,[4] and J.P. Zevallos[5]; *[1]University of North Carolina Hosptials, Chapel Hill, NC, [2]University of North Carolina Hospitals, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill, NC, [4]UNC School of Medicine, Chapel Hill, NC, [5]Washington University School of Medicine, St. Louis, MO*

Purpose/Objective(s): Radiation therapy (RT) is a major treatment modality for patients with laryngeal squamous cell carcinoma (LSCC). It is well documented that a subset of patients will experience RT failure, however the mechanism of RT resistance remains poorly understood. In this case series, we used an a priori list of the somatic genes associated with RT resistance. In a preplanned analysis of two study cohorts (1) all LSCC patients and (2) early-stage LSCC patients with nonoperative management, we compared mutational profiles using targeted next-generation DNA sequencing (NGS) stratified by radiation-resistance (RR) and radiation-sensitivity (RS).

Materials/Methods: Tumor samples were sequenced by NGS using UNCSeq Version 8.0. All samples were eligible regardless of TNM stage,

HPV status, or treatment with RT alone, concurrent chemotherapy, or upfront laryngectomy. We defined radiation-resistance as persistent or recurrent disease within 3 years of receiving treatment. Early-stage LSCC was defined as stage I or II tumors without lymph node involvement. Candidate genes associated with the radiation resistance included NFE2L2, KEAP1, CUL3, HRAS, NRAS, NOTCH2, NOTCH3, KRAS, RAF1, BCL-2, and BIRC5.

Results: Twenty LSCC tumors were categorized as either radiation sensitive (RS, N=9) or radiation resistant (RR, N=11). Six were early-stage tumors (RR: N=3 and RS: N=3). Basic demographic factors were balanced between the 2 groups. Among all 20 samples, we found increased somatic mutations in the NOTCH pathway in RR patients (NOTCH 2: 44% vs. 0%, $P = .04$; NOTCH 3 44% vs. 11%, $P = .19$). In the 6 early-stage LSCC patients, we found all 3 RR tumors to have mutations in the KEAP1/NFE2L2 pathway, while none of the RS tumors had mutations ($P = .014$).

Conclusion: In RR patients, there was a higher somatic mutational burden involving the NOTCH family. Interestingly, all early-stage LSCC patients with RR (N=3) had mutations in the KEAP1/NRF2 oxidative stress pathway. In LSCC patients, downregulation of the KEAP1/NRF2 oxidative stress pathway may result in RT resistance. Further validation in a larger population is warranted. Alterations in both the NOTCH and KEAP1/NRF2 oxidative stress pathway may serve as genomic determinants to predict radiation resistance in LSCC.

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Radiosensitization Through Targeting Molecular Alterations in Adenoid Cystic Carcinoma

A.D. Swick,[1] A.M. Javaid,[1] P. Prabakaran,[1] K.P. Nickel,[1] R. Hu,[2] G.K. Hartig,[3] J.Y. Bruce,[4] and R.J. Kimple[1]; *[1]Department of Human Oncology, University of Wisconsin, Madison, WI, [2]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, [3]Department of Surgery, Division of Otolaryngology and Head and Neck Surgery, University of Wisconsin, Madison, WI, [4]Section of Hematology Oncology, Department of Medicine, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Adenoid cystic carcinoma (ACC) is a relatively rare cancer that typically arises in salivary tissues of the head and neck. There are currently no approved systemic agents for ACC and no data supporting the delivery of chemoradiation for ACC patients. The scarcity of validated model systems has hampered research efforts. We report the establishment and propagation of an ACC patient−derived xenograft (PDX), genomic evaluation of cancer-associated mutations, and in vivo response profiles to personalized radiosensitization agents based on next-generation sequencing.

Materials/Methods: An ACC PDX was established and maintained in NOD-SCID gamma (NSG) mice directly from the patient. Common cancer-associated mutations were identified using the Illumina TruSeq Amplicon Cancer panel. PDXs were treated with focal radiation or chemotherapy selected based on the genomic profile of the cancer. Focal radiation was delivered at 5 Gy x 8 fractions twice weekly for 4 weeks. Tumor size was measured over time and comparisons between treatment groups made by repeated measures ANOVA. Target inhibition in vivo was confirmed via western blot of tumor lysates and IHC of FFPE tissue.

Results: The histologic and physical characteristics of the primary human tumor are maintained in this ACC PDX. Mutations in the receptor tyrosine kinases (RTKs) cKit and KDR/VEGFR2 were identified. No mutations were identified in EGFR, RAS, or PIK3CA. Several targeted therapies were selected including dovitinib, a multi-RTK inhibitor, BEZ235, a PI3K/mTORC inhibitor, and cetuximab, an EGFR mAB. Target inhibition was confirmed by western blot and IHC. Radiation temporarily halted tumor growth. Treatment with molecularly targeted agents prolonged time to tumor doubling compared to control treatment ($p<0.05$ for each). Chemoradiation resulted in significant tumor regression which persisted more than 2 months after the end of treatment.

Conclusion: PDXs are a powerful model system for investigating potential radiosensitizers based on individual tumor characteristics. Our ACC PDX represents one of only a handful of tools for studying this rare disease. These preliminary data identify the rationale to investigate selected molecular drug/radiation combinations for ACC, particularly when driven by tumor-specific genetic biomarkers. Expansion of these studies may be valuable to advance the design of new treatment strategies for ACC.

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Therapy Resistance in Head and Neck Cancer Stem Cells

A.M. Maas, L.J. Abel, H. Barnwell, A. Bo, L.J. Sudmeier, K.P. Nickel, and R.J. Kimple; *Department of Human Oncology, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Cancer stem cells (CSC) can play an important role in cancer recurrence due to their resistance to therapy. We sought to identify and characterize the CSC population in head and neck cancer cell lines and to identify approaches to improve the therapeutic index in these difficult to treat cancers.

Materials/Methods: CSCs were identified by their ability to grow as tumorspheres on low-attachment plates. Flow cytometry of CSCs was used to confirm CSC specific activities. CSCs were expanded by growing tumorspheres in suspension culture. Tumorigenicity was assessed by injecting 50 and 500 cells subcutaneously in nude mice. Expression of stem cell related genes (NANOG, OCT4, SOX2) was assessed by quantitative real-time PCR and in situ hybridization. Radiation and chemotherapy resistance was assessed by colony formation assay.

Results: Sphere frequency (spheres formed/cell plated) in head and neck cancer cell lines ranged from 0.3% to 5.0% and were seen in 17 of the 19 investigated cell lines. A subset of cell lines was selected for further analysis (2 non-sphere forming and 5 sphere forming). Sphere-forming cell lines had higher ALDH activity, and a greater proportion of side-population cells than non-sphere forming cell lines. Cells derived from tumorspheres displayed higher expression of stem cell marker genes Nanog, OCT4 and SOX2 compared to differentiated attached cells. SOX2 expression was assessed in a TMA from patients with known therapy response. A trend toward higher SOX2 expression was seen in patients with disease persistence compared to those with disease control (P=ns). Data extracted from the Recurrent and Metastatic Head and Neck Cancer dataset from The Cancer Genome Atlas revealed worse overall survival in patients with alteration in SOX2 ($P = .02$). Subcutaneous flank tumors were established in nude mice when injected with as few as 50 (13/16) and 500 (15/16) spheroid derived cells whereas non-CSCs did not initiate any tumors under identical conditions. Sphere-initiating cells demonstrated resistance to radiation and conventional chemotherapies compared to differentiated attached cells. Cetuximab and cisplatin were shown to have minimal effects on sphere formation and sphere frequency (average surviving fraction [SF]: 1.01 and 0.913). Radiation had a moderate effect on sphere formation and frequency in UM-SCC47 (average SF: 0.679), but had minimal effect on UM-SCC6 (average SF: 0.962).

Conclusion: Cancer stem cells can be identified in existing head and neck cancer cell lines, are capable of forming tumors in nude mice, and are resistant to treatments typically used for the treatment of head and neck cancer. The presence of CSCs correlates with worse outcomes in head and neck cancer patients.

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Testing Personalized Medicine Using Patient-Derived Xenografts of Head and Neck Cancer

A. Swick,[1] L.J. Abel,[1] K.P. Nickel,[1] R. Hu,[2] D.T. Yang,[2] J.Y. Bruce,[3] M.E. Witek,[1] G.K. Hartig,[4] T.M. McCulloch,[4] A. Wieland,[4] P.M. Harari,[1]

P.F. Lambert,[5] and R.J. Kimple[1]; *[1]Department of Human Oncology, University of Wisconsin, Madison, WI, [2]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, [3]Section of Hematology Oncology, Department of Medicine, University of Wisconsin, Madison, WI, [4]Department of Surgery, Division of Otolaryngology and Head and Neck Surgery, University of Wisconsin, Madison, WI, [5]Department of Oncology, University of Wisconsin, Madison, WI*

Purpose/Objective(s): We have established a repository of head and neck cancer patient–derived xenografts (PDXs) to support the translational mission of the University's Head and Neck Cancer SPORE. We have used mutational profiling of these tumors to identify actionable cancer associated mutations to match tumor to targeted therapy.

Materials/Methods: PDXs are established with fresh tissue obtained through the University's Translational Sciences Biocore BioBank. Tumor is implanted into nod-SCID gamma (NSG) mice, passaged, and cryopreserved. Tumor identity is confirmed by short tandem repeat testing of patient tumor and PDX. Passage-to-passage stability is assessed by histologic and immunohistochemical analysis. Common cancer-associated mutations are assessed using an amplicon sequencing approach. Tumor size is measured over time and comparisons between treatment groups are made using the extra-sum-of-squares f test.

Results: We have established 40 head and neck cancer PDXs. These derive from a diverse group of patients reflecting heterogeneity in primary tumor site, nodal disease, and overall AJCC staging. Most (38/40) are squamous cell carcinomas, however one adenoid cystic carcinoma, and one NUT midline carcinoma have been established. HPV- PDX comprise the majority although we have been successful at establishing 4 HPV+ PDXs. Mutational analysis has identified expected alterations based on previously reported large scale sequencing of human tumors. Contrary to expectation, activating mutations in PIK3CA show poor correlation with response to the epidermal growth factor receptor inhibitor cetuximab or to downstream inhibition of the MTOR complex.

Conclusion: This growing repository of PDXs have been established from a broad spectrum of head and neck cancers. They represent a powerful experimental model system for investigating potential cancer therapies including personalized medicine.

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Hafnium Oxide Nanoparticles as a Promising Emergent Treatment for Head And Neck Cancer

C. Le Tourneau,[1] V. Calugaru,[1] J.O. Thariat,[2] C. Florescu,[3] X. Mirabel,[4] F. Jegoux,[5] T. Jouffroy,[1] J. Rodriguez,[1] C. Hoffmann,[1] B. Dodger,[6] V. Moreno Garcia,[7] M. Dimitriu,[8] L. Levy,[8] and E. Calvo[6]; *[1]Institut Curie, Paris, France, [2]Centre Antoine-Lacassagne, Nice, France, [3]CENTRE FRANCOIS BACLESSE, caen, France, [4]Centre Oscar Lambret, Lille, France, [5]Centre Hospitalier Universitaire de Rennes, Rennes, FL, France, [6]START Madrid, Madrid, Spain, [7]Hospital Fundación Jimenez Diaz, Madrid, Spain, [8]Nanobiotix, Paris, France*

Purpose/Objective(s): In the treatment of head and neck cancer, tumor response has been improved by combining radiation therapy (RT) with chemical agents, radiosensitizers and monoclonal antibodies. However, these associations come with challenging limitations in terms of pharmacology, local control, clinical outcome benefits or patient quality of life. In addition, high doses of radiation may result in several undesired reactions which underline the need for new therapeutic approaches. A new class of material with high electron density, hafnium oxide, was designed at the nanoscale in the form of crystalline 50-nm particles (HfO_2-NP) to efficiently absorb ionizing radiation and increase the radiation dose deposited—"hot spots" of energy deposit—from within the tumor cells to more focused and efficient cell killing.

Materials/Methods: Preclinical studies have demonstrated increase of cancer cell deaths in vitro and marked antitumor efficacy in vivo in the presence of these nanoparticles (HfO_2-NP) exposed to RT, when compared to RT alone. Hafnium oxide nanoparticles efficacy was assessed in cancer epithelial and mesenchymal tumor models and on patient-derived tumor xenografts in nude mice, showing superior antitumor effects over RT alone in terms of complete response and overall survival.

Results: HfO_2-NP (NBTXR3), administered as a single intratumoral injection and activated by RT, is currently evaluated in a phase 1 clinical trial for head and neck cancer [NCT01946867]. So far, patients treated in phase 1 showed good local and systemic tolerance to the product up to the highest dose level and received RT as planned, confirming a very good local safety profile. Regarding the patients, the durability of response so far is superior to 13 months, with some patients at 16 and 22 months follow-up without recurrence.

Conclusion: NBTXR3 nanoparticles constitute a rising hope for head and neck cancer patients as it could lead to a decrease in the long-term adverse effects of RT and an improvement in quality of life, associated with strong locoregional control. Besides, NBTXR3 + RT is also evaluated in clinical trials for soft tissue sarcoma, prostate, liver and rectum cancer and is showing promising results in terms of benefit-risk ratio assessment and efficacy, leading us to believe in its bright prospects for the treatment of head and neck cancer.

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The Effect of MATE1 Polymorphisms on Cisplatin Efficacy in the Treatment of Head and Neck Cancer

M. Mahler,[1] W. Teft,[2] D. Breadner,[3] N. Bukhari,[2] S. Kuruvilla,[4] A. Nichols,[5] D.A. Palma,[6] R. Kim,[2] and E. Winquist[4]; *[1]Schulich School of Medicine, Western University, London, ON, Canada, [2]Western University, London, ON, Canada, [3]LRCP, London, ON, Canada, [4]Department of Oncology, Division of Medical Oncology, Western University, London, ON, Canada, [5]Department of Otolaryngology, Western University, London, ON, Canada, [6]Department of Oncology, Division of Radiation Oncology, Western University, London, ON, Canada*

Purpose/Objective(s): *MATE1* (multidrug and toxin extrusion protein 1/SLC47A1) has an important role in the renal and biliary excretion of endogenous and exogenous organic cations including a number of therapeutic drugs. We recently reported that homozygosity for a single nucleotide polymorphism in *MATE1* (rs2289669) (A/A) was independently protective for cisplatin-related ototoxicity in patients with head and neck squamous cell carcinoma (HNSCC) receiving cisplatin-based chemoradiation. To evaluate whether *MATE1* A/A status had any effect on treatment efficacy we examined cancer outcomes in a subset of our patients expected to have a poorer prognosis.

Materials/Methods: Patients were identified from a prospective, single-center, observational cohort study of 200 HNSCC patients treated with curative intent cisplatin-based chemoradiation. Patients with HPV-related oropharyngeal and primary unknown cancers were excluded. Germline allelic variants of *MATE1* were identified using TaqMan allelic discrimination assays as previously described. The disease specific survival and overall survival of patients with the otoprotective *MATE1* homozygous A/A variant were compared to those *MATE1* wild type (G/G) and heterozygous (G/A) using the log-rank test.

Results: A total of 10 non-HPV-related HNSCC patients were identified and included in the analysis. Median follow-up was 33 months. Twenty-eight (25.7%) patients had disease progression or recurrence and 30

(27.5%) patients died. Sixteen (14.7%) patients expressed the *MATE1* A/A variant. Median disease specific survival was 46.2 months in the *MATE1* A/A patients and not reached in the G/G and G/A patients (hazard ratio 0.66 [95% confidence interval, 0.23 to 1.82]; $P=.42$). Median overall survival was 55.27 months in the *MATE1* A/A patients but also not reached G/G and G/A patients (hazard ratio 1.22 [95% confidence interval, 0.46 to 3.27]; $P=.17$).

Conclusion: Presence of the *MATE1* A/A polymorphism did not compromise treatment efficacy in HNSCC patients receiving cisplatin-based chemoradiation. A small sample size and short duration of follow-up are limitations of our data. The *MATE1* A/A polymorphism is associated with reduced ototoxicity risk from cisplatin without reduced anticancer activity and warrants further investigation in the treatment of HNSCC.

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Predictors of Response to Cetuximab, Cisplatin, and Radiation Within a Head and Neck Cancer Cell Line Repository

L.J. Abel,[1] H. Barnwell,[1] A. Bo,[1] R.A. Alexandridis,[2] C. Longhurst,[2] K.P. Nickel,[1] D.T. Yang,[3] and R.J. Kimple[1]; *[1]Department of Human Oncology, University of Wisconsin, Madison, WI, [2]Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, [3]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI*

Purpose/Objective(s): We have established a head and neck cancer cell line repository to support the translational research efforts of the University's Head and Neck Cancer SPORE grant. To aid investigators in model selection, we have assessed the response of these cells to standard treatments including cisplatin, cetuximab, and radiation; identified cancer stem cells; and performed comprehensive assessment of cancer-associated mutations and protein expression.

Materials/Methods: Head and neck cancer cell lines were obtained from commercial sources (ATCC, DSMZ, Millipore), cell line identity confirmed by short tandem repeat testing, HPV status assessed by in situ hybridization, protein expression assessed by reverse phase protein array, and cancer associated genomic alterations determined by next-generation sequencing. Colony formation was used to assess cells' response to cisplatin, cetuximab, and radiation. Cancer stem cells were identified by growth in low-attachment plates.

Results: Within a repository of head and neck cancer cell lines average plating efficiency was 6.3% (range 2%-25%). Median surviving fraction after 2 Gy, 30 nM cetuximab, and 10 um cisplatin was 54% (range 24-81%), 32% (range 1%-117%), and 63% (range 17%-111%), respectively. Cancer stem cells were identified in 89% of HNC cell lines by spheroid growth assay, although significant differences in the efficiency of spheroid growth were seen. Comprehensive profiling by RPPA and cancer hotspot mutation sequencing are currently pending.

Conclusion: We have established a repository of head and neck cancer cell lines with molecular and genetic annotation to facilitate head and neck cancer research and aid investigators in selecting a relevant cell line model for their research.

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Nigella Sativa: Protecting the Oral Cavity During X-Irradiation in a Mouse Model

R. Moayer,[1] D. Schaue,[2] G. Fishbein,[3] W.H. McBride,[2] and M. St. John[4]; *[1]University of California Los Angeles Department of Otolaryngology - Head & Neck Surgery, Los Angeles, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]Ronald Reagan UCLA Medical Center, Anatomic Pathology, Los Angeles, CA, [4]UCLA David Geffen School of Medicine, Department of Head and Neck Surgery, Los Angeles, CA*

Purpose/Objective(s): Despite advances in radiation delivery, mucositis and xerostomia continue to be debilitating problems for patients undergoing treatment for head and neck cancers. Nigella sativa oil (NSO) is produced from an annual flowering plant that has shown biochemically reproducible and significant cytoprotective properties through anti-inflammatory and anti-oxidant mechanisms when given orally. The goal of this study is to determine whether topical NSO demonstrates radioprotection in oral cavity tissues in mice.

Materials/Methods: Eight-week old, female C3H mice (n=78) are randomly assigned to five groups. They either receive 15 Gy or 18 Gy to the head according to previously established radiation-induced xerostomia and mucositis models. Topical medication, or sham NSO (saline), is administered according to the following schedule: 1mL applied evenly to oral cavity once daily 3 days prior to radiation, 15 minutes prior to radiation on the day of radiation, and then daily for 14 days following radiation. One control group receives topical NSO (without radiation). Endpoints are histopathological changes and weight loss.

Results: Weight will be monitored throughout as a measure of food intake, and the mucosal reactions scored daily for signs of inflammation, swelling, ulceration and loss of surface integrity. Subgroups of mice will be sacrificed in intervals starting at day 10 post-irradiation and checked for normal tissue responses including ulceration, reduction in intermolar eminence and salivary gland hypofunction. Histological analyses will be performed on tongue, floor of mouth, buccal mucosa, submandibular gland, and parotid tissues by a single pathologist who will grade radiation tissue damage according to previously described scale. T-tests will be performed to detect significant differences between groups and a P-value $<.05$ regarded as statistically significant.

Conclusion: NSO promises to significantly improve the quality of life of head and neck cancer patients undergoing radiation treatment with and without chemotherapy by alleviating debilitating normal tissue toxicity. Additional studies confirming the therapeutic gain (absence of tumor protection) as well as on optimal timing and dosing are warranted if this trial is successful.

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Phase 2 Study of Apatinib, A Novel VEGFR Inhibitor in Patients With Recurrent and/or Metastatic Adenoid Cystic Carcinoma of the Head and Neck: Preliminary Results

S. Dou, L. Zhang, R. Li, and G. Zhu; *Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Purpose/Objective(s): Recurrent/metastatic adenoid cystic carcinoma (ACC) is an incurable disease with no standard treatments. Apatinib is a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2(VEGFR-2). This study was conducted to assess the efficacy and safety of apatinib in patients with incurable, recurrent/metastatic(R/M) ACC of the head and neck.

Materials/Methods: This multicenter, open-label, single arm study enrolled patients with pathologically confirmed recurrent and/or metastatic ACC of the head and neck for whom at least 1 line of systemic chemotherapy had failed as well as a disease radiographic progression was suggested within three months. The primary endpoint of this study was progression-free survival (PFS). Apatinib was administered as 500 mg daily. Secondary endpoints included best objective response (BOR), disease control rate (DCR), overall survival (OS), and toxicity (Clinical trial information: NCT02775370).

Results: Between April 2016 and May 2017, 32 patients were registered and evaluable for efficacy analysis. The median progression-free survival (PFS) of all 32 patients was 4 months (range 1-11 months). Tumor shrinkage was achieved in 24 (75%); 14 (43.8%) had confirmed partial responses (ORR). Seventeen (53.1%) patients had stable disease, 8 of whom had disease stability for > 4 months, DCR was 90.6% (29/32). The recurrent diseases had better response rates than metastatic diseases. Twenty (62.5%) patients experienced dose reduction during treatment. The most common grade 3/4 treatment-related AEs were hypertension (31.3%), hand-foot syndrome (9.4%), proteinuria (12.5%) and fatigue (6.3%). Of three possibly drug-related SAEs recorded in the study, 2 deaths occurred and were both considered to be the result of disease progression. The other one was grade 2 diarrhea needing hospitalization.
Conclusion: Apatinib exhibited objective efficacy in R/M ACC patients with manageable toxicity. Further prospective studies that enroll more patients with longer follow-up time are warranted.
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Acinic Cell Carcinoma of the Major Salivary Glands: Analysis of Prognostic Factors in 2,950 patients

C. Quinn, J.R. Robbins, M.E. Shukla, S. Firat, B. Massey, C.J. Schultz, S. Wong, B. Campbell, and M. Stadler; *Medical College of Wisconsin, Milwaukee, WI*

Purpose/Objective(s): Acinic cell carcinoma is an uncommon neoplasm of the major salivary glands that is typically categorized as a low-grade tumor. However, certain subsets of patients with this disease have a poor prognosis. The purpose of this study was to better assess the prognostic factors influencing survival, with a focus on patients who might benefit from lymph node dissection and/or adjuvant radiation after primary surgical treatment.
Materials/Methods: The National Cancer Database (NCDB) identified 3,100 cases of acinic cell carcinoma of the major salivary glands for the years 2004-2013. A total of 2,950 cases met inclusion criteria and had primary surgical management with documented treatment course and follow-up data. Kaplan-Meier curves were created to evaluate survival outcomes and multivariate Cox regression analysis was used to identify prognostic factors associated with survival.
Results: The 2,857 cases (96.8%) were parotid gland tumors. Of these, 1,960 patients (66.4%) had some extent of regional lymph node sampling, with 453 patients (15.3%) having ≥ 10 lymph nodes removed. A subset of 1,233 patients (41.8%) received postoperative radiation. Kaplan-Meier survival analysis indicated that sex, age, race, insurance status, CDCC comorbidity score, tumor size, lymph node status, and surgical margin status, all had a significant impact on overall survival ($P<.001$). Multivariate analysis demonstrated that tumor size ≥3cm (hazard ratio 2.057, $P<.001$, CI 1.541-2.747) and the number of positive lymph nodes (1 positive node hazard ratio 3.063, $P<.001$, CI 2.046-4.586; >1 positive node hazard ratio 6.320, $P<.001$, CI 4.363-9.156) had the strongest association with decreased five-year survival. Advanced age (hazard ratio 1.050, $P<.001$, CI 1.037-1.063), male sex (hazard ratio 1.485, $P=.011$, CI 1.095-2.013), and positive surgical margins (hazard ratio 1.508, $P=.010$, CI 1.102-2.064) were also associated with decreased five-year survival.
Conclusion: While acinic cell carcinoma is considered a low-grade neoplasm with good overall prognosis, primary tumor size and lymph node involvement have a strong negative impact on survival. This in-depth analysis of various prognostic factors clearly showed these clinical and pathologic factors to be the primary drivers of patient outcomes. This novel observation may be used to help guide patient counseling and overall management of this disease.
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Lymph Node Status	Tumor Size	5-yr Survival (OS)
No positive nodes	< 3 cm	95%
No positive nodes	≥ 3 cm	85%
1 positive node	< 3 cm	78%
1 positive node	≥ 3 cm	55%
>1 positive node	< 3 cm	46%
>1 positive node	≥ 3 cm	36%

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Comprehensive Genomic Profiling and Precision Pathology for Clinically Advanced Salivary Gland Myoepithelial Carcinoma

C.V. Ikpeazu,[1] J.A. Elvin,[2] J. Vergilio,[2] J. Suh,[2] S. Ramkissoon,[3] K. Wang,[2] D. Bowles,[4] H. Somerset,[5] J. Russell,[6] S. Ali,[2] A. Schrock,[2] D. Fabrizio,[2] G. Frampton,[7] V. Miller,[2] P. Stephens,[2] L. Gay,[2] and J. Ross[8]; *[1]University of Miami, Miami, FL, [2]Foundation Medicine, Cambridge, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]TEVA ONCOLOGY, Boston, MA, [5]University of Colorado School of Medicine, Denver, CO, [6]Moffitt Cancer Center, Tampa, FL, [7]Foundation Medicine, Cambridge, MA, [8]Albany Medical College, Albany, NY*

Purpose/Objective(s): Myoepithelial carcinomas of salivary glands (MyC) are generally low-grade malignancies that can arise de novo or in the background of a pre-existing pleomorphic adenoma (CPA). However, on occasion, MyC can present or progress into inoperable locally advanced and/or metastatic disease.
Materials/Methods: DNA was extracted from 40 microns of FFPE sections from 24 cases of relapsed, refractory and metastatic MyC. Comprehensive genomic profiling (CGP) was performed using a hybrid-capture, adaptor ligation-based next-generation sequencing assay. Tumor mutational burden (TMB) was calculated from a minimum of 1.11 Mb of sequenced DNA and reported as mutations/Mb. The results were analyzed for all classes of genomic alterations (GA), including base substitutions (sub), insertions and deletions (short variants), fusions, and copy number changes including amplifications (amp) and homozygous deletions.
Results: At the time of CGP, 10 (42%) MyC were stage III and 14 (58%) were stage IV. Of 22 cases where the primary site was known, 16 (73%) arose in the parotid, 1 (5%) in the submandibular SG, and 5 (22%) from accessory SG.

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MyC cases	24
Genomic alterations (GA)/case	2.3
Clinically Relevant GA (CRGA)	*RICTOR* amp & *PIK3CA* sub (21% each) *PTCH1* & *PDGFRB* sub (8 % each) *NF1* & *BRCA2* sub (4% each)
Non-actionable GA	*CDKN2A* loss (25%) *CDKN2B* & *HRAS* sub (21% each) *TERT*, *MYC*, *TP53* & *NOTCH1* subs (13% each)
TMB > 20 Mut/Mb	2 (8%)
TMB < 10 Mut/Mb	22 *(92%)

* No cases of *ERBB2* GA and no cases of MSI-high status.

Conclusion: Clinically advanced MyC are similar to the usually less aggressive SG tumors, adenoid cystic, and acinic cell carcinomas in having a low frequency of GA, a low *TP53* mutation frequency, low TMB, and general paucity of CRGA when compared to the usually more aggressive adenocarcinomas which may feature targetable driver alterations in *ERBB2* and other pathways. However, the findings of potentially targetable alterations in *RICTOR, PTCH1*, *NF1,* and *BRCA2* and the presence of high TMB, albeit in a relatively small percentage of MyC cases, encourage the continued use of CGP.
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Outcomes Following Radiation Therapy for Anaplastic Thyroid Cancer

A. Bell,[1] J. Ma,[1] B. Lok,[1] J.E. Leeman,[2] C.J. Tsai,[2] E.S. Anderson,[1] N. Riaz,[2] S.M. McBride,[1] I. Ganly,[1] A. Shaha,[1] E. Sherman,[3] and N. Lee[2]; *[1]Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [3]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Anaplastic thyroid cancer is a highly aggressive malignancy with dismal survival rates. The role of radiation therapy for this disease has not been clearly defined. Herein, we report on a large cohort of locally advanced or metastatic anaplastic thyroid cancer treated with radiation therapy in the pre-operative or adjuvant settings.

Materials/Methods: We identified 104 patients who received definitive or postoperative radiation therapy for anaplastic thyroid cancer between 1984-2017. We assessed overall survival (OS), locoregional control (LRC), and distant metastasis (DM) using the Kaplan-Meier method and performed survival analysis using Cox proportional hazard models.

Results: The median age at diagnosis was 63 (range 28-87). The median follow-up was 5.5 months in the entire cohort and 72 months in surviving patients. Twenty-seven patients (26%) had evidence of metastatic disease at diagnosis or developed metastasis prior to radiation therapy start. Ninety-nine patients (98%) received concurrent chemotherapy with radiation, and 52 (50%) received trimodality therapy with surgical resection followed by concurrent chemoradiation. Of those patients receiving surgical intervention, 37 (67%) had close surgical margins and 33 (59%) had positive lymph nodes. Of the patients who received systemic therapy, 70 (70%) received doxorubicin, 25 (25%) received paclitaxel and pazopanib, and 5 (5%) received other systemic agents. Median radiation dose was 5940cGy (range 600-7025cGy). Ninety (87%) patients died at the time of last follow-up. For those patients who were M1 at time of diagnosis (n=27), 10 underwent trimodality treatment and 17 proceeded with chemoradiation only. The median OS for the entire cohort was 5.6 months after initiation of radiation. The 1-year rates of OS and LRC were 31±5% and 81%±5%, respectively. DM was assessed among patients with non-metastatic disease at radiation therapy start (n=76). The 1-year rate of DM in patients with locally advanced disease at diagnosis was 33%±6%. Patients who received a radiation dose >5000 cGy had longer 1-year OS (38% vs. 11%, log-rank $P<.001$) compared to those receiving dose <5000 cGy. Multivariate Cox regression restricting to those patients without DM at diagnosis and controlling for age, sex, surgical status, and concurrent chemotherapy, radiation demonstrated persistent OS benefit of receiving radiation >5000 cGy (Hazard Ratio=0.3; 95% CI=0.2-0.7) and surgical resection (Hazard Ratio=0.5; 95% CI=0.3-0.9). There was no difference in LRC and DM between patients receiving different doses of radiation.

Conclusion: Results from the current study suggest a beneficial role of aggressive radiation therapy in addition to surgical resection in the management of anaplastic thyroid cancer.

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Suboptimal Outcomes in Patients With Cutaneous Squamous Cell Cancer of the Head and Neck With Nodal Metastases Treated With Surgery and Radiation therapy

S. Koyfman,[1] V. Varra,[2] J.L. Geiger,[3] C.A. Reddy,[1] N.P. Joshi,[1] D.J. Adelstein,[3] B.B. Burkey,[4] J. Scharpf,[4] B. Prendes,[4] E. Lamarre,[4] R.R. Lorenz,[4] B. Gastman,[2] B. Manyam,[1] and N.M. Woody[1]; *[1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [4]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): We review outcomes of patients with nodal metastases from cutaneous squamous cell cancer of the head and neck (cSCC-HN) treated with surgery and radiation therapy (RT) to characterize survival, failure patterns, and factors associated with disease recurrence.

Materials/Methods: Patients with a history of cSCC-HN who presented with metastases to the parotid and/or cervical lymph nodes in the absence of a mucosal primary tumor were included in this IRB approved study. All patients underwent parotidectomy, neck dissection and adjuvant ipsilateral RT (median dose 60Gy), with or without concurrent systemic therapy. Patients with distant metastases, satellitosis at the primary site, or who were treated with palliative intent were excluded. Immunosuppressed patients included patients on chronic immunosuppressive medication (e.g. transplants, rheumatic disease) and those with chronic leukemias. Kaplan-Meier analysis was used to calculate disease-free (DFS) and overall survival (OS). Cumulative incidence curves were generated for disease recurrence (DR) which included locoregional (LRF) and distant failure (DF). Univariate (UVA) and multivariate analyses (MVA) for disease recurrence were performed using Cox proportional hazards regression.

Results: Of the 75 patients included in this study (57 immunocompetent; 18 immunosuppressed), the median age was 72 (31-94), and median follow-up was 18 months. Seventy percent of patients were staged as a primary T0/X, while 1%, 17% and 12% were T1, T2 and T4 respectively. The most common nodal stage was N2b (59%) followed by N1/2a (38%) and N3 (3%). Thirty-four patients (45%) had poorly differentiated tumors, 32 (42%) had perineural invasion, 22 (29%) had lymphovascular invasion. Extracapsular extension (ECE) was present in 62 patients (82%) and was similar in the immunocompetent and immunosuppressed cohorts. Eleven patients (14.5%) received cisplatin or cetuximab concurrently with RT. LRF occurred in 18 pts (24%) and DF in 14 (18%). 2yr OS, DFS and DR were 60%, 49% and 40% respectively. Immunosuppressed patients had significantly lower 2 yr DFS (28% vs 55%; $P=.003$) and higher disease recurrence rates (61% vs 34%; $P=.04$) compared to immunocompetent patients. On MVA, immunosuppression (HR 2.2; $P=.05$) and the use of chemotherapy (HR 2.7; $P=.02$) were the only significant predictors of DR. In a separate analysis of only immunocompetent patients, the presence of ECE was the only factor associated with DR ($P<.0001$). No immunocompetent patient failed in the absence of ECE.

Conclusion: Patients with nodal metastases from cutaneous SCC of the head and neck have suboptimal outcomes despite surgery and RT. The presence of ECE and immunosuppression are major drivers of disease recurrence. Treatment intensification in these cohorts, perhaps with immunotherapy, merits investigation.

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Extracapsular Nodal Extension Predicts Death and Recurrence in Merkel Cell Carcinoma (MCC)

G. Rabinowits,[1] E. Harris,[2] T. Chen,[2] A. Giobbie-Hurder,[2] M.M. Reilly,[3] J.D. Schoenfeld,[4] D.N. Margalit,[4] L. Wang,[3] C. Yoon,[3] and M. Thakuria[3]; *[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [2]Dana-Farber Cancer Institute, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Purpose/Objective(s): Stage III Merkel cell carcinoma (MCC) constitutes a heterogeneous group of patients (pts). This study was performed to identify predictors of recurrence and survival among pts with stage III MCC.

Materials/Methods: This is a single-institution retrospective review of stage III MCC pts treated from 1999-2013. Associations were tested between clinical and pathologic features, recurrence status, and overall survival (OS). Age, sex, perineural and lymphovascular invasion, extracapsular nodal extension (ECE) , surgical margin status, and treatment modality and location were collected. Cox regression analysis was used to identify predictors of OS and multivariable logistic regression analysis was used to identify predictors of recurrence.

Results: We identified 127 consecutive pts with recurrence status available. Sixty-one pts had stage IIIA and 66 stage IIIB MCC; 86 (68%) were male and 20 (16%) immunosuppressed. The median follow-up was 64 (56-75) months. Primary tumor sites included extremity (52; 40%); head and neck (33; 26%); trunk (12; 9.4%); unknown primary (30; 23.6%). There were 12 (9.4%) pts with satellite lesions. Ninety-five percent underwent surgery: 15 (12%) had positive surgical margins and 74 (58%) clear margins $\leq$ 5mm at the primary site; and 40 (31%) had lymph node dissection. Twenty-four (19%) pts had ECE and 27 (21%) did not. Ninety-eight percent had radiation therapy (95 [75%] to the primary site and 115 [91%] to the regional nodes); 35% had chemotherapy. Thirty-nine patients had all 3 treatment modalities and 78 did not have chemotherapy. Fifty-eight (46%) pts recurred (31 distant and 27 non-distant). Recurrence was associated with the presence of satellite lesions ($P=.012$), lower extremity (LE) primary site ($P<.001$) and surgical margins $\leq$ 5mm ($P=.002$) or positive ($P=.004$) by Fisher's exact test; and LE primary site ($P<.001$) and ECE ($P=.024$) by multivariable logistic regression analyses. The odds of recurrence for patients with LE as primary site was more than 4 times higher than those with head and neck as primary site (OR:4.22, 95% CI: 1.1-16.1) and those with ECE were almost 5 times higher than the odds for pts without ECE (OR: 5.84, 95%CI: 1.46-23.25). Predictors for decreased OS included age>70 ($P=.046$), immunosuppression ($P=.027$), presence of satellite lesions ($P=.002$), ECE ($P=.026$), surgical margins $\leq$ 5mm ($P=.012$) or positive ($P<.001$), regional node not treated ($P=.004$) by log-rank test; and immunosuppression ($P=.009$), ECE ($P=.028$), and margin $<$ 5 mm ($P<.001$) by Cox regression analysis.

Conclusion: This is the first analysis identifying ECE as an independent predictor of recurrence and mortality for patients with stage III MCC.

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Clinical PET/CT Imaging and Histopathology Demonstrate Expression of Prostate-Specific Membrane Antigen in Salivary Gland Adenoid Cystic Carcinomas

A.P. Kiess,[1] J. Bishop,[2,3] H. Kang,[2] S. Rowe,[2] C. Shen,[4] M. Brummet,[2] D. Eisele,[2] M. Brait Rodriguez,[2] P. Ha,[5] and M.G. Pomper[2]; *[1]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]University of Texas Southwestern, Dallas, TX, [4]University of North Carolina, Chapel Hill, NC, [5]University of California San Francisco, San Francisco, CA*

Purpose/Objective(s): Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancer and mildly expressed in normal prostate, salivary glands, and kidney. PSMA-targeted imaging and therapeutic agents are under investigation in clinical trials. We hypothesized that PSMA may also be expressed in salivary gland malignancies

Materials/Methods: We investigated the expression of PSMA by immunohistochemistry in a variety of human salivary gland malignancies and 11 normal parotid glands using de-identified individual patient samples. We also investigated expression in two tissue microarrays with samples from a total of 88 patients with adenoid cystic carcinoma (AdCC). For 76 patients, there were 3 samples available. Each sample was graded by an expert head and neck pathologist according to H-score (percentage of positive cells x staining intensity ranging 0-3+), and mean H-score was calculated for each patient. In addition, 3 patients with metastatic AdCC were enrolled on an IRB-approved protocol and underwent [^{18}F]DCFPyL PSMA PET/CT imaging according to methods previously published.

Results: We observed elevated luminal expression of PSMA in ductal epithelial cells of adenoid cystic carcinomas, acinic cell carcinomas, and androgen receptor-positive salivary ductal carcinomas. PSMA was also expressed in tumor neovasculature, as observed in most solid tumors. In tissue microarrays of AdCC, PSMA was expressed (mean H-score $\geq$ 5) in 38% of patients and highly expressed (mean H-score $\geq$ 20) in 15%. In normal parotid tissue mean PSMA H-score was 1.8 (s.d. 3.8). In all 3 patients with AdCC who underwent PSMA PET/CT imaging, there was specific uptake in AdCC tumors. The range of SUV_{max} (lean body mass corrected) was 1.0 to 6.3 for AdCC tumors (up to 5 per patient), compared to SUV_{max} of 13.0 to 18.1 for normal parotid glands. Tumor sites included cervical nodal metastases and lung metastases.

Conclusion: We have demonstrated expression of PSMA in human salivary gland adenoid cystic carcinomas using both histopathology and clinical PSMA PET/CT imaging. PSMA-targeted ^{177}Lu-based radiopharmaceutical therapies have shown promising safety and efficacy in patients with metastatic prostate cancer. Such therapies should also be investigated in patients with PSMA-positive AdCC and other salivary gland malignancies.

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Molecular Signatures of Radiation Response in Human-Derived Anaplastic Thyroid Cancer and Poorly Differentiated Thyroid Cancer

A.V. Phan; *University of Colorado Denver, Aurora, CO*

Purpose/Objective(s): Anaplastic thyroid cancer (ATC) and poorly differentiated thyroid cancer (PDTC) are rare yet, highly lethal thyroid tumors. Patients with ATC display heterogeneous tumor responses to radiation therapy, suggesting significant genomic diversity underlying the

radiation survival phenotype. It remains unclear how the molecular profiles of ATC subtypes mediate a radiosensitive (RS) or radioresistant (RR) phenotype. In this study, we sought to identify molecular profiles associated with RR in ATC subtypes by leveraging cancer genomic data with characterized phenotypic radiation survival profiles of ATC and PDTC cell lines.

Materials/Methods: Eight human ATC and PDTC cell lines (C643, SW1736, BCPAP, T238, CAL62, KHM-5M, 8505C, and KTC-2) were profiled using next-generation sequencing and microarray analysis. Clonogenic survival assays were performed for each cell line. Irradiation (IR) was performed at 0, 2, 4, 6, and 8 Gy, and cells were incubated for 8-10 days post-IR. Colonies were counted and survival fractions (SF) were calculated relative to plating efficiency. Data were fitted to the linear quadratic model, producing SF values at 2 Gy (SF2) and 4 Gy (SF4). Cell lines were classified as RR or RS based on SF2 and SF4 values and correlated to mutation profile. Hierarchical clustering was performed to determine the genomic profile of RR and RS cell lines.

Results: We identified five cell lines (8505C, CAL62, KTC-2, KHM-5M, and T238) as being RR and three cell lines (SW1736, BCPAP, and C643) as RS by SF2 and SF4. Several genes were found to be associated with radioresistance. Mutations within Class IA PI3K genes (PIK3CA, PIK3R1, and PIK3R3) were found within RR cell lines. Gene set enrichment analysis of microarray data revealed a gene signature associated with RR cell lines, including genes involved in response to DNA damage (C16ORF5), inflammation (CXCR4), and response to stimulus (VSTM1). Our data also show that cell lines that are RR to conventional 2 Gy regimen might benefit from higher dose per fraction. This suggests that in these cell lines a hypofractionated regimen might provide a higher therapeutic ratio than conventionally fractionated regimen. We are currently testing this in a novel orthotopic model of thyroid cancer.

Conclusion: We developed a genomic signature that is associated with radioresistance in thyroid cancer cell lines. We are currently investigating a novel orthotopic model of thyroid cancer to demonstrate the applicability of genotypic data in a preclinical model.

Author Disclosure: **A.V. Phan**: None.

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Postoperative Therapy for Salivary Gland Adenoid Cystic Carcinomas

R.J. Cassidy III,[1] J. Switchenko,[2] M.W. El-Deiry,[3] R.H. Belcher,[4] J. Zhong,[1] C. Steuer,[5] N.F. Saba,[5] M.W. McDonald,[6] D.S. Yu,[7] T. Gillespie,[8] and J.J. Beitler[9]; *[1]Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [2]Department of Biostatistics & Bioinformatics, Rollins School of Public Health, Atlanta, GA, [3]Otolaryngology, Winship Cancer Institute of Emory University, Atlanta, GA, [4]Otolaryngology, Emory University, Atlanta, GA, [5]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, [6]Department of Radiation Oncology, Winship Cancer Institute at Emory University, Atlanta, GA, [7]Emory University, Atlanta, GA, [8]Department of Surgery, Emory University School of Medicine, Atlanta, GA, [9]Department of Radiation Oncology and Winship Cancer Institute, Emory University, Atlanta, GA*

Purpose/Objective(s): To assess the impact of postoperative radiation on overall survival (OS) for patients with nonmetastatic, definitively resected salivary gland adenoid cystic carcinomas (ACC), as well as to determine patient, tumor, and treatment factors associated with receipt of radiation.

Materials/Methods: The National Cancer Database (NCDB) was queried from 2004 to 2014 for surgically resected nonmetastatic salivary gland ACC. Logistic regression, Kaplan-Meier, and Cox proportional-hazard models were utilized. Propensity-score matched (PSM) analysis was employed to reduce confounding variables.

Results: A total of 3,136 patients met entry criteria: 2,252 (71.8%) received postoperative radiation with 223 (7.4%) also receiving postoperative chemotherapy. Overall, 6.4% of patients were cN+ and 7.4% of patients had unexpected nodal disease after elective neck dissection.

Abstract 253; Table Multivariable Cox-proportional hazard analysis for overall survival

Variable	Level	Hazard Ratio (95% CI)	P-Value
Age (years)	–	1.04 (1.03-1.05)	<0.01
Sex	Male	1.27 (1.03-1.56)	0.02
	Female	–	–
Insurance Status	Not Insured	0.76 (0.45-1.31)	0.33
	Medicaid/Medicare	–	–
	Private	0.67 (0.51-0.89)	<0.01
Charlson-Deyo Comorbidity Score	0	0.72 (0.56-0.94)	
	1+	–	–
Distance to Treatment Facility	<10 miles	0.96 (0.71-1.29)	0.78
	10-50 miles	0.77 (0.57-1.03)	0.08
	>50 miles	–	–
Pathological Stage	I	–	–
	II	1.55 (1.07-2.24)	0.02
	III	2.08 (1.45-3.00)	<0.01
	IVA/IVB	4.29 (3.07-6.00)	<0.01
Surgical Margins	Positive	1.24 (1.01-1.53)	0.04
	Negative	–	–
Receipt of Adjuvant Radiation	Yes	0.93 (0.73-1.19)	0.57
	No	–	–
Treatment Facility	Community Center	1.05 (0.95-1.15)	0.68
	Academic Center	–	–
	Comphrehensive Community Center	1.11 (0.95-1.27)	0.15
Treatment Facility Location	Northeast	1.36 (0.95-1.94)	0.13
	South	1.48 (1.09-2.02)	0.01
	Midwest	1.22 (0.88-1.69)	0.22
	West	–	–

Patients who lived closer to their treatment facility, had advanced pathological stage, and had positive margins were more likely to receive postoperative radiation. Black patients and uninsured patients were less likely to receive radiation. Older age, male sex, advancing stage, and positive surgical margins were associated with worse OS. Patients with private insurance and lower medical comorbidities had improved OS (see table). Receipt of postoperative radiation had no association with OS on Kaplan-Meier or Cox proportional-hazard models. After PSM, when balancing for cofounders, postoperative radiation remained unassociated with OS (HR = 0.98, 95% CI: 0.74-1.30).

Conclusion: In this NCDB series of nonmetastatic resected salivary gland ACC, postoperative radiation was frequently given with a minority also receiving chemotherapy. Black patients and uninsured patients were less likely to receive radiation. Postoperative radiation had no association with OS, even when balancing for patient, tumor, and treatment variables.

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Prognostic Value of Upfront Nonsurgical Management and/or Surgical Margin Status for Advanced Sinonasal Malignancies

Y. Yu, I. El-Sayed, M.W. McDermott, P.V. Theodosopoulos, C. Glastonbury, and S.S. Yom; *University of California, San Francisco, San Francisco, CA*

Purpose/Objective(s): We hypothesized that resectability and surgical margin status would correlate with long-term outcomes despite addition of aggressive multimodality therapy.

Materials/Methods: Review of medical records of all patients treated with definitive intent for primary sinonasal malignancies from March

1995-May 2015. Patients with melanoma, sarcoma, lymphoma, and adenoid cystic carcinoma were excluded. Disease extent, stage, treatments, and margin status were recorded. Between-group differences in disease-free survival (DFS), overall survival (OS), and freedom from local progression (FFLP) were evaluated using Kaplan-Meier estimation and log-rank test. Multivariate analysis was performed using Cox Proportional Hazards models.

Results: A total of 103 patients were treated for cancers of the nasal cavity (68) and maxillary (22), ethmoid (8), sphenoid (4), and frontal (1) sinuses. Eighty had surgery ± adjuvant therapy. Of 18 patients treated non-operatively, 7 completed induction chemotherapy and (chemo)radiation, one had chemotherapy, and 10 had (chemo)radiation. Fifty-four patients had squamous cell carcinoma (SCC), 33 esthesioneuroblastoma (ENB), 6 sinonasal undifferentiated carcinoma (SNUC), 5 sinonasal neuroendocrine carcinoma (SNEC), and 5 adenocarcinoma or adenosquamous carcinoma. Sixty-six percent (39/59) of patients with SCC or adenocarcinoma had T4 disease. Intracranial extension was identified in 47% (47/103) patients. Surgical margins were positive in 55% (44/80) of resections, but gross total resections (GTR) were achieved in 86% (73/85). At a median follow-up of 5.6 years (0.1-17 years), 33 patients recurred and 34 expired. We observed 19 local, 6 regional, and 18 distant recurrences. At 3 years, DFS, OS, and FFLP were 58%, 69% and 62% in the entire cohort, respectively. Among resected patients, positive margins were associated with worse 3-year DFS (47% vs 79%, $P<.001$), OS (56% vs 91%, $P=.005$), and FFLP (50% vs 82%, $P=.004$). In non-operated patients, 3-year DFS, OS and FFLP were very similar: 47%, 56%, and 53%, respectively. For patients with SCC, those treated non-operatively had similar DFS (HR 0.94, $P=.9$), OS (HR 1.1, $P=.8$), and FFLP (HR 1.2, $P=.78$) to those with positive margins. All ENBs were resected and, compared to SCC, were associated with better DFS ($P=.06$), OS ($P=.01$), and FFLP ($P=.02$). In the surgical group, there were 4 intracranial infections and 1 stroke. In the non-operative group, 1 patient died from stroke during induction therapy.

Conclusion: Excellent outcomes were achieved after complete resections with negative margins. For patients with SCC, upfront necessity for non-operative treatment yields outcomes similar to surgery with inability to clear margins, which is not remediated by adjuvant therapy.

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Isolated Leptomeningeal Progression from Sinonasal Carcinomas: Implications for Staging Workup and Treatment

R. Dagan,[1] C.M. Bryant,[1] W.M. Mendenhall,[1] R.J. Amdur,[2] C.G. Morris,[1] P.T. Dziegielewski,[3] B.J. Boyce,[3] J.M. Justice,[3] D.C. Lanza,[4] R. Fernandes,[5] P. Pirgousis,[5] and D. Tavanaiepour[6]; *[1]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL, [2]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [3]Department of Otolaryngology, University of Florida College of Medicine, Gainesville, FL, [4]Sinus & Nasal Institute of Florida, St. Petersburg, FL, [5]Department of Oral and Maxillofacial Surgery, University of Florida College of Medicine, Jacksonville, FL, [6]Department of Neurosurgery, University of Florida College of Medicine, Jacksonville, FL*

Purpose/Objective(s): To determine the rate of isolated leptomeningeal progression among patients treated for locally advanced sinonasal carcinomas and to evaluate associated risk factors.

Materials/Methods: The records of 120 patients who completed treatment with either adjuvant or primary radiation therapy for sinonasal carcinomas were retrospectively reviewed. The majority of patients had T4 disease (68%), underwent surgery (84%), and also received chemotherapy (72%). Median follow-up was 3.2 years among living patients. Patterns of recurrence were detailed, including first site of progression. Leptomeningeal progression was coded based on a review of imaging and clinical records and the rate progression was estimated using the Kaplan-Meier method. Risk factors were evaluated using proportional hazard regression.

Results: A total of 27 (23%) patients developed distant metastases (DMs), including 20 (17%) with isolated DMs. The 3-year rate of freedom from DM was 73% (81% for freedom from isolated DMs). Leptomeningeal progression was the single most common site of isolated DM progression and occurred in 9 of the 20 (45%) patients with an average disease-free interval of 1.2 years (range, 0.1-4.3 years) after initiation of radiation therapy. High-grade histology ($P=.0003$), intracranial invasion ($P<.0001$), and neuroendocrine differentiation ($P=.061$) were associated with isolated leptomeningeal progression while surgery ($P=.872$) and the presence of gross disease at the time of radiation therapy ($P=.339$) were not associated with leptomeningeal progression.

Conclusion: Isolated leptomeningeal progression is a common pattern of DMs among patients with advanced sinonasal carcinomas. Intracranial invasion, neuroendocrine differentiation, and high-grade histology were associated with an increased risk for this unique pattern of recurrence. We suggest cerebrospinal fluid (CSF) cytology and contrast-enhanced spine MRI in addition to established staging evaluations for this patient subset. To date there are no data regarding the role of CSF-directed therapy, such as craniospinal irradiation or intrathecal chemotherapy, but these are areas of potential investigation to reduce the risk of leptomeningeal progression in patients with positive findings on CSF cytology or spine MRI.

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Mutational Landscape of Cutaneous and Sinonasal Melanoma

T. Heineman,[1] K. Badran,[1] and M. St.John[2]; *[1]University of California Los Angeles, Los Angeles, CA, [2]UCLA David Geffen School of Medicine, Department of Head and Neck Surgery, Los Angeles, CA*

Purpose/Objective(s): Sinonasal mucosal melanomas (SNMM) comprise a minority of all melanomas (< 1 %). The prognosis of SNMM remains poor with a 20%-28% 5-year survival rate. As the sinonasal cavity is not associated with sun exposure like cutaneous melanomas (CM), the mutational origins are assumed to be different. Individual genes have been examined in SNMM compared to CM, such as KIT, BRAF, and NRAS; however, a comprehensive comparison of available SNMM mutations compared to CM mutations in the Cancer Genome Atlas (TCGA) has not been performed.

Materials/Methods: We analyzed direct sequencing results of 151 SNMM samples reported in a recent publication by Zebary et al. and compared the results to 479 CM samples in the TCGA. All TCGA data was access using cBioPortal web interface.

Results: In analyzed SNMM tumors, mutations occurred in KIT, NRAS, and BRAF genes in 7.8%, 19.3%, and 2.9% of samples, respectively. CM tumors had mutations in these same three genes in 6.0%, 51.4%, and 26.6% of samples, respectively. Differences in NRAS and BRAF were statistically significant ($P<.05$).

Conclusion: SNMM and CM have distinct mutational fingerprints. Genetic analysis of these tumors is essential to better understand their origins and provided the basis for targeted therapy, which may provide the needed advance to improve survival in SNMM.

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Patterns of Care and Radiation Therapy Utilization Among Patients With Soft Tissue Sarcoma of the Head and Neck: A National Cancer Database Analysis

J.K. Kim,[1,2] S. McBride,[3] N. Riaz,[1] J.E. Leeman,[1] D. Spielsinger,[1] C. Sabol,[1] T. Waldenberg,[3] T. Brinkman,[1] N. Lee,[1] and C.J. Tsai[1]; [1]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Department of Radiation Oncology, SUNY Downstate Medical Center, Brooklyn, NY,* [3]*Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): To identify the patterns of radiation therapy (RT) utilization and factors associated with overall survival (OS) in patients with soft tissue sarcoma of the head and neck.

Materials/Methods: Using the National Cancer Database, we identified patients with invasive soft tissue sarcoma of the head and neck diagnosed between 2004 and 2013, who survived >3 months after diagnosis, had known vital status, and histologic confirmation. Patients with unknown RT use and those who did not receive any treatment at the reporting facility were excluded from our analysis. Multivariable logistic regression models were used to identify patient and tumor characteristics associated with RT use. Multivariable Cox regression models were used for survival analysis.

Results: Final analysis included 1435 patients, 61.5% were male (n=882) and 608 patients (42.4%) received some form of RT. The median age at diagnosis was 55 years (18-90 years). Of the patients who received RT, 200 (32.9%) had RT without definitive surgery, 25 (4.1%) had pre-op RT, and 383 (63.0%) had post-op RT. The median total dose of pre-op RT was 50 Gy (9.9-73.8 Gy) and post-op RT was 60 Gy (1.2-183.75 Gy). The most common known histology was chondrosarcoma (n=293, 20.4%) and the most common disease site was nasal cavity/sinus (n=690, 48.1%). The median follow-up time after diagnosis for the entire cohort was 36.4 months (3.1-135.9). The median OS in months was 114.1 for the entire cohort, 30.9 for RT without definitive surgery, 54.4 for pre-op RT, 121.3 for post-op RT, and median OS for surgery alone was not reached. In multivariable logistic regression, patients with poorly-differentiated tumors, rhabdomyosarcoma or spindle cell sarcoma, primary site of nasal cavity/sinus, nonmetastatic disease, positive margins, and chemotherapy use were more likely to receive RT than those with moderate or well-differentiated tumors, chondrosarcoma, primary site of oral cavity, oropharynx, hypopharynx, or larynx, metastatic disease, negative margins, and no chemotherapy use. In multivariable Cox regression, age<60, higher tumor grade, chondrosarcoma, tumor size <5 cm, primary site of larynx, local or partial/wide local excision, and negative margins were associated with improved OS. RT use was not significantly associated with OS. In the subset of patients receiving RT with surgery, there was no difference in OS between pre-op and post-op RT.

Conclusion: In a national hospital–based cohort of head and neck soft tissue sarcoma patients, there was no association between RT use and OS. RT was more likely to be used in patients with poorly-differentiated tumors, rhabdomyosarcoma, spindle cell sarcoma, primary site of nasal cavity/sinus, positive margins, and chemotherapy use. Younger age, higher grade, chondrosarcoma, tumor size <5 cm, primary site of larynx, partial/local surgery, and negative margins were associated with improved OS.

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Incidence and Distribution of Nodal Metastases in Sinonasal Malignancy

S.K. Alapati,[1] A. Unsal,[2] J. Cracchiolo,[1] B.R. Roman,[1] N. Lee,[3] and M. Cohen[4]; [1]*Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Rowan University, Camden, NJ,* [3]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY,* [4]*Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Cervical lymph node drainage pathways of sinonasal malignancies (SNM) have not yet been well-established in the literature. We present the largest population-based cohort of SNM to investigate the frequency and pattern of cervical node involvement.

Materials/Methods: The Surveillance, Epidemiology, and End Results registry was queried from 2004 to 2014, identifying patients with sinonasal squamous cell carcinoma (SCC), adenocarcinoma, adenoid cystic carcinoma (ACC), sinonasal undifferentiated carcinoma (SNUC), mucosal melanoma, and esthesioneuroblastoma. Cases were assessed by frequency of cervical lymph node level, distant metastasis, and primary subsite.

Results: A total of 4,171 SNM cases were identified, 527 of which presented with cervical nodal disease (12.6%). Level II and level I diseases were most commonly identified (36.1 and 29.5%). This finding was consistent despite histology and primary subsite involved. Regional disease was most commonly seen in SNUC (22.4%) and SCC (15.2%), and least commonly in ACC (4.1%). Malignancies of the maxillary sinus demonstrated the highest rate of nodal disease (19.6%), followed by the sphenoid sinus (15.9%). No cases of nodal disease were identified amongst frontal sinus malignancies. The parotid and level I/level II nodes were least involved in cases with distant metastasis (6% and 10%). Conversely, suboccipital/retroauricular and level VII (mediastinal) nodes most frequently presented with distant metastasis (67% and 33%).

Conclusion: Although cervical node involvement in SNM is infrequent compared to other head and neck sites, levels II and I were overwhelmingly involved when present. Knowledge of these sinonasal drainage patterns will ultimately help guide the treatment of the neck in select cases.

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Clinical Effect of Dose Escalation of Lenvatinib After Disease Progression in Patients With Metastatic Thyroid Cancer

M. Tahara, T. Enokida, T. Fujisawa, Y. Ueda, and S. Okano; *National Cancer Center Hospital East, Kashiwa, Japan*

Purpose/Objective(s): Lenvatinib (LEN)—an oral multikinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT—significantly prolonged progression-free survival vs placebo in the SELECT study. However, treatment option after disease progression remain limited. Dose escalation of VEGFR-targeted TKI after disease progression in patients with metastatic renal cell carcinoma can result in extended duration of therapy and an antitumor effect (Ornstein M, Clin Genitourinary Cancer 2017). The objective of the current analysis was to investigate the tolerability and clinical effect of LEN dose escalation after disease progression.

Materials/Methods: We conducted a retrospective review of patients with metastatic thyroid cancer who were treated with LEN and received a dose escalation after disease progression. The patient- and disease-related characteristics were collected from electronic medical records. The Kaplan-Meier method was used to summarize the treatment duration for the escalated doses.

Results: Out of 62 thyroid cancer patients treated with LEN, a total of 10 patients who underwent dose escalation after disease progression were identified. Five were male; median age was 67 years (51-81); pathology was PTC/FTC/ATC in 6/2/2 cases. Before disease progression, the median treatment duration was 22.3 months (2.9-55.1). Median ratio of escalated dose was 59% (20-150). Four (40%) patients had a decreased in tumor burden and 2 achieved stable disease with improvement of symptom. The median treatment duration after dose escalation was 5.8 months (range 0.5 to 14.9 months). At the last follow-up examination, 6 patients continued to be treated at escalated doses and 7 patients are alive. Median overall survival was 23.7 months. No grade 4 adverse events occurred after dose escalation by planned drug holidays according to the time occurring adverse events.

Conclusion: Dose escalation of LEN after disease progression for select patients with metastatic thyroid cancer could result in the extended duration of therapy and antitumor effect.

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Access to Care and Trends in Papillary Thyroid Carcinoma Incidence Rates in the United States

M. Lango,[1] A. Moten,[2] and D. Flieder[3]; [1]*Fox Chase Cancer Center, Philadelphia, PA,* [2]*Temple University Hospital, Philadelphia, PA,* [3]*Fox Chase Cancer Center/ Temple University Health System, Philadelphia, PA*

Purpose/Objective(s): Increases in thyroid cancer incidence rates have largely been attributed to increases in rates of diagnosis among those with greater access to care. Changes in incidence rates among populations with less access to care has not been well-described.

Materials/Methods: Patients with papillary thyroid carcinoma (PTC) diagnosed from 2004-2013 from the Surveillance, Epidemiology, and End Results (SEER 18) database were included. Patients were mapped to SEER counties stratified by median income quartile or rural-urban continuum code designation, factors associated with decreased access to care. Changes in PTC age-adjusted incidence rates from 2003 to 2014 were analyzed using SEER Stat 8.3.4 and Joinpoint 4.5.0.1. Cox regression was used in survival analyses.

Results: Over 824,670 person-years, the lowest and highest age-adjusted incidence rates were both observed in metropolitan regions, varying by county median family income quartile; intermediate incidence rates were observed in rural areas. From 2004-13, the age-adjusted incidence rates increased in both high and low-income counties (Table). In high-income areas (Quartile 3-4), incidence rates leveled off in 2009-13, while in low-incidence areas, incidence rates continued to increase over the entire period; the average annual percentage change (AAPC) increased significantly in all income quartiles. However, patients with PTC from low-income counties more frequently presented at an older age and with distant metastases. The disease specific and overall survival of PTC patients from low-income counties were significantly worse, when accounting for patient age, sex, tumor stage and histologic variant and year of diagnosis.

Conclusion: While the PTC incidence rates are lower in low-income regions, the age-adjusted incidence has been increasing in both high- and low-income regions. Nevertheless, patients from low-income regions present with more advanced disease and have worse survival. Policies that promote equitable care are needed.

Abstract 260; Table Trends in age-adjusted incidence rates for papillary thyroid carcinoma by county income level

Median Income Quartile	Time segment	APC	95% CI	*P*-value	AAPC	95% CI	*P*-value
First Quartile	2004-13	4.9	(3.2-6.6)	0.001	4.9	(3.2-6.6)	0.001
Second Quartile	2004-13	5.9	(4.2-7.6)	0.001	5.9	(4.2-7.6)	0.001
Third Quartile	2004-10	7.3	(5.5-9.2)	0.001	5.4	(3.9-6.9)	0.001
	2010-13	1.7	(-2.6-6.2)	0.4			
Fourth Quartile	2004-9	7.6	(7.1-8.2)	0.001	5.5	(5.2-5.8)	0.001
	2009-13	2.9	(2.3-3.6)	0.001			

Abbreviations: APC, annual percentage change; AAPC, average annual percentage change; CI confidence interval. * SEER counties ranked by median family income, with those in the First Quartile having the lowest median income.

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Gene Expression in Nasopharyngeal Carcinoma by Laser Capture Microdissected Transcriptome Sequencing

J.K. Tay,[1,2] C. Zhu,[3] J. Sunwoo,[1] Q.T. Le,[4] and R.B. West[3]; [1]*Otolaryngology-Head and Neck Surgery, Stanford University School of Medicine, Stanford, CA,* [2]*Otolaryngology-Head and Neck Surgery, National University Health System, Singapore, Singapore,* [3]*Department of Pathology, Stanford University School of Medicine, Stanford, CA,* [4]*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA*

Purpose/Objective(s): Nasopharyngeal carcinoma (NPC) is an Epstein-Barr virus (EBV)–associated epithelial malignancy endemic to several parts of the world including Southeast Asia. These tumors have a significant stromal infiltrate resulting in challenges in obtaining sufficiently pure tumor epithelial cells for gene expression profiling. Tumor biopsies comprise 2-3 mm specimens, while surgical resections are rare as chemotherapy and radiation therapy are the standard treatment for primary disease. With these challenges, large studies of pure NPC tumors have not been reported. We aimed to overcome these sampling limitations and obtain histologically pure tumor and paired-normal sequencing libraries to identify dysregulated genes and pathways in NPC.

Materials/Methods: We performed laser capture microdissection on a cohort of NPC tumors treated at a single institution. Tumor cells, as well as regions of histologically normal epithelial cells and lymphoid infiltrate in the same specimen, were separately microdissected from paraffin-embedded NPC diagnostic biopsies. We applied a novel 3' end RNA-Seq technique (Smart-3SEQ) developed in our lab to allow for the accurate quantification of transcript abundance in dissected FFPE samples comprising only a few hundred cells. Briefly, this involves selecting for RNA fragments containing the poly-A tail, template switching, and incorporating a unique molecular identifier for each unique RNA transcript. RNA libraries were prepared, sequenced, and mapped to the human hg19 and EBV genomes. Differentially expressed genes were identified with DESeq2, using a corrected *P*-value of .05.

Results: Unsupervised hierarchical clustering demonstrated that gene expression profiles of tumor cells, normal epithelial cells, and lymphoid cells clustered into their respective groups. Differential gene expression analysis between a set of tumor and patient-matched normal epithelial cells identified significantly dysregulated genes. Among the pathways, genes involved in cilia assembly and flagella transport were highly expressed in normal epithelial cells ($P < .001$), while genes involved in cell cycle ($P < .001$) and cellular differentiation ($P = .03$) were significantly dysregulated in tumor cells. We were also able to identify a subgroup of NPC tumors that had differential expression of EBV-latent genes.

Conclusion: Gene expression profiling with Smart-3SEQ from archival tissue successfully overcomes issues with tumor purity in NPC, allowing for differentially expressed human and viral genes to be confidently identified. The dysregulated genes and pathways identified through this specialized approach will provide invaluable insight into the biology of this unique malignancy.

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The Effect of Hospital Volume and Insurance Status on Overall Survival in Sinonasal Carcinoma: A National Cancer Database (NCDB) Analysis

S. Trivedi,[1] J. Switchenko,[2] M.R. Patel,[3] C. Steuer,[4] M.W. El-Deiry,[5] K.A. Higgins,[6] C.A. Solares,[7] M.W. McDonald,[8] D.M. Shin,[9] T. Gillespie,[10] J.J. Beitler,[6] and N.F. Saba[11]; [1]*Department of Medicine, Emory University School of Medicine, Atlanta, GA,* [2]*Department of Biostatistics & Bioinformatics, Rollins School of Public Health, Atlanta, GA,* [3]*Department of Otolaryngology, Emory University, Atlanta, GA,* [4]*Department of Hematology and Medical Oncology, Emory University, Atlanta, GA,* [5]*Otolaryngology, Winship Cancer Institute of Emory University, Atlanta, GA,* [6]*Department of Radiation Oncology and Winship Cancer Institute, Emory University, Atlanta, GA,* [7]*Department of Otolaryngology Emory University, Atlanta, GA,* [8]*Department of Radiation Oncology, Winship Cancer Institute at Emory University, Atlanta, GA,*

[9]*Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA,* [10]*Department of Surgery, Emory University School of Medicine, Atlanta, GA,* [11]*Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA*

Purpose/Objective(s): Although sinonasal malignant neoplasms are rare, accounting for 3% of malignancies in the upper aerodigestive tract, they continue to have a poor prognosis. The 5-year disease-free survival rate is approximately 40% and has remained largely unchanged over the past 3 years. As yet, there is limited data regarding the factors that affect survival outcomes in patients with sinonasal carcinomas.

Materials/Methods: Recent publications examined the role of clinical factors that affect overall survival (OS) in patients with sinonasal cancers however, the effect of hospital volume and medical insurance on OS is yet unknown. Using NCDB data, we examined the effect of hospital volume and medical insurance on patients' OS. The number of cases treated at each facility was calculated, and the threshold for distinguishing high volume vs. low volume was determined using the 80th percentile of the number of cases treated per facility. Insurance status was categorized as not insured, private insurance, and Medicaid/Medicare/Other government. OS was estimated using the Kaplan-Meier method, and OS was compared using log-rank tests. Multivariable Cox proportional hazards models were fit for OS as a function of center volume, insurance, histology, pathologic T-stage, facility type, age at diagnosis, and treatment.

Results: A total of 5000 patients were included in the multivariable analysis (MVA). We found that private insurance was significantly associated with overall survival compared to those who receive government insurance ($p<0.001$) but not compared to those without insurance ($P=.63$). Facility type ($P=.82$) and facility volume ($P=.06$) did not have a statistically significant effect on OS.

Conclusion: This retrospective analysis represents the largest study in sinonasal carcinoma to date. One significant limitation of this study is that we were unable to assess for disease free survival using NCDB data, only overall survival. However, these data confirm findings from smaller studies that demonstrate the effect of patient age, tumor stage and histology on survival outcomes. Additionally, it provides information on how hospital volume and medical insurance can affect the survival of patients with sinonasal carcinomas.

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Adjuvant Radiation is Associated With Decreased Overall Survival Among Patients With Lymph Node Positive Medullary Thyroid Carcinoma: A National Cancer Database Analysis

M. Vakil,[1] T. Ow,[1] S. Kim,[2,3] V. Mehta,[1] and H. In[3,4]; [1]*Department of Otorhinolaryngology - Head and Neck Surgery, Albert Einstein College of Medicine, Bronx, NY,* [2]*Gangdong Hana ENT Clinic, Hana Hospital, Seoul, Korea, Republic of (South),* [3]*Department of Surgery, Albert Einstein College of Medicine, Bronx, NY,* [4]*Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY*

Purpose/Objective(s): Medullary thyroid carcinoma (MTC) originates from parafollicular cells, which do not take up radioactive iodine. For patients with identified lymphatic metastases and advanced regional disease, adjuvant radiation to the loco/regional lymph node basin is thought to decrease risk of recurrence and improve loco/regional control after thyroidectomy. However, studies assessing the benefit of postoperative radiation in this setting are limited.

Materials/Methods: MTC patients diagnosed between 2004 to 2013 were identified from the National Cancer Database (NCDB). Analysis was limited to patients with lymph node positive disease without evidence of distant metastasis. Demographics, tumor characteristics, and outcomes were compared between patients who did and did not get external beam radiation therapy (EBRT) after thyroidectomy. Subgroup analysis examined patients with high risk of recurrence including those having a margin positive resection or extrathyroidal extension (ETE). Kaplan-Meier and Cox regression analyses were performed using SAS 9.4 (Cary, NC).

Results: A total of 1,334 MTC patients with lymph node metastases were identified, of which 265 received EBRT (19.87%). The use of EBRT was associated with being older than 45 years old, male sex, tumor size greater than 4 cm, stage 4 disease, positive surgical margin, and ETE. Kaplan-Meier analysis showed marked lower overall survival for EBRT compared to those that did not receive radiation ($P<.0001$). Cox regression analysis showed that after controlling for age, gender, income, tumor size, positive surgical margin, ETE, Charlson-Deyo Score, lymphovascular invasion, and stage, EBRT was found to have increased overall mortality (HR 1.872, 95% CI 1.427-2.457). Subgroup analysis on high risk MTC patients also showed increased risk of mortality (HR 1.747, 95% CI 1.278-2.387).

Conclusion: The use of external beam radiation therapy was found to be associated with reduced overall survival for patients with lymph node positive MTC. Prospective studies examining the appropriate application of radiation or alternative adjuvant strategies for patients with loco/regionally advanced MTC are needed.

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Exploratory Analysis of Prognostic and Predictive Factors of Lenvatinib for Radioiodine-Refractory Differentiated Thyroid Cancer

C. Suzuki,[1] N. Kiyota,[1,2] Y. Imamura,[1] H. Goto,[1] H. Suto,[1] N. Chayahara,[1] M. Toyoda,[1] Y. Ito,[3] A. Miya,[3] A. Miyauchi,[3] N. Otsuki,[4] K.I. Nibu,[4] and H. Minami[1]; [1]*Department of Medical Oncology/Hematology, Kobe University Graduate School of Medicine, Kobe, Japan,* [2]*Kobe University Hospital Cancer Center, Kobe, Japan,* [3]*Department of Surgery, Kuma Hospital, Kobe, Japan,* [4]*Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe, Japan*

Purpose/Objective(s): Prognosis of patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC) is generally poor, with a 10-year survival rate of approximately 10%. However, prognosis of RR-DTC is diverse and RR-DTC patients (pts) are usually asymptomatic. Thus, the optimal timing of treatment initiation with multi-targeted kinase inhibitors, including lenvatinib (LEN), for RR-DTC pts remains to be defined. Here, we explored predictive factors of LEN for RR-DTC pts.

Materials/Methods: We retrospectively reviewed the clinical records of 26 consecutive pts with RR-DTC from 2012 to 2016. Tumor size was evaluated by computed tomography (CT) according to RECIST ver1.1. Thyroglobulin-Doubling-Time (Tg-DT) and Tumor-Doubling-Time (TDT) were calculated using the Doubling Time and Progression Calculator (http://www.kuma-h.or.jp/english/) at baseline, and the relationship between Tg-DT, TDT, tumor burden, and other clinical characteristics and efficacy of LEN was evaluated. Receiver operating characteristic curve was used for determining cutoff values.

Results: A total of 24 RR-DTC pts who were treated with LEN were evaluable for response and eligible for this analysis. All of the pts were confirmed to have disease progression within a year before starting LEN. Median age was 62 years (range, 30-83). Median follow-up period was 25.4 months (range, 1.3-57.7). Median treatment duration of LEN was 18.2 months (range, 0.5-57.2). Median treatment duration of LEN at a dose of 14 mg or more (TD-LEN $\geq$14 mg) was 2.8 months (range, 0.5-49.3). Median Tg-DT and TDT before treatment was 0.63 years (range, 0.23-5.85) and 0.74 years (range, 0.08-2.85), respectively. Median maximum tumor diameter (MaxTD) of target lesions at baseline was 29.0 mm (range, 12.1-88.3). Median total tumor diameters (ToTD) of target lesions at baseline was 68.1 mm (range, 28.6-145.7). There was no significant

relationship between baseline Tg-DT and TDT and efficacy of LEN. TD-LEN ≥14 mg within 12 weeks was a significant poor prognostic factor for PFS (2-y rate 32% vs 78%, $P=.018$) but not for overall survival (OS). MaxTD at baseline ≥ 30.8 mm was associated with significantly worse PFS and OS (2-y rate 24% vs 71%, $P<.01$, 2-y rate 35% vs 100%, $P<.01$, respectively). ToTD at baseline ≥64.6 mm tended to be associated with worse PFS (2-y rate 38% vs 71%, $P=.09$) and significantly worse OS (2-y rate 47% vs 100%, $P<.01$).

Conclusion: Allowing for this study's small sample size and retrospective design, the results suggest that MaxTD and ToTD at baseline and TD-LEN ≥ 14 mg may predict the efficacy of LEN. Further prospective analysis with a large data set to validate these results is warranted.

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The Role of Adjuvant Radiation Therapy in Head and Neck Sarcomas

G.Q. Yang,[1] S. Manickavel,[2] I. Passioura,[2] J.J. Caudell,[1] D.E. Oliver,[1] and A.O. Naghavi[1]; *[1]H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology, Tampa, FL, [2]University of South Florida College of Medicine, Tampa, FL*

Purpose/Objective(s): Locoregional control (LRC) with surgery alone in soft tissue sarcomas of the head and neck may be sub-optimal due to anatomic constraints. We hypothesized that adjuvant radiation (RT) may improve locoregional control in head and neck sarcomas.

Materials/Methods: After IRB approval, we identified patients with head and neck sarcoma from a retrospective database of sarcoma patients. Clinical features of high and low grade, T1 and T2, and patient age were compared with Pearson Chi-square and Mann-Whitney U test as appropriate. LRC and overall survival (OS) were calculated from the date of initial diagnosis and estimated via the Kaplan-Meier method and comparisons made via the log-rank test. Cox proportional hazards model was used for multivariate analysis (MVA).

Results: A total of 315 patients with head and neck sarcoma were available for analysis, with 151 patients treated with surgery alone, and 164 treated with adjuvant RT. Median follow-up of the entire cohort was 41 months. There was a trending proportion of T2 disease in patients receiving adjuvant RT compared to surgery (37% and 23% respectively, $P=.07$). Patients had similar age, and high- versus low-grade proportions. On univariate analysis, there were no significant differences between the surgery versus adjuvant RT cohorts in 3 year LRC (69% vs 68%, $P=.63$) and OS (66% vs 61%, $P=.16$). Subset analysis of high grade (3/4) patients (n=136), showed a non-significant improvement in 3-year LRC (71% vs 59%, $P=.08$) favoring adjuvant RT, but with no difference in 3-year OS ($P=.43$). However, on MVA, controlling for differences in patient age, T stage, and grade, adjuvant RT was associated with a trend towards improved LRC (HR 0.65, 95% CI 0.4-1.1, $P=.10$).

Conclusion: Patients with head and neck sarcomas did not appear to benefit from the addition of adjuvant RT. Although high-grade tumors had an absolute LRC improvement of 12% at 3 years, this was not significant. Larger retrospective series or further prospective studies are required to elucidate the potential benefit of adjuvant RT.

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Withdrawn

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Positive Surgical Margin in Favorable Stage Differentiated Thyroid Cancer

C.E. Mercado,[1] P.A. Drew,[2] C.G. Morris,[1] P.T. Dziegielewski,[3] W.M. Mendenhall,[4] and R.J. Amdur[1]; *[1]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [2]Department of Pathology, University of Florida College of Medicine, Gainesville, FL, [3]Department of Otolaryngology, University of Florida College of Medicine, Gainesville, FL, [4]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL*

Purpose/Objective(s): The significance of a positive margin in favorable stage well-differentiated thyroid cancer (DTC) is controversial, with little published data on the subject. This study reports the outcome of consecutively treated favorable stage patients with match-pair comparison to a negative margin group.

Materials/Methods: The main study population is the 25 patients treated between 2003 and 2013 at our institution with the following characteristics: Papillary or Follicular carcinoma with classic histology, total thyroidectomy +/- node dissection, stage T1-3 N0-1b M0, positive surgical margin at the primary site, adjuvant I-131 (≥ 150 mCi in 92%), and age > 18 years at time of I-131 treatment. Outcome endpoints were clinical (visible disease) and biochemical (thyroglobulin-only) recurrence-free survival. Matched pair analysis involved a 1:1 match with negative margin cases treated at our institution during the same time period, with each patient matched for overall stage and I-131 dose.

Results: Recurrence-free survival in our positive margin patients was 71% at 10 years. No patient was rendered tumor free with additional treatment. Only one patient died of thyroid cancer. Recurrence free survival at 10 years was worse with a positive (71%) versus negative (90%) margin, but the P value was 0.14.

Conclusion: In our series of patients with classic histology, favorable stage, and moderate dose I-131 therapy, the cure rate was suboptimal (71%) in patients with a positive surgical margin and worse than in patients with a negative margin. Further study is needed to determine the safety of observation or low-dose I-131 in positive margin cases.

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Cost of Surveillance Imaging in Head and Neck Cancer Patients Treated With Definitive Radiation therapy

S.P. Ng,[1] M. Kamal,[1] C. Pollard III,[1] J. Berends,[2] Z. Ayoub,[1] A.S.R. Mohamed,[1] G.B. Gunn,[1] S.J. Frank,[1] H.D. Skinner,[1] J. Phan,[1] W.H. Morrison,[1] D.I. Rosenthal,[1] A.S. Garden,[1] J.M. Johnson,[1] S. Lai,[1] E.M. Sturgis,[1] and C.D. Fuller[1]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The University of Texas Health Science Center San Antonio, San Antonio, TX*

Purpose/Objective(s): The goal of surveillance is to detect potentially salvageable recurrence, allowing early salvage treatment and thereby improving clinical outcomes. Currently, there are limited data on the optimal frequency of imaging for head and neck cancer patients treated with definitive radiation therapy. This study aims to evaluate the cost effectiveness of surveillance imaging in this group of patients.

Materials/Methods: Eligible patients included those with a demonstrable disease-free interval (≥ 1 follow up scan without evidence of disease and a subsequent visit/scan) treated between 2000-2010. Age, tumor site and

stage, induction chemotherapy use, dose/ fractionation, mode of detection of recurrence, salvage therapy, and number and modality of scans were recorded. Deaths from disease recurrence or from other causes were also recorded. Imaging costs were calculated based on the 2016 Medicare fee schedule.

Results: A total of 1508 patients were included. Median overall survival was 99 months (range: 6-199). Mean imaging follow-up period was 70 months. Of the total, 190 (12.6%) patients had disease recurrence—107 locoregional (LR) and 83 distant. Of the relapsed group, 119 (62.6%) were symptomatic and/or had an adverse clinical finding associated with recurrence. Majority (80%) of LR relapses presented with a clinical finding, while 60% of distant relapses were detected via imaging alone in asymptomatic patients. There was no difference between the successful salvage rates and overall survival between those with relapses detected clinically or via imaging alone. Seventy percent of relapses occurred within the first 2 years posttreatment. In those who relapsed after 2 years, the median time to relapse was 51 months (2 LR and 11 distant relapses). After 2 years, the average cost for detecting a salvageable recurrence for image-detected group was $395,223.09, and the cost for preventing 1 recurrence-related death for image-detected disease was $474,267.70. The number of scans required to detect a salvageable recurrence in an asymptomatic patient after 2 years was 1539.

Conclusion: Surveillance imaging in asymptomatic patients without clinically suspicious findings beyond 2 years requires judicious consideration.

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Discontinuation of Curative Head and Neck Irradiation: Etiologies and Outcomes

S. Lazarev, Z. Ghiassi-Nejad, V. Gupta, B. Miles, B. Scarborough, K. Misiukiewicz, B. Reckson, R. Sheu, and R.L. Bakst; *Icahn School of Medicine at Mount Sinai, New York, NY*

Purpose/Objective(s): There is scarcity of valid clinical data on survival after premature discontinuation of curative radiation therapy (PDCRT) for head and neck (H&N) cancers. This makes it challenging to advise patients seeking to withdraw from treatment early. In this study, we aimed to characterize causes of PDCRT and assess overall survival in this subset of patients

Materials/Methods: A total of 1176 patients received H&N radiation therapy at our institution in the period 2010-2017. Of these patients, 59 (5%) were unable to complete a full course of prescribed curative RT and were included in the analysis. Mean follow-up time was 18 months (0-81.9 months). Primary endpoints were causes of PDCRT and overall survival (OS). PDCRT causes were classified into five categories: discontinuation against medical advice (DAMA), medical comorbidity, RT toxicity, disease progression, and social factors. Survival was examined using the life-table method and log-rank test.

Results: DAMA (32%), medical comorbidity (24%), and RT toxicity (18%) accounted for the majority of PDCRT causes. Of 59 analyzed patients, most were men (80%), ≥60 years old (59%), white (68%), lived ≥ 10 miles from hospital (61%), were undergoing a longer (definitive) course of RT (59%), and receiving bilateral neck irradiation (70%). At the same time, the majority of patients had ECOG ≤1 (78%) and ≤1 comorbidities (56%) at the start of the treatment. Most common primary sites were oropharynx (37%), larynx (20%), and oral cavity (12%). During RT, 66% of patients had treatment interruptions and 34% required inpatient admission. Supportive Oncology service was involved in care of only 20% patients on treatment. Radiation Therapy Oncology Group grade ≥2 dysphagia was observed in 47% patients, mucositis in 46%. Median prescribed dose was 69.96 Gy (range, 50-72 Gy). Median completed radiation dose was 50.9 Gy (range, 2-68 Gy). At the time of analysis, 25 (42%) deaths were recorded. Two-year and 4-year OS rates was 56% and 43%. There was a trend toward improved survival with total completed dose ≥ 50 Gy vs < 50 Gy, 67% vs 40% ($P = .06$).

Conclusion: To the best of our knowledge, this is the largest modern study examining clinical outcomes after PDCRT. The principal reason for treatment withdrawal remains DAMA, and hence more effort need to be focused on educating and providing support to meet the unique needs of this challenging patient population. Addressing psycho-social and quality of life aspects may help increase completion rates of this often life-saving treatment. Overall survival appears to be poor after PDCRT. Advising a patient that reaching at least 50 Gy could offer a better chance for survival could prove vital.

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Sparing All Salivary Glands With IMRT for Head and Neck Cancer: Longitudinal Study of Patient-Reported Xerostomia and Head and Neck Quality Of Life

P.G. Hawkins,[1] J.Y. Lee,[1] Y. Mao,[2] P. Li,[3] F. Worden,[4] P.L. Swiecicki,[4] M.L. Mierzwa,[1] M.E. Spector,[5] M. Schipper,[3] and A. Eisbruch[1]; *[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]Sun Yat-sen University Cancer Center, Guangzhou, China, [3]Department of Biostatistics, University of Michigan, Ann Arbor, MI, [4]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [5]Department of Otolaryngology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): While parotid-sparing intensity modulated radiation therapy (IMRT) has demonstrated superiority to conventional RT in terms of observer-rated xerostomia, patient-reported outcome measures (PROMs) have only marginally improved. We investigated how sparing all salivary glands affects PROMs.

Materials/Methods: Patients treated to the bilateral neck with all-gland-sparing IMRT answered xerostomia (XQ) and head-and-neck quality of life (HNQOL) questionnaires. Longitudinal regression was used to assess the relationship between questionnaire scores and mean bilateral parotid gland (bPG), contralateral submandibular gland (cSMG), and oral cavity (OC) doses. Marginal R^2 and Akaike information criterion (AIC) were used for model evaluation.

Results: A total of 252 patients completed approximately 600 XQ and HNQOL questionnaires. On univariate analysis, bPG, cSMG, and OC doses significantly correlated with XQ-summary, XQ-eating, and HNQOL-eating scores. On multivariate analysis, bPG and OC doses significantly correlated with XQ-summary, XQ-eating, and HNQOL-eating scores; and cSMG dose with HNQOL-summary. Combining doses to all three structures yielded the highest R^2 for XQ-summary, XQ-rest, XQ-eating, and HNQOL-eating. In the 147 patients who received a mean cSMG dose =< 39 Gy, there were no failures in contralateral level IB.

Conclusion: Reducing doses to all salivary glands maximizes PROMs. A cSMG dose constraint of =< 39 Gy does not increase failure risk.

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Two-Year Prospective Patient Reported Outcomes Related to Dysphagia After Intensity Modulated Proton Therapy for Oropharyngeal Cancer

K.A. Hutcheson,[1] R. Ye,[2] P. Blanchard,[3] G.B. Gunn,[4] C.D. Fuller,[3] J.S. Lewin,[1] and S.J. Frank[3]; *[1]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [4]The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Characterize longitudinal change in swallowing related quality of life during and after intensity modulated proton therapy (IMPT) for oropharyngeal cancer.

Materials/Methods: The MD Anderson Dysphagia Inventory (MDADI) was administered prospectively at baseline, end of IMPT, and 10 weeks, and 6 , 12, and 24 months after IMPT as part of a prospective proton therapy registry. MDADI 19-item composite and subscale scores were plotted longitudinally. Pairwise tests were Bonferroni corrected for multiple comparisons ($P<.003$).

Results: Sixty-six patients with a mean age of 62 were included. Almost all had stage III/IV disease (96%) and 71% were treated with concurrent chemotherapy. A majority had T1-T2 primary tumors (80%); 84% had p16 positive disease and 41% were never smokers. Mean composite MDADI was 88.2±13.4 at baseline, dropping significantly to a nadir of 59.4±14.2 at end of IMPT ($P<.001$) with significant partial recovery by 10 weeks post-IMPT to 74.9±14.2 ($P<.001$) with stable average performance thereafter through 2 years ($P>.003$ compared to previous time point). Poor MDADI (score<60) were reported in 7%, 61%, 20%, and 13% of patients at baseline, end-IMPT, 10 weeks, and 2 years after IMPT, with 14% of patients showing persistently depressed MDADI Δ>20 at 2 years. Physical subscale performed lower than emotional or functional subscales at all points.

Conclusion: Herein, we provide novel, prospective benchmark data suggesting potentially early recovery of perceived swallowing per MDADI after IMPT in OPC survivors. Expected performance patterns lend support to validity of MDADI after proton therapy.

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The Risks of Developing Hypothyroidism With Immune Checkpoint Inhibitors

M. Nagasaka,[1,2] R. Alhasan,[3] N. Abdallah,[2] S. Patel,[1,2] H.E. Kim,[1,2] S. Kim,[1,2] and A. Sukari[1,2]; *[1]Karmanos Cancer Institute, Detroit, MI, [2]Wayne State University, Detroit, MI, [3]Michigan State University, East Lansing, MI*

Abstract 272; Table

	Hypothyroidism			
	Unadjusted*		Adjusted	
	OR (95% CI)	Signif	OR (95% CI)	Signif
Age	1.012 (0.986,1.04)	0.373	1.021 (0.992,1.053)	0.163
Agent				
Single#	Reference (Ref)		Ref	
Combination&	1.855 (0.873,3.829)	0.099	4.078 (1.532,11.525)	*0.006*
Primary tumor				
Hodgkin/Head and Neck	Ref		Ref	
Others	0.629 (0.256,1.706)	0.331	0.261 (0.081,0.844)	*0.023*
Clinical trial				
Off	Ref		Ref	
On	0.776 (0.39,1.522)	0.462	0.403 (0.154,0.974)	0.051

Univariable and multivariable logistic regression analyses of factors associated with toxicities (Grade 2+)*, univariable logistic regression; $, multivariable logistic regression; #, Nivo and Pembro; &, Nivo+ and Pembro+.

Purpose/Objective(s): PD-1 inhibitors work by reinstating natural anti-cancer immune-mediated cytotoxicity. Data on the characteristics of patients (pts) who are more likely to experience certain adverse events (AE) are limited. We focused on evaluating the risks for developing hypothyroidism in pts who were treated with PD-1 inhibitors.

Materials/Methods: Data from pts who received ≥ 1 dose of PD-1 inhibitors between August 2011 to August 2016, were captured from our single-institutional pharmacy database. AE of hypothyroidism among others were recorded and graded based on CTCAEv4 during follow up. Baseline pt characteristics were statistically compared between subjects who received PD-1 inhibitors on a clinical trial versus the standard of care by Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Univariable and multivariable logistic regression models were fit to assess associations between toxicities (Grade0-1 vs. Grade2+) and predictors (age, agent, primary tumor, and trial status).

Results: A total of 231 pts received ≥ 1 dose of PD-1 inhibitors prior to data cutoff. Median age was 65 (24-92) off trial (n=125) and 59. 5 (25-79) on trial (n=106). Of these, 117 (51%) had non-small cell lung cancer (NSCLC), 41 (18%) renal cell carcinoma (RCC), 24 (10%) melanoma, 18 (8%) Hodgkin's lymphoma (HL), 9 (4%) head and neck squamous cell carcinoma (HNSCC), and 15 others were included. Forty-two (18%) pts had ≥ grade 2 hypothyroidism. Hypothyroidism was more likely to develop with combination vs single agent PD-1 inhibitors (adjusted $P=.006$) after adjusting for age, primary tumor, and trial status (on vs off). HL and HNSCC pts had higher odds to experience grade 2 ≥ hypothyroidism (adjusted $P=.023$) than those with other primary tumors, after adjusting for age, agent (single vs combination) and trial status (Table1). Prior radiation to the head and neck area may have contributed to the higher risk in this cohort. Further analysis to evaluate the correlation between prior radiation and development of hypothyroidism is ongoing.

Conclusion: The risk of developing hypothyroidism associated with immune checkpoint inhibitors was significantly higher with HNSCC and HL patients.

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Model Based Radiation Therapy: Submandibular Dose-Response NTCP-Curve Based on Objective Measurements

C. Terhaard,[1] J. Vermaire,[1] T. Dijkema,[2] M. Philippens,[1] P. Braam,[2] J. Roesink,[3] and C.P. Raaijmakers[1]; *[1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Radboudumc, Nijmegen, Netherlands, [3]University Medical Center Utrecht, Utrecht 3584CX, Netherlands*

Purpose/Objective(s): Submandibular gland (SMG) normal tissue complication probability (NTCP) curves will be part of model-based

indication for proton therapy in the Netherlands. Subjective measurements of xerostomia and sticky saliva reflect whole saliva, and are not suitable for the determination of the SMG NTCP curve. Therefore, we performed direct measurements of salivary flow, including the SMG flow. Based on a large database with a broad mean SMG dose distribution we obtained NTCP curves 6 weeks and 1 year after therapy.

Materials/Methods: We utilized dose-response data of 200 head-and-neck patients, obtained from prospective salivary gland function studies. SMG flow was measured before, 6 weeks, and 1 year after therapy. Thirty patients were treated after unilateral neck dissection. Patients with N2c or N3 nodes were excluded. Tumors were localized in the oropharynx (69%), larynx (14%), nasopharynx (9%), oral cavity (4%), and hypopharynx (3%), 38% were N_0, 32% T_{3-4}. Treatment consisted of conventional RT, non-SMG sparing IMRT, SMG sparing IMRT, in 34, 84, and 82 patients, respectively. The mean dose to the ipsilateral submandibular gland was 62Gy, for the contralateral submandibular gland 47 Gy (range 0-72 Gy). Flow rates were converted to the baseline unilateral SMG flow rate, and compared with the contralateral SMG mean dose. Data were fitted to logistic regression (LR) and the Lyman-Kutcher-Burman (LKB) model, with a complication defined as a flow 6 weeks/ 1 year after therapy <25% of the flow before therapy [1].

Results: There was a highly significant correlation between increasing mean SMG dose and decreasing absolute and relative SMG flow 6 weeks and 1 year after therapy. Mean contralateral SMG dose could be divided in five groups: ≤30 Gy (n=30), 30-40 Gy (28) 40-50 Gy (32), 50-60 Gy (57), > 60 Gy (53), the complication rate at 6 weeks was 22%, 50%, 73%, 76% and 86%, respectively; at 1 year 30%, 31%, 75%, 86% and 94%, respectively (P<.001). The D50 after 6 weeks was 31 Gy (95% CI 24-37), and 28 Gy (95% CI 21-34) after 1 year after analysis with the LKB model; 33 Gy (26-40) and 34 Gy (28-40), respectively, using the LR model.

Conclusion: This NTCP-curve for submandibular gland function is based on the largest database of objective measurements in the literature. For planning purposes, usually a mean SMG-dose constraint of 40 Gy is chosen. We recommend a mean SMG dose of less than 30 Gy. [1] Dijkema et al. *Int J Radiat Oncol Biol Phys*. 2010:78;449-453.

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Smoking Cessation After Treatment of Squamous Cell Head and Neck Cancer: The Impact of Survivorship Counseling

J. Bodmann,[1] B.A. Harr,[2] C.A. Reddy,[2] D. Ives,[1] J. Ferrini,[1] J.L. Geiger,[1] S. Koyfman,[2] N.P. Joshi,[2] N.M. Woody,[2] and D.J. Adelstein[1]; *[1]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Continued tobacco abuse after diagnosis and treatment of squamous cell head and neck cancer (SCHNC) is associated with an increased risk of treatment failure and second primary malignancies. The purpose of this study is to characterize patients more likely to stop smoking after head and neck cancer treatment and explore the impact of survivorship counseling on tobacco cessation.

Materials/Methods: Patients with locoregionally advanced SCHNC who underwent definitive treatment at a single institution were retrospectively analyzed from an IRB-approved database. All patients analyzed were eligible for survivorship visits, which included smoking cessation counseling beginning at 6 months after completing treatment. Patients with persistent disease, those lost to follow up or deceased at 1 year were excluded. All patients were considered to be active smokers and had smoked cigarettes within 90 days of their cancer diagnosis. Smoking rates 1 year after completion of therapy were analyzed using logistic regression and multivariate analysis.

Results: A total of 175 patients treated from 2011-2016 were identified. The sample was comprised largely of Caucasian (78.9%) males (76.6%). The majority of patients had either larynx (38.3%) or oropharynx (37.1%) cancer. All patients were smokers with an average of 39.4 pack-year history of smoking. All patients received radiation therapy (RT), 68% of patients received chemotherapy, and 33.1% underwent surgery; 13.1% were treated with RT alone. Of all patients analyzed, 61.7% had stopped smoking 1 year after completing therapy. In multivariable analysis, patients who quit smoking were more likely to be female (P=.0395), not heavily consume alcohol (P=.0003), have a lower T-stage (P=.0262) and have received multimodality treatment versus RT alone (P=.0018). Survivorship visits were completed for 62 (35.4%) patients 3.9- 43.6 months after completing therapy. Those who received survivorship counseling within the first year after treatment, 73.9% had stopped smoking. In patients who received survivorship counseling after treatment, there was a univariate trend (P=.12) towards smoking cessation when compared to those patients not counseled.

Conclusion: Although many patients are able to successfully quit smoking after treatment of SCHNC, heavy alcohol drinkers, patients with more advanced T-stages, and those treated with RT alone are less likely to stop smoking. In this targeted population, survivorship counseling may play a role in smoking cessation.

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Patient Perspectives of Head and Neck Survivorship Care

S. Massa,[1] R. Rhode,[2] C. Mckinstry,[2] N. Osazuwa-Peters,[2] G. Ward,[2] and R. Walker[2]; *[1]Saint Louis University School of Medicine, Saint Louis, MO, [2]Saint Louis University, St Louis, MO*

Purpose/Objective(s): With increasing head and neck Cancer survival, survivorship care is increasingly stressed by guidelines and patients alike. However, an understanding of the patient's perspectives is lacking. This study assesses patient views on the value and burdens of survivorship care.

Materials/Methods: A cross-sectional survey gathered data from adult patients with squamous cell carcinoma of mucosal head and neck sites. Patients with active disease or less than 3 months from treatment completion were excluded. A novel survey tool assessed income, employment and the financial, logistical and psychological burdens of clinic visits (assessed on continuous 100% scales). Retrospective chart review gathered clinical data. Results were compared based on sex, time from diagnosis, and desired visit frequency using univariate tests. Multivariate linear regression models were created to identify factors associated with increased stress.

Results: To date, 63 of 200 patients have completed this study. Respondents were 71.4% male, 87.3% white, with mean age of 62.5 years and follow up ranging 3-36 months. Household income was <$30,000 for 29 (46.0%) and 22 (34.9%) live alone. Most patients were satisfied with the frequency of tests (73.0%) and visits (74.6%). Patients desiring more visits were less often white (50.0% vs 81.8%, P=.046), had less advanced disease (stage IV 25% vs 64%, P=.515), lower incomes (<$30,000 100% vs 72.7%, P=.108), and lived alone (75.5% vs 54.5%, P=.050). These patients reported less spousal support (P=.039) and more often required medical transport (50% vs 27.3%, P=.087). Concern for recurrence was most stressful (61.5%), followed by medical care costs (38.6%), travel logistics (26.3%), and time away (22.5%) and cost of travel (22.7%). Patients desiring more visits reported more stress (62.1% vs 29.3%, P<.001), especially from recurrence (93.8% vs 69.6%, P=.04) and cost of travel (63.8% vs 32.3%, P=.001). In the multivariate model, higher overall stress was only significantly associated with dual modality treatment compared with surgery alone (P<.05).

Conclusion: HNC survivors are generally satisfied with survivorship care. Patients with higher stress related to visits and less spousal support desire more frequent visits. This may be attributable to a high concern for recurrence and the associated relief if no recurrence is found. These results will help guide patient-centered survivorship care.

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Postoperative Radiation Effects on Lymphopenia, Neutrophil to Lymphocyte Ratio, and Clinical Outcomes in Palatine Tonsil Cancers

A.J. Lin,[1] Y.J. Rao,[1] R.I. Chin,[2] J.L. Campian,[3] D. Mullen,[1] D. Thotala,[1] M.D. Daly,[1] H.A. Gay,[1] D.E. Hallahan,[1] D. Adkins,[3] and W.L. Thorstad[1]; *[1]Washington University in St. Louis, Department of Radiation Oncology, St. Louis, MO, [2]Saint Louis University School of Medicine, St. Louis, MO, [3]Washington University in St. Louis, Department of Medical Oncology, St. Louis, MO*

Purpose/Objective(s): Radiation-induced lymphopenia and pretreatment neutrophil to lymphocyte ratio (NLR) have been associated with head and neck cancer relapse. We hypothesized unilateral neck radiation could reduce rates of iatrogenic immunosuppression, and posttreatment NLR may be a useful prognostic clinical biomarker.

Materials/Methods: Patients with palatine tonsil squamous cell cancer treated with postoperative radiation therapy (RT) at a single institution from 1997-2013 were reviewed retrospectively for grade 3-4 (ALC < 500 cells/mm^3) and grade 4 (ALC < 200 cells/mm^3) lymphopenia. Acute lymphopenia was evaluated at 3 weeks, 6 weeks, and 9 weeks after start of RT (60-70Gy). Prolonged lymphopenia was evaluated at 6 months and 12 months post-RT. Neutrophil counts were analyzed to calculate NLR. Receiver operating characteristic (ROC) analysis was used to determine NLR thresholds which were predictive of clinical outcomes. Logistic regression was used to determine clinical and treatment-related predictors of lymphopenia and elevated NLR. Kaplan-Meier and Cox analyses were done to show the association of lymphopenia and elevated NLR with locoregional control (LRC), freedom from distant metastases (FFDM), and overall survival (OS).

Results: Out of 154 patients treated with postoperative RT, 99 patients had ALC recorded at least at baseline and within 1 year of starting RT. Patients receiving bilateral neck RT (n = 70) and unilateral neck RT (n = 29) were predominantly stage IVA (79% vs 93%, respectively), p16+ (90% vs 96%, respectively), and received concurrent chemotherapy (69% vs 86%, respectively). Acute grade 3-4 lymphopenia occurred in 79% of bilateral neck RT patients and 58% of unilateral neck RT patients, $P = .03$. Acute grade 4 lymphopenia occurred in 15% of bilateral neck RT patients and none of the unilateral neck RT patients, $P = .04$. There were no significant differences in late grade 3-4 (21% vs 5%) or grade 4 (3% vs 0%) lymphopenia. Unilateral neck RT protected against acute grade 3-4 lymphopenia (OR = 0.322, 95% confidence interval [CI] 0.113-0.920) and acute NLR > 11.875 (OR = 0.156, 95% CI 0.043-0.568), but not late lymphopenia or late elevated NLR in logistic regression. Lymphopenia at any timepoint and pre-RT NLR was not associated with LRC, FFDM, or OS. Acute NLR > 11.875 correlated with worse OS (HR = 4.403, 95% CI 1.177-16.475). Late NLR > 6.875 independently correlated with significantly worse FFDM (HR = 15.942, 95% CI 1.852-137.190) and OS (HR = 12.020, 95% CI 3.024-47.778).

Conclusion: Unilateral neck radiation for tonsil cancer reduces rates of acute grade 3-4 lymphopenia. Elevated acute and late NLR may help identify postoperative palatine tonsil patients who are at higher risk of metastasizing and subsequent mortality.

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Comparison of Clinician-Observed Versus Patient-Reported Toxicities Associated With Definitive Radiation for Older Patients With Head and Neck or Lung Cancer

D.H. Moon,[1] B.S. Chera,[1,2] A. Deal,[2] Y. Wang,[2] and N.A. VanderWalde[3]; *[1]University of North Carolina Hospitals, Chapel Hill, NC, [2]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, [3]University of Tennessee Health Science Center and West Cancer Center, Memphis, TN*

Abstract 277; Table

Symptom	MD underreporting vs patient (%)
Fatigue	80
Anorexia	89
Diarrhea	40
Nausea	70
Vomiting	30
Pain	68
Dysphagia	50
Xerostomia	80
Dyspepsia	47
Mucositis	65

Purpose/Objective(s): Accumulating evidence suggests disagreement between clinician-observed and patient-reported symptoms associated with cancer therapy, but this discrepancy in an older population receiving definitive radiation therapy (RT) is not well-understood. The concordance between clinician- and patient-reported toxicities and their association with poor tolerance to treatment were assessed.

Materials/Methods: Patients ≥65 years old with newly-diagnosed head and neck or lung cancer receiving definitive RT +/- chemotherapy (CT) were enrolled on a prospective, observational study (NCT01752751). Clinician-reported toxicities were evaluated using CTCAE v4.02, and patient-reported toxicities were evaluated using PRO-CTCAE (patient-reported outcomes version of CTCAE). Patient's quality of life was assessed using EORTC QLQ-C30 questionnaire. Raw agreement between clinician and patient report of toxicities were assessed at baseline, during treatment (every 2 weeks), and at 6 weeks posttreatment. Association of clinician- and patient-reported symptoms with poor tolerance to therapy was assessed using the Jonckheere−Terpstra test. Poor tolerance was defined by hospitalization, >3-day treatment delay, change in treatment regimen (RT or CT), or death.

Results: Of the 50 patients enrolled on the study, 45 were available for analysis. Median age was 71 (31% ≥75 years of age), 60% of patients had head and neck primary, and 47% received concurrent CT with RT. In comparing CTCAE vs PRO-CTCAE, there was good agreement at baseline except fatigue, anorexia, and pain, where clinicians under-reported the grade/severity. The discrepancy increased during treatment with patients reporting higher severity in 66%, 65%, and 62% of the time for anorexia, fatigue, and xerostomia, respectively. At follow-up, the proportion of clinicians under-reporting the severity of symptoms vs patients was ≥50% in 7 of the 10 categories assessed (Table). CTCAE vs EORTC QLQ-C30 mirrored these findings. Clinician-observed symptoms associated with poor tolerance included fatigue, nausea, and dysphagia at 4 weeks. Patient-reported symptoms associated with poor tolerance included dysphagia (PRO-CTCAE) and nausea (EORTC QLQ-C30) at 2 weeks and diarrhea (PRO-CTCAE) at 4 weeks.

Conclusion: Clinicians under-report toxicities during and after definitive RT in older patients with head and neck or lung cancer. Yet, select toxicities reported by both patients and clinicians during treatment predicted for poor tolerance to therapy. Assessments by both patients and clinicians provide valuable and complementary information to help guide management.

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Predicting Dysphagia in Patients With Head and Neck Carcinomas Treated With Radiation Therapy Using Fluoroscopic Swallow Study Data

R.P. Shukla,[1] B.M. Kellum,[2] B.A. Dyer,[3] L.M. Evangelista,[4] A.F. Bewley,[4] D.G. Farwell,[5] M. Kuhn,[6] P. Belafsky,[5] M.E. Daly,[3] and S.S.D. Rao[7]; *[1]Oregon Health and Science University, Portland, OR, [2]University of Nevada, Reno, NV, [3]University of California Davis Comprehensive Cancer*

Center, Sacramento, CA, [4]UC Davis Medical Center, Sacramento, CA, [5]UC Davis Health System, Sacramento, CA, United States, [6]University of California, Davis, Sacramento, CA, [7]University of California, Davis, School of Medicine, Sacramento, CA

Purpose/Objective(s): Dysphagia can be a debilitating early and late side effect of radiation therapy (RT) and improved prediction tools are necessary. The purpose of this investigation was to evaluate the association between treatment, patient, and disease characteristics, and swallowing dysfunction in patients undergoing RT for head and neck carcinoma (HNC).

Materials/Methods: The data of all individuals undergoing RT for HNC between 01/01/15 and 12/31/16 were abstracted from an oncologic database. Swallowing metrics including objective measures from video fluoroscopic swallow studies (VFSS), Functional Oral Intake Score (FOIS), and the validated 10-item Eating Assessment Tool (EAT-10) were prospectively collected. VFSSs are routinely performed pre- and 3 months posttreatment in all patients at our institution. Secondary variables included patient demographics, Karnofsky performance status (KPS), tumor and pathologic characteristics, use of surgery and chemotherapy, delivered radiation doses, and organ-at-risk radiation doses. Factors associated with the development of poor swallowing outcomes were analyzed. Clinically significant changes in swallowing scores were defined as a change of >1 out of 7 points for FOIS, and a change of >3 out of 40 points for EAT-10. VFSS data were designated either 'normal' or 'abnormal' based on known normal limits. Data was analyzed using univariate analysis with Chi-square and t-tests.

Results: A total of 102 pts with complete swallowing data were evaluated. Median age was 64 (20-89) and 75% were male. Oropharynx was the predominant subsite (41%), followed by oral cavity (20%), and 67% had early-stage tumor (T1-2). 62% of pts underwent surgery and 52% received concurrent chemotherapy (CC). Median prescribed RT dose was 6600 cGy (4500-7440). Mean pre-and posttreatment EAT-10 scores for the cohort were 7.9 and 10.3, respectively ($P=.01$). Mean pre- and posttreatment FOIS was 6.1 and 5.9 respectively ($P=.22$). Mean anterior-posterior upper esophageal sphincter opening significantly decreased from 1.74 cm to 1.59 cm ($P=.04$). Univariate analysis comparing individual patient changes showed an increase in FOIS values in pts with T3-4 tumors versus T1-2 ($P=.024$) and for pts who received CC ($P=.006$). Increased EAT-10 dysphagia metrics were associated with higher mean pharyngeal dose, 4349 cGy versus 3545 cGy ($P=.015$). No association was observed between objective fluoroscopic data and age, gender, or KPS ($P>.05$).

Conclusion: Higher T stage and CC were significantly associated with poor functional swallowing outcomes after RT for HNC. Upper esophageal sphincter opening diameter significantly decreased after RT. A higher mean pharyngeal RT dose was associated with an increase in dysphagia symptoms. Ongoing studies correlating objective swallow data and RT in HNC pts may help elucidate predictors of dysphagia.

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Evaluation of NCCN Guideline Adherence in Elderly Head and Neck Cancer Patients: A Single Institution Study

J. Metkus,[1] K. Daniels,[2] J. Hamilton,[2] L. Sweeny,[2] D. Cognetti,[3] J.M. Curry,[4] and A. Luginbuhl[1]; *[1]Thomas Jefferson University Hospital, Philadelphia, PA, [2]Thomas Jefferson University, Philadelphia, PA, [3]Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA, [4]Sidney Kimmel Cancer Center at Thomas Jefferson University Hospital, Philadelphia, PA*

Purpose/Objective(s): Head and neck cancer (HNC) is becoming more a disease burden of the elderly. The National Comprehensive Cancer Network (NCCN) treatment guidelines can be difficult to follow in this cohort of patients due to increasing comorbidities, side effect tolerability, and goals of care. The purpose of this analysis was to compare elderly patients who followed NCCN treatment guidelines versus those who did not in terms of overall survival (OS), disease free survival (DFS), hospital readmission and treatment-related complications (TRC).

Abstract 279; Table Survival-, treatment-, and hospital-related comparisons between NCCN and non-NCCN cohort

N = 159		Combined Data	Non-NCCN cohort (N= 67)	NCCN cohort (N=92)	*P* value
Age		86.1	85.4	86.5	.106
Charleston Index		8.1	7.9	8.3	.371
OS (months)		17.4	17.9	17.1	.625
DFS (months)		15.5	17.4	13.9	.866
Locoregional Recurrence:		22 (13.8%)	7 (10.4%)	15 (16.3%)	.356
Distant Metastasis:		28 (17.6%)	17 (25.4%)	11 (12.0%)	.035
Length of Stay		5.0	5.9	4.3	.059
Treatment-related Complications		82 (51.6%)	43 (64.2%)	39 (42.4%)	.010
30-day Readmission		68 (42.8%)	30 (44.8%)	38 (41.3%)	.746
Discharge Destination	Home	99 (62.3%)	41 (61.2%)	58 (63.0%)	.303
	Rehab	37 (23.3%)	13 (19.4%)	24 (26.1%)	
	SNF	22 (13.8%)	12 (17.9%)	10 (10.9%)	

Materials/Methods: Single-center retrospective analysis of 159 patients >80 years old undergoing treatment at a tertiary academic institution. NCCN guideline recommendations were made in a blinded fashion by faculty in the department. Multivariate analysis was used to compare the two groups to evaluate significant differences in OS, DFS, Recurrence, Hospital Readmission rates, and TRC.

Results: A total of 159 patients were identified >80 that were diagnosed with HNC. Of this group, 67 (42%) patients did not complete appropriate NCCN guideline treatment and 92 (58%) patients underwent appropriate NCCN treatment. Multivariate analysis was conducted to evaluate the differences between the two groups. Table 1 summarizes treatment, survival and hospital related data. The two groups did not have a significant difference in comorbid conditions, evaluated using the Charleston index ($P=.371$). In addition, the groups showed no significant difference in OS ($P=.625$), DFS ($P=.826$), length of stay ($P=.059$), 30-day readmission ($P=.746$) or discharge destination after surgery ($P=.303$). The non-NCCN group was found to have a statistically significant higher amount of TRC (43 vs 39, $P=.010$), and distant metastasis (17 vs 11, $P=.035$).

Conclusion: Various reasons, such as comorbid medical conditions, exist why elderly patients do not complete recommended oncologic therapy. When controlling for tumor stage, subsite, and elderly comorbid conditions, our institution's elderly patients (>80 years old) demonstrate an increase in metastasis when full therapy is not followed but this did not translate into a decrease in overall survival.

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Increased Risk of Cranial Nerve Palsy in 10-Year Survivors of Head and Neck Cancer After Primary Surgery and Adjuvant Radiation

Y. Dong, J.A. Ridge, T. Li, T.M. Churilla, M. Lango, J. Bauman, and T.J. Galloway; *Fox Chase Cancer Center, Philadelphia, PA*

Purpose/Objective(s): To characterize the late complication of cranial nerve palsy (CNP) among 10-year survivors after radiation therapy for head and neck cancer (HNC).

Materials/Methods: We retrospectively evaluated patients treated with curative-intent radiation for HNC between 1990-2005 at a single institution with systematic multidisciplinary follow-up ≥10 years. CNP was diagnosed by exclusion. Patients with new CNP appreciated on clinic examination were evaluated with imaging and biopsy as necessary. When evaluation did not identify a structural or malignant cause to the new CNP,

it was attributed to a late complication of treatment. Cox model was used for multivariable analysis (MVA) for time to CNP after completion of radiation. Parameters included in MVA were subsite of primary disease (pharynx/larynx vs others), T-stage (T3-T4 vs T1-T2), N-stage (N2-N3 vs N0-N1), primary surgery before radiation (yes vs no), postradiation neck dissection (yes vs no), chemotherapy (yes vs no), radiation dose (continuous variable).

Results: We identified 112 patients with follow-up ≥ 10 years (median 12.2 years). The primary tumor sites were pharynx (42%), oral cavity (34%), larynx (13%), and other (11%). Forty-four percent underwent surgery before radiation, 24% had post-radiation neck dissection, and 47% received chemotherapy. Nearly all patients (96%) were treated with 2D radiation planning with prescription to isocenter, with a median prescribed radiation dose of 70 Gy (50-75 Gy). A total of 16 (14%) patients were found to have late complication of at least one CNP, including 6 with 2 separate CNPs, and 1 with 3 separate CNPs. The median time to first documented CNP among these 16 patients was 7.7 years (range 0.6-10.6 years). The most common CNP was XII deficit in 8 patients (7%), appreciated as a flaccid, atrophied hemi-tongue with ipsilateral deviation on protrusion. Next was cranial nerve X deficit in 7 patients (6%), appreciated as a vocal cord paralysis on laryngeal examination. Others included cranial nerve V deficit in 3 patients, appreciated as facial numbness over the distribution of trigeminal nerve, and cranial nerve XI deficit in 2 patients, appreciated as weakness or atrophy of trapezius muscle. On MVA, treatment with primary surgery was the only significant factor associated with the development of CNP after completion of radiation, with hazard ratio (HR) of 7.1 (95% CI 1.4-37.3), $P=.02$. Chemotherapy approached significance in MVA for increased risk of CNP, with HR of 4.0 (95% CI 0.8-18.0), $P=.07$.

Conclusion: Iatrogenic CNP can develop years after completion of head and neck cancer treatment. Patients who underwent surgery prior to radiation seemed to have significantly increased risk of late CNP.

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Long-Term Patient-Reported Quality of Life After SBRT for Recurrent, Previously-Irradiated Head and Neck Cancer

J. Thomas,[1] D.C. Ling,[2] D.A. Clump II,[2] R.L. Ferris,[3] U. Duvvuri,[3] J. Ohr,[4] and D.E. Heron[2]; *[1]University of Pittsburgh School of Medicine, Pittsburgh, PA, [2]Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [3]Department of Otolaryngology, Eye & Ear Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, [4]Department of Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA*

Purpose/Objective(s): Stereotactic body radiation therapy (SBRT) is increasingly used for recurrent head and neck cancer (rHNC). While the safety and efficacy of SBRT in this setting has been demonstrated, late toxicity rates have been reported as high as 18.9% with long-term follow-up. Our previous work has examined patient-reported quality of life (PR-QOL) in this population, with a median follow-up time of 6 months. Herein, we report PR-QOL in a cohort of patients with a minimum post-treatment follow-up of 1 year and aim to identify potential predictors of PR-QOL such as late toxicity.

Materials/Methods: A retrospective review was performed on 64 patients who underwent SBRT for previously irradiated rHNC. PR-QOL was evaluated before and after treatment using the University of Washington Quality of Life Questionnaire, a validated 100-point Likert-scale survey measuring overall, health-related PR-QOL, and PR-QOL in specific head and neck domains. The Mann-Whitney U test was used to identify significant differences in the overall PR-QOL between groups of patients dichotomized by the following variables: age >65, sex, re-irradiation interval <24 months, tumor volume >25 cc, smoking history >10 pack-years, squamous vs. non-squamous tumor histology, prior chemotherapy use, previous salvage surgery, concurrent biologic use, baseline overall PR-QOL <50 vs ≥50, and the presence or absence of grade ≥3 late toxicities.

Results: At a median survey follow-up of 21 months, the presence of grade ≥3 late toxicities was associated with decreased overall QOL at 3-24 months posttreatment. Mean overall PR-QOL in patients with and without grade ≥3 late toxicities, respectively, was 40 versus 69 at 3 months ($P < .01$), 52 versus 62 at 6 months ($P = .08$), 48 versus 66 at 9 months ($P = .02$), 53 versus 64 at 12 months ($P = .05$), and 40 versus 65 at 24 months ($P = .02$), respectively. Baseline overall PR-QOL <50 was associated with decreased QOL at 1-12 months posttreatment, but not beyond. Mean overall PR-QOL in patients with baseline overall PR-QOL <50 and ≥50, respectively, was 45 versus 65 at 1 month ($P < .01$), 43 versus 73 at 3 months ($P < .01$), 40 versus 64 at 6 months ($P < .01$), 46 versus 65 at 12 months ($P = .01$), 50 versus 56 at 18 months ($P = .66$), 45 versus 60 at 24 months ($P = .20$), and 60 versus 60 at 36 months ($P = 1.00$). Tumor volume >25 cc was associated with decreased PR-QOL at 6-18 months posttreatment. Mean overall PR-QOL in patients with tumor volume >25 cc and ≤25 cc, respectively, was 53 versus 66 at 6 months ($P = .03$), 55 versus 69 at 12 months ($P = .04$), and 49 versu. 63 at 18 months ($P = .07$)

Conclusion: Patients with grade ≥3 late toxicities or tumor volume >25 cc tend to report reduced long-term overall PR-QOL following SBRT for previously irradiated rHNC. Patient selection should be optimized to minimize the risk of late toxicities in this population.

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Health-Related Quality of Life Following Radiation Therapy for Oropharyngeal Carcinoma

G. Rajeev-Kumar, A. Kelley, V. Gupta, and R.L. Bakst; *Icahn School of Medicine at Mount Sinai, New York, NY*

Purpose/Objective(s): While substantial research exists on physical toxicities from radiation therapy (RT) for oropharyngeal cancers (OPC), emotional health is understudied. The purpose of this study was to analyze self-reported emotional and physical well-being before and after RT and how these impact patients' overall health-related quality of life (HRQOL). We predicted that decline in mood and anxiety would be strongly correlated with worsening physical function.

Materials/Methods: We collected University of Washington Quality of Life (UWQOL) questionnaires prospectively and identified OPC patients treated with curative intent with RT from 2013 to 2016 who had completed questionnaires post RT for up to 3 years of follow-up. The UWQOL domains of swallow, taste, and saliva were assessed for physical function and compared to the domains of mood and anxiety (emotional). The domains were scored evenly from 0 to 100 with 100 corresponding to the response representing the best HRQOL.

Results: A total of 67 patients were evaluated. Patient characteristics included: median age 59 (range 31-81); 76.0% male; 59.7% stage IV. Radiation was delivered in the definitive setting in 46.3% of patients and adjuvantly in 53.7%. Mean radiation dose was 64.3 Gy with 50.7% receiving concurrent chemotherapy. After an initial decline following RT, swallowing was the only physical domain that improved beyond baseline ($P=.043$). Taste remained significantly worse for 18 months ($P<.001$) and saliva at all time points ($P<.001$). In contrast, mood (≥ 6 months) and anxiety (at all time points) were significantly better following RT. Mood but not anxiety directly correlated with physical toxicities at consult and immediately after RT. However, after 18 months, there was no significant

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Months post-RT	Before RT	3	6	12	18	24	30	36
Domain *Mean (SD)*								
Swallow	78 (24)	70* (26)	74 (24)	84* (18)	79 (19)	81 (21)	82 (21)	86 (18)
Saliva	93 (20)	52* (29)	52* (29)	69* (23)	66* (23)	64* (22)	71* (21)	66* (19)
Taste	81 (29)	47* (35)	54* (30)	72 (28)	61* (28)	72 (21)	78 (20)	78 (14)
Mood	75 (20)	80 (27)	81* (22)	89* (16)	85* (18)	88* (21)	86* (16)	90* (17)
Anxiety	64 (30)	73* (29)	83* (17)	85* (22)	78* (30)	93* (13)	87* (15)	79* (22)

*$P<.05$ for comparison between pre- and post-RT scores; higher scores correspond to better QOL.

correlation between emotional- and physical-QOL domains except for correlation between anxiety and saliva at 36 months ($r = 0.665$, $P=.018$).
Conclusion: In our cohort of patients, emotional health improved over time despite decline in physical function. Physical and emotional health are most strongly associated immediately before and after RT but not at later time points. Therefore, resources addressing emotional health should be allocated at earlier time points in the course of treatment.
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Factors Impacting the Development of Neck Fibrosis in Head and Neck Cancer Patients Following Radiation Therapy

C.L. Pratson,[1] C.H. Shelton,[2] B.N. Brodish,[3] P. Lepera,[1] and A.W. Ju[4]; *[1]East Carolina University, Brody School of Medicine, Greenville, NC, [2]Outerbanks Radiation Therapy, Nags Head, NC, [3]Eastern Carolina ENT, Greenville, NC, [4]East Carolina University, Greenville, NC*

Purpose/Objective(s): To evaluate the demographic factors associated with greater incidence and severity of neck fibrosis in head and neck cancer patients following radiation therapy at an institution that treats a relatively large percentage of non-Caucasian and underserved patients
Materials/Methods: We retrospectively reviewed the medical records of patients treated at a single tertiary care center for primary cancers of the head and neck between 2013 and 2017 who received at least 6 months follow-up. Chi-square and Mann-Whitney U tests were used in the univariate analysis. A multiple logistic regression model to predict the development of neck fibrosis was developed using variables deemed significant or approaching significance on univariate analysis.
Results: The median follow-up for our patient cohort was 30.5 months. Of the 66 patients included in our study, 33 were Caucasian, 32 African-American, and 1 another ethnicity. Thirty patients were either uninsured or insured by Medicaid and 36 had either Medicare or private insurance. Neck fibrosis was graded in patients using CTCAE v4. On univariate analysis, neck fibrosis of any grade was shown to be more common in both non-Caucasian patients ($P=.028$) and patients that were uninsured or insured by Medicaid ($P=.014$). Neck fibrosis was more likely in subjects who were actively smoking ($P=.001$) or actively drinking alcohol during treatment ($P=.026$) as well as in subjects with higher AJCC 7ed Stage at diagnosis ($P=.035$), recurrent cancer ($P=.042$), and treatment during middle age (45-65 years old) or younger ($P=.0001$). Variables that retained significance on multivariate analysis included smoking during treatment ($P=.016$), alcohol use during treatment ($P=.033$), and younger age ($P=.001$)
Conclusion: Ongoing smoking and alcohol use during treatment appear to contribute to the development of fibrosis in our patient population following head and neck radiation therapy. Younger patients also had higher risk for developing neck fibrosis. On univariate analysis, ethnicity and insurance status had a role in the development of neck fibrosis as well. Although ethnicity and insurance status were not independent risk factors on multivariate analysis, they may still aid in identifying an at-risk patient population. Identification and intervention directed at patients who are at high risk for fibrosis prior to treatment has the potential to improve long-term quality of life. Further study is needed to confirm this trend across a larger patient population.
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Two-Year Prevalence of Dysphagia and Related Outcomes in Head and Neck Cancer Survivors: An Updated SEER-Medicare Analysis

K.A. Hutcheson,[1] Z. Nurgalieva,[1] G.B. Gunn,[2] S. Giordano,[3] H. Zhao,[3] M. Bhayani,[4] and C. Lewis[1]; *[1]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Department of Health Service Research, The University of Texas MD Anderson Cancer Center, Houston, TX, [4]NorthShore University Health System, Evanston, IL*

Purpose/Objective(s): Using a national database, we aimed to examine prevalence of dysphagia at the population level in head and neck cancer (HNC) survivors.
Materials/Methods: Surveillance, Epidemiology, and End Results (SEER)-Medicare data were retrospectively analyzed among 16,194 eligible HNC patients treated between 2002 and 2011. Claims were used to estimate prevalence of 3 swallowing-related endpoints within 2 years of treatment: dysphagia, stricture, and aspiration pneumonia and derive treatment- and site-specific estimates. Multiple logistic regression was conducted with stepwise backward selection.
Results: Dysphagia, stricture, and aspiration pneumonia were prevalent, occurring among 45.3% (95% CI: 44.5-46.1), 10.2% (95% CI: 9.7-10.7), and 8.7% (95% CI: 8.2-9.1) of all patients, respectively. Prevalence of aspiration pneumonia and stricture remained stable over the decade, but dysphagia increased by 11.7%. Prevalence of all swallowing-related endpoints was highest among those treated with chemoradiation. Relative to single modality surgery, single modality radiation was associated with 2.1 (95% CI: 1.8-2.4), 1.3 (95% CI: 0.97-1.6), and 1.4 (95% CI: 1.1-1.8) greater odds of dysphagia, stricture, and aspiration pneumonia respectively. Relative to single modality RT, multimodality surgery+RT or CRT was associated with 1.5 (95% CI: 1.3-1.7), 1.7 (95% CI: 1.4-2.1), and 1.2 (95% CI: 0.95-1.5) or 2.9 (95% CI: 2.5-3.3), 2.3 (95% CI: 1.9-2.8), and 1.6 (95% CI: 1.3-2.0) greater odds of dysphagia, stricture, and aspiration pneumonia, respectively. Relative to multimodality surgery+RT, CRT was associated with 1.9 (95% CI: 1.7-2.2), 1.3 (95% CI: 1.1-1.5), and 1.3 (95% CI: 1.1-1.6) greater odds of dysphagia, stricture, and aspiration pneumonia respectively.
Conclusion: Prevalence of dysphagia, stricture, and aspiration pneumonia were similar in the decade studied (2002 to 2011) when comparing to published rates using similar methodology in an earlier decade (1992-1999), suggesting persistence of this morbidity in the decade in which IMRT was popularized.
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Temporal Lobe Radiation Necrosis After Primary Radiation Involving the Skull Base With Proton Therapy: An Institutional Experience

K.L. Pitter,[1] A. Lee,[1,2] C.H.J. Chow,[3] K. Sine,[4] O. Cahlon,[1] S. McBride,[1] C.J. Tsai,[1] J.E. Leeman,[1] N. Riaz,[1] D.S. Higginson,[1] T. Waldenberg,[1] M. Cohen,[5] I. Ganly,[5] J.O. Boyle,[5] R.J. Wong,[5] C.W. Brennan,[5] S.S. Baxi,[6] E. Sherman,[6] L. Michel,[6] and N. Lee[1]; *[1]Department of Radiation*

Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Radiation Oncology, SUNY Downstate Medical Center, Brooklyn, NY, [3]Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, Hong Kong, [4]ProCure Proton Therapy Center, Somerset, NJ, [5]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, [6]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Purpose/Objective(s): To analyze clinical and dosimetric factors for the occurrence of temporal lobe necrosis (TLN) among patients without prior radiation who then received proton therapy involving the skull base in the upfront setting.

Materials/Methods: We sought to identify patients without prior radiation who received proton therapy involving the skull base and had clinical and radiographic follow up. Analyzed factors included age, histology, stage, and composite mean dose to 2 cc and composite max pixel dose for the temporal lobes. Outcomes of interest included the grade of TLN, incidence of TLN, as well as time to development of TLN from treatment.

Results: Between 09/2013 and 03/2017, we identified 142 patients who received proton radiation to the skull base and temporal lobes (n=121 proton only, n=21 IMRT with proton boost) with a median follow-up time of 15 months (range 1-45) and median age of 59 years (14-89). The most common primary tumor was salivary gland (49.7%), followed by sinonasal (24.5%), cutaneous (11.8%) and nasopharynx (5.6%). The majority of patients (86.4%) had nonrecurrent tumors with >T3 primaries (51.2%), and the most common histologies were squamous cell carcinoma (27.2%), adenocystic carcinoma (25.1%), and other salivary histologies (25.1%). The median prescribed dose was 66 CGE (range 14.80-77) for proton only and 24 CGE (range 10-26) for proton boost plans. The total mean dose to 2 cc and max pixel dose to the temporal lobes of 49.86 CGE (IQR 40.02-63.35) and 57.38 CGE (IQR 53.3-73.2), respectively. Seven patients (4.9%) developed TLN at a median time of 9 months (3-27). The median total mean dose to 2 cc and max pixel dose to the temporal lobes for TLN patients was 71.3 CGE vs 54.5 CGE (P =.013) and 75.4 CGE vs. 62.77 CGE (ns). Five of the 7 patients with TLN had CTCAE grade 1 events with only radiographic evidence and 2 had grade 3 events requiring resection for symptomatic management. Both patients have had symptomatic improvement since surgery.

Conclusion: We found that proton therapy for head and neck cancers with skull base exposure resulted low rates of symptomatic temporal lobe necrosis. Consistent with previous publications, our data show an increase in the rate of TLN with temporal lobe doses > 70 Gy. Further detailed dosimetric data with longer follow-up data are underway to better ascertain the significance of these findings. Prospective evaluation is needed to further characterize TLN for patients treated with proton therapy to the skull base.

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The Risk of Carotid Stenosis in Head and Neck Cancer Patients After Radiation Therapy

D.J. Carpenter, Y.M. Mowery, G. Broadwater, A. Rodrigues, A.J. Wisdom, R.W. Clough, and D.M. Brizel; *Duke University Medical Center, Durham, NC*

Purpose/Objective(s): Head and neck radiation therapy (RT) is a risk factor for cerebrovascular disease, but the carotid artery dose-response relationships are unknown. We evaluated the incidence of carotid artery stenosis (CAS) in head and neck cancer (HNC) patients undergoing RT to assess whether a dose-response effect exists between carotid artery dose and CAS.

Materials/Methods: Retrospective review of records was performed for HNC patients undergoing carotid ultrasound screening after curative or adjuvant RT between January 2000 and May 2016. CAS was defined as ≥50% stenosis on imaging or symptomatic cerebrovascular disease (stroke or transient ischemic attack [TIA]). Actuarial CAS rates were calculated by Kaplan-Meier method. Univariate analyses were utilized to predict time to CAS based on carotid dosimetric and clinical parameters. Multivariate models were used to predict CAS risk.

Results: A total of 366 patients met inclusion criteria. Median time from RT completion to last follow-up was 4.1 yr. Actuarial risk for cerebrovascular disease (asymptomatic CAS, stroke, or TIA) was 35.1% (95% CI 27.0-44.7%) at 9 years. Univariate analysis showed that smoking (HR 1.7; 95% CI 1.1-2.7), hyperlipidemia (HR 1.6; 95% CI 1.03-2.6), diabetes (HR 2.8; 95% CI 1.6-4.8), coronary artery disease (HR 2.4; 95% CI 1.4-4.2), and peripheral artery disease (HR 3.6; 95% CI 1.1-11.6) were significantly associated with increased CAS. Carotid dose parameters were not significantly associated with CAS. In multivariate analysis, diabetes was independently correlated with time to CAS (HR 1.9; 95% CI 1.1-3.4).

Conclusion: CAS incidence is high after head and neck radiation therapy, gradually rising over time. No clear dose-response effect between carotid dose and CAS was identified. Carotid artery screening and preventative strategies should be employed in this high-risk patient population.

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Quality of Life Impact of Planned Superselective/Selective Neck Dissection After De-Intensified Chemoradiation Therapy

K. Wang, D.H. Moon, R.J. Amdur, N.C. Sheets, C. Shen, R. Green, S. Patel, A. Zanation, B. Thorp, T. Hackman, M. Weissler, W.M. Mendenhall, and B.S. Chera; *University of North Carolina Hospitals, Chapel Hill, NC, [2]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [3]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL*

Purpose/Objective(s): To investigate the impact of planned post-chemoradiation (CRT) neck dissection (ND) on quality of life in patients with HPV-associated oropharynx cancer enrolled on two similar prospective de-intensification trials where the major difference was the use or non-use of a planned post-CRT ND.

Materials/Methods: Patients were enrolled on two sequential multi-institutional phase 2 prospective trials: LCCC 1120 (NCT01530997) and LCCC 1413 (NCT02281955). Eligibility criteria included 1) T0-3, N0-2c, M0, 2) HPV+/p16+, and 3) minimal smoking history or abstinence ≥ 5 years. Patients received 60 Gy radiation alone or with concurrent weekly cisplatin 30 mg/m2. Patients on LCCC 1120 received planned post-CRT superselective/selective ND of originally involved nodal levels. Patients on LCCC 1413 received surveillance PET with salvage ND reserved for suspicion of persistent disease. Quality of life was compared between trials, with data censored at disease progression and/or salvage surgery. Quality of life was assessed using the EORTC H&N-35 and EAT-10 (swallowing) questionnaires, as well as a single question assessing shoulder symptoms, at 3 months (3M), 6 months (6M), 12 months (12M), 18 months (18), and 24 months (24M). One-sided t-tests and Fisher exact tests were used.

Results: A total of 44 patients were enrolled on LCCC 1120, of whom 37 node-positive patients receiving planned post-CRT ND were analyzed. A total of 110 patients were enrolled on LCCC 1413, of whom 95 patients with posttreatment data were analyzed. Thirty-one patients on LCCC 1120 and 33 patients on LCCC 1413 have completed the final 24M endpoint. The median numbers of dissected levels and nodes were 2 and 12, respectively, for patients enrolled on LCCC 1120. There was no difference in baseline quality of life or shoulder symptoms in patients receiving vs. not receiving post-CRT ND. Other than a slightly worse post-CRT overall H&N-35 score at 3M in patients receiving post-CRT ND (31 vs 26, P=.054), there were no other differences in overall H&N-35 or EAT-10 scores. Patients with post-CRT ND did have worse pain and mouth-opening ability at 6M, but these differences were not significant at later time points. However, patients receiving ND appeared to have more clinically significant shoulder-specific symptoms. In patients receiving ND

vs. not receiving ND, there was a greater proportion both with shoulder stiffness not affecting activity (at 12M: 34% vs 18%, $P=.05$; at 24M: 40% vs 10%, $P=.008$) and shoulder stiffness affecting work (at 12M: 20% vs 8%, $P=.08$; at 24M: 17% vs 3%, $P=.10$).

Conclusion: The use of post-CRT superselective/selective neck dissection does not appear to affect general head and neck–specific or swallowing quality of life indices other than transient worsening in pain and mouth opening. However, post-CRT ND was associated with a higher rate of shoulder-specific symptoms, which persisted to late time points.

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Functional Swallowing Outcomes Using FEES Evaluation After Swallowing-Sparing IMRT in Unilateral Versus Bilateral Neck Radiation

M. Tam,[1] J. Mojica,[2] N.S. Kim,[3] D. No,[1] Z. Li,[4] T. Tran,[2] M. DeLacure,[2] B. Givi,[2] A. Jacobson,[2] M. Persky,[2] and K.S. Hu[1]; *[1]NYU Langone Health, Department of Radiation Oncology, New York, NY, [2]NYU Langone Health, Department of Otolaryngology, New York, NY, [3]New York University, New York, NY, [4]NYU Langone Health, Department of Medical Oncology, New York, NY*

Purpose/Objective(s): We evaluated swallowing outcomes using flexible endoscopy in patients who receive unilateral and bilateral neck radiation therapy. Additionally, we evaluated the dosimetric effect of unilateral radiation therapy on the vallecula, larynx, pharyngeal constrictor muscles.

Materials/Methods: We retrospectively evaluated 58 patients with head and neck cancer who underwent posttreatment flexible endoscopic evaluation of swallowing (FEES) function. IMRT was used to limit radiation dose to the pharyngeal constrictors. Pharyngeal residue in the vallecular and pyriform sinuses was measured after volitional clearing using a validated 5-point Yale Pharyngeal Residue Severity (YPRS) rating scale. Penetration and aspiration severity was measured using a validated 8-point Pentration Aspiration Scale (PAS). Higher scores indicate decreased swallowing function. Both measures were evaluated using intake of thin, puree, and solid consistencies. Dmean and Dmax to the vallecula, larynx, and pharyngeal constrictor muscles were calculated.

Results: Between October 2015 and May 2017, 13 patients received unilateral irradiation and 45 patients received bilateral irradiation. The mean time to FEES evaluation was 7.7 months (range, 0.7 to 27 months). All patients received prescription radiation doses of 66-70 Gy. Patients receiving ipsilateral irradiation included tonsillar subsite (92%) compared with those who received bilateral irradiation which included tonsil (42%), base of tongue (36%), and buccal mucosa (11%). Patients receiving ipsilateral irradiation were younger compared with those receiving bilateral irradiation (59 vs 66, $P = .048$) but no significant differences in gender, T stage, N stage, p16 status, smoking status, or chemotherapy use. Patients receiving unilateral irradiation showed better volitional clearing in the vallecula with thin consistencies (YPRS rating scale 1.6 vs 2.3; $P = .04$) and the pyriform sinus with solid consistencies (YPRS rating scale 1.3 vs 2.3; $P = .03$). Additionally, patients receiving unilateral irradiation showed decreased aspiration with solid consistencies (PAS score 1.0 vs 2.7; $P = .04$). Patients receiving ipsilateral irradiation when compared to those receiving bilateral radiation therapy had lower mean doses to the middle pharyngeal constrictor (45 Gy vs 56 Gy; $P = .001$), larynx (36 Gy vs 47 Gy; $P = .001$), and vallecula (50 Gy vs. 61 Gy; $P = .005$).

Conclusion: Patients receiving unilateral neck irradiation received significantly lower radiation doses to the vallecula, middle pharyngeal constrictor, and the larynx and experienced excellent swallowing functional outcomes. Further assessment should be performed with FEES to evaluate for long-term functional outcomes. Additional evaluation of dose sparing to the vallecula should be performed prospectively to potentially improve swallowing function.

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A National Sample of Medical Expenses for Head and Neck Cancer Patients

S. Massa,[1] N. Osazuwa-Peters,[2] R. Walker,[2] and G. Ward[2]; *[1]Saint Louis University School of Medicine, Saint Louis, MO, [2]Saint Louis University, St Louis, MO*

Purpose/Objective(s): Head and neck cancer (HNC) is more common among socioeconomically disenfranchised individuals, making medical costs particularly burdensome. Since 1997, the Medical Expenditure Panel Survey (MEPS) has assessed the nation's patient experiences with healthcare and related expenses. The present study utilizes this database to assess the financial burden of HNC with comparisons to other cancer patients.

Materials/Methods: Publicly available data from MEPS household and provider surveys were extracted from 1998 to 2014. Complex sampling methods were accounted for by weighting and balanced repeated replication techniques. Cancer diagnoses, including HNC, were identified by the clinical classification system derived from ICD-9 codes. HNC patients were compared to other cancer patients on demographics, income, employment, and health status using t and chi-squared tests as appropriate. Within the HNC subset, predictors of total medical expenses and relative expenses (proportionate to gross income) were assessed with univariate and multivariate linear regression modeling.

Results: Of 13,808 cancer patients surveyed, 398 reported HNC (weighted 278,159 and 10,385,684, respectively). Compared to other cancers, HNC patients were more often non-white race (33.0% vs 25.7%, $P=.032$), publicly insured (35.4% vs 26.0%, $P=.028$) with lower-income class (poor 12.0% vs 8.3%, $P=.022$), and lower health status (poor 16.8% vs 8.1%, fair 13.3% vs 7.5%, respectively; $P<.001$). Education, age, geographic region, and employment were similar ($P>.05$). Mean total medical expenses for HNC patients were higher than other cancers ($15,371 vs $12,544), but did not reach significance ($P=.070$). Among HNC, expenses were highest for black race ($17,253 vs white $13,138), near poor ($14,905 vs high income $11,592), and unemployed ($13,970 vs employed $10,387). However, only region (Northeast $20,579, Midwest $11,165, West $9,641; $P<.04$) and Asian race ($8,486 vs White $13,138; $P<.001$) were statistically significant. In the multivariate model, higher expenses relative to income was associated with prior marriage ($\beta=-0.314$, $P=.028$), female sex ($\beta=-0.469$, $P=.005$), Asian race ($\beta=-0.763$, $P\leq.001$), Midwest region ($\beta=-0.531$, $P=.047$), and total income ($\beta=-5.9E-5$, $P<.001$).

Conclusion: HNC results in a substantial additional burden to an already financially strained population. Additional research is needed to explore causes for the wide variation in total and relative expenses.

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A Review of Quality of Life and Utility Determination Studies for Health Outcomes Research in the Management of Head and Neck Cancer

R. Mailhot Vega,[1] J.M. Frakes,[2] J.J. Caudell,[3] L.B. Harrison,[2] H. Gold,[4] and K.S. Hu[1]; *[1]NYU Langone Health, Department of Radiation Oncology, New York, NY, [2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, [3]H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology, Tampa, FL, [4]NYU Langone Health, Department of Population Health, New York, NY*

Purpose/Objective(s): With multidisciplinary improvements in techniques, technologies, and systemic therapies with multiple approaches to successful outcomes, there is a need to help patients and practitioners understand different healthcare states to tailor treatment to patients' priorities. Utilities are a quality of life metric for patient preference of health states and are essential for cost-effectiveness analysis (CEA). To best inform future CEAs of head and neck squamous cell cancer (HNSCC) with

focus on oropharyngeal primaries (OPC) receiving definitive (chemo)radiation, we conducted a systematic review of the literature to identify recent publications that evaluate utilities for posttreatment health states.
Materials/Methods: A PubMed literature search was conducted to identify publications since 2007 that evaluate utility values for health states for HNSCC. To comprehensively identify health state values, we also included CEAs published since 2007 to assess the utilities used by other researchers for CEA construction. Publications included for review were screened by relevance by title and then abstract. Publications were then read and included by relevance. Included publications presented utility values collected from human participants or were CEAs that compared treatment modalities that included downstream health states from side-effects.
Results: Initial search returned 841 publications, and 651 were published since 2007. A total of 73 relevant abstracts were identified from which 33 CEA-apparent and 16 quality of life—apparent papers were read. Ultimately, 3 publications met inclusion criteria as works that determined preferences and utilities for health states after treatment for HNSCC, and 18 CEAs met inclusion criteria having included posttreatment health states with associated utilities. Health states evaluated include gastrostomy, osteoradionecrosis, pharyngocutaenous fistula, esophageal stenosis, tracheostomy, remission, local recurrence, regional recurrence, distant recurrence, dysphagia, and xerostomia. The least desired toxicity state was permanent gastrostomy (0.81) followed by osteoradionecrosis and esophageal stenosis (0.85). Xerostomia was seen to be preferable to dysphagia.
Conclusion: The publication and utilization of CEAs as decision-aiding tools is on the rise. However, despite the sizeable number of CEAs in the past decade for HNSCC and OPC management, there are relatively few primary sources informing utility data for health states. Future comparative-effectiveness analyses and CEAs for HNSCC and OPC treatment would benefit from further investigation into utility and preference research for posttreatment health states and long-term toxicities.
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Prediction of Feeding Tube Needs in Head and Neck Radiation therapy Patients: Independent Validation of a Feeding Tube Prognostic Tool

N.J. Anderson,[1,2] J. Jackson,[2,3] M. Wada,[2] M. Schneider,[4] M. Rolfo,[2] M. Fahandej,[2] D. Lim Joon,[2] and V. Khoo[2,5]; *[1]Peter MacCallum Cancer Centre, Melbourne, Australia, [2]Olivia Newton John Cancer Wellness & Research Centre, Heidelberg, Australia, [3]Radiation Oncology Centres, Gold Coast, Australia, [4]Department of Medical Imaging and Radiation Sciences, Monash University, Melbourne, Australia, [5]The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Purpose/Objective(s): Head and neck cancer (HNC) and its treatment with radiation therapy (RT) are associated with dysphagia, malnutrition, and weight loss. Enteral feeding via a feeding tube (FT) is a common method of patient nutrition supplementation during and immediately following RT. Advanced T-stage and level 2 nodal involvement (L2) have been internally associated with prolonged FT use in patients with known primary disease sites of the supraglottis, pharynx and oral cavity. We have developed an intuitive, easy-to-use prognostic tool to enable individualized FT prognostication for patients presenting with varying permutations of these key clinical indicators (table 1).The aim of this study was to validate the prognostic value of this FT prognostic tool for utilization in HNC RT patients.
Materials/Methods: Fifty-four patients (N=54) with locally advanced HNC treated with definitive RT (+/- chemotherapy) were retrospectively analyzed. T-stage, L2, prophylactic FT insertion (Yes/No), FT utilization (weeks), and percentage weight change during RT were recorded. Dieticians Association of Australia Guidelines recommends FT insertion for anticipated use in excess of 4-6 weeks. Patients were, therefore, dichotomized into FT indicated (FTI) vs FT not-indicated (FTNI) based their median expected FT dependence. Patients with T-Stage ≤2, without L2 involvement, were classified as FTNI. All other patients were FTI (see table 1). Frequency distributions between groups were analyzed.

Abstract 291; Table Median duration of feeding tube (FT) use for ≥25% of diet (with 95% CI)

Cancer	T stage	Level 2 (L2) nodes involved	Median duration of FT use for at least 25% of diet (weeks)	Feeding Tube Indicated
Oral Cavity, Oropharynx, Nasopharynx, Hypopharynx, Supraglottis	≤T2	No	1 week (0 − 8)	No
		Yes	11 weeks (8 − 13)	Yes
	≥T3	No	15 weeks (10 − 25)	Yes
		Yes	24 weeks (16 − 42)	Yes

Results: Patients with high-risk FT prognostic tool indication were more likely to have FTs inserted (T-Stage≥3, $P<.01$; T-Stage≥3 + L2, $P=.03$). Ninety-seven percent (33/34) of patients who had FTs inserted were FTI. Duration of FT use was as long as, or longer than, that estimated by the tool in 79.4% (27/34) of patients. Of patients who did not receive a FT, 90% (18/20) were FTI. These patients had a significantly greater mean weight loss than FTI patients who had FTs inserted throughout their course of RT (9.7% ± 4.4% vs 6.6% ±4.8%, $P=.03$).
Conclusion: This feeding tube prognostic tool provides a simple, easy-to-use interface, utilizing clinical variables that are readily accessible prior to RT. It enables identification of at-risk patients requiring timely FT intervention, and appears clinically useful in an independent patient cohort. Prospective, multicenter evaluation is indicated to establish the external validity of this tool to improve patient care during and beyond RT.
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Temporal Lobe Radiation Necrosis after Re-Irradiation Involving the Skull Base With Proton Therapy: A Single-Institutional Experience

A. Lee,[1,2] K.L. Pitter,[1] C.H.J. Chow,[3] K. Sine,[4] O. Cahlon,[1] S. McBride,[1] C.J. Tsai,[1] J.E. Leeman,[1] N. Riaz,[1] D.S. Higginson,[1] T. Waldenberg,[1] M. Cohen,[5] I. Ganly,[5] J.O. Boyle,[5] R.J. Wong,[5] C.W. Brennan,[5] S.S. Baxi,[6] E. Sherman,[6] L. Michel,[6] and N. Lee[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Radiation Oncology, SUNY Downstate Medical Center, Brooklyn, NY, [3]Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, Hong Kong, [4]ProCure Proton Therapy Center, Somerset, NJ, [5]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, [6]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): To analyze clinical and dosimetric factors for the occurrence of temporal lobe necrosis (TLN) among patients who received proton therapy involving the skull base in the re-irradiation setting.
Materials/Methods: We performed a retrospective analysis of 92 patients re-irradiated at our cancer center involving the skull base with proton therapy between 09/2013 and 03/2017. The most common primaries treated included the nasopharynx (n=21), paranasal cavity/sinuses (n=14), and major salivary gland (n=10); the most common histologies included squamous cell carcinoma (n=49), adenoid cystic carcinoma (n=12), sarcoma (n=5), and poorly differentiated carcinoma (n=4). Twelve (13.8%) patients had third-course radiation treatment. Follow up interval was defined from the beginning of proton therapy. Analyzed factors included prior radiation dose, composite mean dose to 2 cc and composite max pixel dose to the temporal lobe. Outcomes of interest included the grade of TLN, incidence as well as time to development of TLN among patients treated in the re-irradiation setting.
Results: Of the 92 patients analyzed, 84 (91%) were treated due to recurrent locoregional disease and 4 (4.3%) were treated due to metastatic disease. The median follow-up was 11.5 months (range 0-56) for the entire cohort and 15 months (range 1-44) for living patients; at time of analysis,

43 (47%) patients were still alive. The median prior irradiation dose to the skull base region was 6360 cGy for those without TLN and 6760 cGy for those with TLN ($P = .055$). Median re-irradiation proton dose was 60 CGE without TLN and 7 0CGE with TLN ($P = .419$). Twelve patients (13%) were found to have temporal lobe necrosis with median time to development of 8 months. Of these patients, 6 patients had right-sided TLN, 5 had left-sided, and 1 patient had bilateral TLN. The median total mean dose to 2 cc to the right temporal lobe was 51.87 CGE for those without TLN and 75.10 CGE for those with TLN ($P = .057$); median max pixel dose to the right was 68.80 CGE without TLN and 110.13 CGE with TLN ($P = .040$). On the left side, median total mean dose to 2 cc was 32.29 CGE with no TLN and 59 CGE with TLN ($P = .211$) and median max pixel dose was 55.19 CGE without TLN and 71.34 CGE with TLN ($P = .560$). All patients were determined to have grade 1 TLN per CTCAE 4.0 with only radiographic evidence and were clinically asymptomatic except for one patient with grade 2 toxicity requiring medical management with steroids.

Conclusion: Among patients treated in the re-irradiation setting with proton therapy, 13% of patients developed TLN that was only apparent radiographically except for one who was treated medically. Analysis of more detailed dosimetric data with longer follow-up data are underway to better ascertain the significance of these findings.

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Developing Supportive Care Services Within a Multidisciplinary Head and Neck Cancer Program

D.A. Rapkin,[1] C.L. Williams,[1] S. Lazaro,[1] A.B. Madnick,[2] F. Buen,[1] R. Dafter,[1] E. Abemayor,[1] E.G. Morasso,[3] R.K. Chin,[3] A. Erman,[4] D.L. Jayanetti,[5] M. St.John,[1] and D.J. Wong[6]; *[1]David Geffen School of Medicine at UCLA, Department of Head and Neck Surgery, Los Angeles, CA, [2]Ronald Reagan-UCLA Medical Center, Department of Care Coordination & Clinical Social Work, Los Angeles, CA, [3]David Geffen School of Medicine at UCLA, Department of Radiation Oncology, Los Angeles, CA, [4]Ronald Reagan-UCLA Medical Center, Department of Audiology and Speech Pathology, Los Angeles, CA, [5]UCLA School of Dentistry, Division of Advanced Prosthodontics, Los Angeles, CA, [6]David Geffen School of Medicine at UCLA, Department of Medicine, Division of Hematology/Oncology, Los Angeles, CA*

Purpose/Objectives: Head and neck cancer patients and their support systems experience psychosocial distress which can impact quality of life, alliance with providers, treatment compliance, treatment cost and outcomes. While patient-centered care and patient satisfaction are mandated by organizations such as the American College of Surgeons Commission on Cancer and Centers for Medicare and Medicaid Services, programmatic efforts to address biopsychosocial needs with systematic Supportive Care (SC) are not widely implemented in Head and Neck Cancer Programs (HNCPs). Development of SC, though rich in potential benefits to patients, providers and institutions, presents complexities and challenges which can vary depending on the institutional setting. Herein we describe the evolution of an SC program within the UCLA David Geffen School of Medicine's multidisciplinary HNCP, including goals, institutional setting and history, staffing, distress screening (DS), psychosocial oncologic care, program evaluation, and research.

Materials/Methods: The UCLA Mind Body Team (MBT) is an integral subspecialty group comprised of psychologists and social workers embedded in UCLA HNCP. Between Jan 24, 2014 -Aug 30, 2017, 570 UCLA HNCP patients were screened for distress by our patient navigator or providers prior to being seen at HNCP. Distressed patients were then evaluated formally by the MBT utilizing interview-based assessment and referred for treatment as appropriate.

Results: Among 570 patients presented at UCLA HNCP, approximately 60% had evidence of distress at initial screening. Common indicators of distress include tearfulness, grief, uncontrolled pain, fear related to diagnosis and treatment, difficulty in understanding or remembering information, unusual requests (in number or kind) for assistance, and delays in seeking treatment. Given the large proportion of patients who displayed distress, we developed a one-page DS Tool based on literature review and experience with HNCP patients. Components of our DS tool include: NCCN distress thermometer, a problem check-list tailored to an HN patient population, and a standardized, four item depression and anxiety screening questionnaire (PHQ-4).

Conclusion: Based on our experience, a significant proportion of head and neck cancer patients display distress. Integration of SC, including biopsychosocial DS, within a multidisciplinary HNCP is feasible and sustainable. Future goals include implementation of the DS tool with all HN patients and long-term measurement of effects of SC, including biopsychosocial DS, on patient outcomes. Implementation, integration, and evaluation of SC can enhance our ability to provide quality and effective care, potentially with greater efficiency, enhanced patient satisfaction, and cost containment.

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Correlation of Salivary Gland Dose to Volume Changes Noted During Adaptive Replanning of Head and Neck Radiation Therapy

B. Willen,[1] E. Healy,[2] C. Barney,[2] S.A. Walston Jr,[2] D.J. DiCostanzo,[2] A.S. Ayan,[3] J.L. Wobb,[2] D.L. Mitchell,[2] J.C. Grecula,[2] D.M. Blakaj,[2] and A.D. Bhatt[2]; *[1]Wright State University Boonshoft School of Medicine, Dayton, OH, [2]The Ohio State University Wexner Medical Center, Department of Radiation Oncology, Columbus, OH, [3]The Ohio State University, Columbus, OH, United States*

Purpose/Objective(s): Salivary gland shrinkage is known to occur with radiation therapy (RT) for head and neck cancer. Adaptive Radiation Therapy (ART) is commonly performed during the course of Intensity-Modulated Radiation Therapy (IMRT) due to weight loss and/or tumor shrinkage. Our goal was to investigate changes in parotid (PG) and submandibular gland (SMG) volumes measured on initial and replanning CT. We hypothesize that dose received by gland at the time of replan predicts for quantitative gland volume reduction. Replanning thus has the potential to reduce this effect which ultimately may reduce severity of xerostomia.

Materials/Methods: We analyzed 100 patients who underwent adaptive re-planning (200 plans) between December 2014 to August 2017. Volumetric Modified Arc Therapy (VMAT) based IMRT was used in all. All patients had an initial CT simulation scan (Plan 1) used for radiation planning and a subsequent new CT simulation for adaptive replan (Plan 2). Dose-volume histograms were used to measure mean and maximum doses to right and left PG and SMG. We then correlated these doses to PG and SMG volume changes noted at the time of replan (PG1-PG2; SMG1-SMG2). Univariate and multivariate analyses were performed to identify factors contributing to gland volume changes.

Results: Tumor site included 9 oral cavity, 50 oropharynx, 14 Larynx, 7 Nasopharynx, and 20 others. Treatments were definitive chemo-RT in 67%, adjuvant chemo-RT in 20%, or adjuvant RT alone in 10%. Chemo used was Cisplatin-based 36%, Carboplatin-based 22%, or Cetuximab-based in 28%. Median total RT dose was 70 Gy (60-70 Gy in 30-35 daily fractions). Median time to performing replan was at fraction #21 (42 Gy) and around day 37 of therapy (13-66 days). Mean weight loss at time of replan was -4.3% (-21.3 to +17.5%). Analysis included 181 PG and 116 SMG. Mean dose received at time of replan with corresponding volume change: RPG = 1548 cGy, -13.6%; LPG = 1647 cGy, -14.6%; RSMG = 3359 cGy, -12.7%; LSMG = 3366 cGy, -14.4%. The correlation values of dose received and volume change: RPG r = 0.17, LPG r = -0.21, RSMG r = -0.33, and LSMG r = -0.27 (all with $P < .05$ except RPG, $P = .13$).

Conclusion: Anatomic changes during radiation can result in increased doses to normal tissues and increased risk of toxicity. Our results show a

significant change in gland volume in 3 of 4 salivary glands at the time of replanning with a direct correlation to dose received to the gland. Adaptive replan has the potential to reduce salivary gland doses.

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Will Thyroid Avoidance Planning IMRT Reduce the Rate of Radiation-Induced Hypothyroidism and Improve Healthcare Value?

J.F. Greskovich Jr,[1] N.M. Woody,[2] N.P. Joshi,[2] M.C. Ward,[3] R. Szwedoski,[4] B.B. Burkey,[5] J. Scharpf,[5] J.L. Geiger,[6] D.J. Adelstein,[6] and S. Koyfman[2]; *[1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic Florida, Weston, FL, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Cleveland Clinic Florida, Weston, FL, [5]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH, [6]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): We hypothesize that thyroid gland avoidance planning (TGAP) in definitely treated, stage III/IVA-B, oropharyngeal squamous cell carcinoma (OPSCC) patients will decrease risk of hypothyroidism (HT) and improve healthcare value.

Materials/Methods: 568 pts on an IRB approved registry with stage III/IVA-B, OPSCC treated with definitive RT +/- chemo between Jan'05 and Dec'15 were reviewed. 205 pts were excluded for various reasons-re-RT (n = 22), outside RT (n = 40), unilateral neck RT (n = 43), no TSH values available >6 months after RT (n = 67), previous HT (n = 10), and incomplete records (n = 25)-leaving 363 evaluable pts. 2830 TSH values were present in the study cohort's EMR (®EPIC Systems). TSH>5.0, the upper limit of normal, was considered a surrogate for HT. Three groups were compared for TSH outcomes: 1) 2D-3DRT, 2) IMRT with TGAP, 3) IMRT without TGAP. Outcomes were estimated using cumulative incidence or Kaplan-Meier (K-M) and compared among treatments using Gray or log-rank test.

Results: Pt characteristics were 90% Caucasian, 86% male, with mean age of 58 yrs. (range: 36-81 yrs.). Tumor characteristics were 80% HPV+, 91% stage IVA-B, 54% BOT/42% Tonsil. Treatment characteristics were 57% IMRT, median dose 72 Gy, 88/12% standard/hyperfractionated, 96% concurrent chemo (90% platinum-based). Group 1, 2, 3 had 158, 22, 182 pts, respectively. Considering all pts, K-M estimate for 1YOS/2YOS, 1YDFS/2YDFS, 1YLRF/2YLRF were 97/94%, 94/89%, 5/8%, respectively, with no difference between treatment groups. Mean thyroid dose in the IMRT with TGAP pts was 41.1 Gy (range: 34.3-51.1 Gy). Overall, 220 (61%) pts became HT with TSH>5.0. The 12 and 18 month HT rates for IMRT with TGAP were lower, but not statistically significant, than the IMRT without TGAP and 2D-3DRT groups: 12 mo. HT: 10% vs 26% vs 29%, 18 mo. HT: 29% vs 37% vs 42%, respectively.

Conclusion: IMRT with TGAP may lower the risk of radiation-induced HT in definitely treated stage III or IVA-B OPSCC but more evaluable patients and longer follow up is necessary for proof of principal. If TGAP lowers rate of HT then a cost-savings and improved healthcare value will be realized. Further study into the dose-volume-HT relationship will be investigated in our future studies.

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Comparative Analysis of Toxicity of Cisplatin and Cetuximab in Locally Advanced Head and Neck Cancers Receiving Concomitant Chemoradiation

J. Deck, R. Chaudhari, M. Formica, S. Sinha, A. Anand, A. Poudel, S.S. Hahn, and A. Gajra; *SUNY Upstate Medical University, Syracuse, NY*

Purpose/Objective(s): To compare the acute toxicity of cisplatin and cetuximab in patients with locally advanced head and neck cancer (LA-HNSCC) receiving concurrent chemoradiation. Standard of care for locally advanced head and neck squamous cell carcinoma is concurrent chemotherapy (cisplatin or cetuximab) and radiation therapy. Cetuximab has been validated as an effective agent in a randomized trial by Bonner et al (NEJM, 2006) showing improved overall survival when compared to radiation alone. There is limited data comparing cetuximab and cisplatin concomitant with radiation therapy. A phase 2 trial by Magrini et al (JCO, 2015) showed similar efficacy and differing toxicity profiles between these two agents with high rates of acute toxicity seen in the cetuximab arm. We present acute toxicity data from patients treated with concurrent chemoradiation at our institution.

Materials/Methods: After institutional review board approval, patients with LA-HNSCC treated from June 2012 to December 2015 were identified from hospital electronic medical record. Data regarding demographics, disease site, stage, radiosensitizing agent used, and treatment-related toxicities, including breaks in treatment, were collected. Data were analyzed using Chi-square, Fisher's exact test, and univariable and multivariable logistic regression.

Results: Of 185 consecutive patients with LA-HNSCC treated with definitive concurrent chemoradiation, 103 patients received cisplatin and 82 patients received cetuximab. In univariate analysis, cisplatin was associated with significantly greater CTCAE hematologic toxicity ($P<.0001$). Multivariate analysis further demonstrates that age ≥ 70 ($P=.02$) and laryngeal, hypopharyngeal or supraglottic disease site ($P=.01$) were predictive of hematologic toxicity with cisplatin. Cetuximab was associated with a statistically significant increase in radiation dermatitis ($P=.03$) and acneiform rash ($P=.0001$) compared with cisplatin. There was a trend towards increased mucositis with cetuximab. Rates of dose reduction of systemic therapy neared significance, with lower reductions seen in patients receiving cetuximab ($P=.05$). There was also a trend towards increased emergency room visits and hospital admission with cisplatin, but this was not significant. Other toxicity variables analyzed, including G-tube placement, duration of G-tube insertion, and breaks in chemotherapy or radiation therapy, were not statistically different between the two cohorts.

Conclusion: Concurrent chemoradiation with either concurrent cetuximab or cisplatin is well tolerated. Concurrent cisplatin with radiation results in significantly worse hematologic toxicity while concurrent cetuximab resulted in significantly increased radiation dermatitis and acneiform rash. This is in contrast to published data showing greater rates of acute toxicity with cetuximab.

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Relevance in Standardizing Hearing Apparatus Contours

G. Tolekidis,[1] M. Thoma,[1] M. Choi,[2] and A.Z. Diaz[1]; *[1]Rush University Medical Center, Chicago, IL, [2]Rush-Riverside Cancer Institute, Bourbonnais, IL*

Purpose/Objective(s): The potential for sensorineural hearing loss (SNHL) is an unfortunate reality with patients who receive radiation therapy (RT) to the head and neck (H&N) region. A review of the literature seems to indicate there is a lack in standards for contours associated with SNHL. The range of contoured structures reported by institutions include the tympanic cavity, Eustachian tube, mastoid process, cochlea, vestibule, inter auditory canal (IAC), and various combinations of the aforementioned items. At our institution, we have historically contoured the cochlea, vestibule, and a portion of the inner auditory canal as a single volume for each side (i.e. the bony labyrinth of the inner ear) and used that structure for optimization and dosimetric analysis. This retrospective study examines how much dose the cochlea, vestibule, and IAC individually received when the bony labyrinth of the inner ear was contoured and used as an avoidance structure during planning.

Materials/Methods: Twenty consecutive patients who received IMRT for H&N cancer in 2015 at our institution were selected for this study. A Phillips Brilliance Big Bore 16 slice CT scanner was used for the RT

simulation and images were acquired at a slice thickness of 3 mm. Contouring was done on a Phillips Pinnacle treatment planning system (TPS) and planned on an Accuray TomoTherapy TPS. The dose was transferred from the TomoTherapy TPS to the Pinnacle TPS where dose statistics were collected. A paired t-test analysis was performed with 40 data points of each structure (20 entries from each anatomical side) using SPSS software.
Results: Mean dose to our planning bony labyrinth organs at risk (OAR) was 12.95 Gy (standard deviation (SD) 9.96; standard error mean (SEM) 1.58). Cochlea mean dose = 13.66 Gy (10.42 SD; 1.65 SEM); Vestibule mean dose 12.05 Gy (9.57 SD, 1.51 SEM); and IAC mean dose = 14.24 Gy (11.35 SD, 1.80 SEM). Statistically significant differences were seen as we compared mean doses between our bony labyrinth to the cochlea ($P = .0168$) and the vestibule ($P = .0001$), but not to the IAC ($P = .0877$).
Conclusion: Our results showed significant differences between the mean dose of the bony labyrinth versus the mean doses to the cochlea and vestibule but not with the IAC when the bony labyrinth of the inner ear is contoured as a single structure instead of having separate delineation of its components. Considering that there is ongoing research investigating the potential differences in tolerances for the various hearing structures, it is important to keep in mind that nonstandard or ill-defined contouring of these structures may result in variations of dosimetric data between studies. This may lead to false correlations between dose given to OAR's and clinical effect.
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Withdrawn

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Functional Outcomes in Veterans With Intermediate- and High-Risk Oropharyngeal Squamous Cell Carcinoma: Analysis of Long-Term Survivors

S. Kansara,[1] C. Stach,[2] A. Sikora,[1] and V.C. Sandulache[1]; *[1]Baylor College of Medicine, Houston, TX, [2]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX*

Purpose/Objective(s): Oropharyngeal squamous cell carcinoma (OPSCC) incidence is rapidly increasing in the general population. Data from the Veterans Health Administration (VHA) registry demonstrates a lagging, but similar, increase in OPSCC incidence. Veterans with OPSCC have more comorbidities compared to the general population and high rates of tobacco use, resulting in a large number of patients with "intermediate-risk" OPSCC. In this group, functional outcomes remain understudied and underreported, creating a significant knowledge gap.
Materials/Methods: We reviewed patients with a diagnosis of squamous cell carcinoma of the oropharynx (OPSCC) treated at the Michael E. DeBakey Veterans Affairs Medical Center between 2005 and 2015 with at least 2 years of clinical follow-up. Functional status was ascertained using 1) gastrostomy / tracheostomy status, 2) patient-reported diet, and 3) modified barium swallow (MBS) results.
Results: A total of 104 patients met inclusion criteria; African Americans made up 15% of the population. The most common stage at presentation was T2N2b; the 2 most common sites were tonsil (44/104) and base of tongue (39/104). Most (90%) patients were smokers and 60% of tumors were p16+. Primary radiation was administered to 96 patients and 75 patients received concurrent chemotherapy; 87/104 patients were treated with IMRT. Mean follow-up was 5.9 years. Nearly half (49/104) of all patients underwent gastrostomy placement prior to or during treatment; 4 patients required a tracheostomy. At last follow-up, 13 patients required gastrostomy and 1 patient remained tracheostomy dependent. Although gastrostomy placement did not correlate with pretreatment MBS results, disease site or T&N stage, gastrostomy at last follow up correlated strongly with T4 stage. T4 stage correlated with both pre- and posttreatment pharyngeal dysfunction measured via MBS. MBS studies obtained in patients at >1 yr posttreatment demonstrated deterioration of both oral and pharyngeal function compared to pretreatment studies. Although 38 patients reported some dysphagia at last follow-up, 89/104 maintained a regular or soft diet and only 5/104 were NPO. With the exception of patients with T4 tumors, there was no significant correlation between patient diet and MBS results in the posttreatment setting.
Conclusion: Veterans with OPSCC often present with locoregionally advanced disease advanced, in the setting of significant smoking history, consistent with an intermediate-risk phenotype. Overall, functional status for survivors is excellent with the exception of patients with T4 disease. Because a majority of patients exhibit worsening dysfunction over time, aggressive dysphagia rehabilitation during and posttreatment completion must be incorporated into treatment paradigms throughout VHA facilities which treat OPSCC.
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Gender Differences in Radiation Therapy Effects in Male and Female Patients With Head and Neck Cancer

B.R. Page,[1] P. Han,[2] L.C. Peng,[1] Z. Cheng,[3] J. Harkness,[2] C. Shen,[4,5] A. Choflet,[6] E. Cecil,[2] X. Hui,[1] N.C. Schmitt,[7] I. Shpitser,[2] T.R. McNutt,[8] and H. Quon[1]; *[1]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins Medicine, Baltimore, MD, [4]University of North Carolina, Chapel Hill, NC, [5]University of North Carolina Hospitals, Chapel Hill, NC, [6]Johns Hopkins Hospital, Department of Radiation Oncology and Molecular Radiation Sciences, Baltimore, MD, [7]Department of Otolaryngology - Head and Neck Surgery, Johns Hopkins University, Baltimore, MD, [8]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, MD*

Purpose/Objective(s): Previous studies have suggested lower risk of HNC incidence in women, and furthermore associated with a decreased risk in women who use exogenous hormone replacement therapy or have pregnancies under age 35. Other recent data suggest association with smoking, alcohol, and occupational history in women may have an effect on incidence. To date, few studies have discussed differences with regard to side effects, or measures of coping mechanisms with diagnosis and treatment in women with head and neck cancers undergoing radiation therapy.
Materials/Methods: Utilizing prospectively collected data at the point of care in an institutional database, patients treated for head and neck cancers were assessed with both clinician-assessed measures (mucositis, dermatitis, presence of thrush, performance status using the CTCAE grading scales) and patient-reported outcomes (PRO) to include Functional Assessment of Cancer Therapy (FACT) scores (General, Head and Neck) assessed at baseline, during radiation therapy, and in follow-up.
Results: From 2010-2017, 363 patients (86 female) were included with a mean age of 59 years (male) and 56.2 (female). Diagnoses included cancers of the oral cavity (37%, n=133), oropharynx (23%, n=84), larynx (11%, n=39) and nasopharynx/sinonasal (5%, n=11), and upper aerodigestive (12%, n=44). Higher FACT scores were found in men on the FACT subscales at baseline (before radiation therapy initiation) and one year after radiation therapy, but not for the FACT-Social Well Being. Such differences were significant among patients with BMI 30 kg/m^2. There was no significant difference between male and female patients on FACT scores at 3-6 mos (45-180 days) and 6-12 mos after the treatment (180-360 days). There were no differences between KPS, mucositis, presence of thrush, and dermatitis scores. Higher FACT scores were observed in males compared to females among those with higher baseline pain scores or those that utilized a feeding tube.
Conclusion: Assessing measures of coping and side effects to include distress, functioning, and social well-being, as well as the traditional clinician assessment (mucositis, dermatitis, presence of thrush, performance status), may be helpful in further understanding the side effects and coping mechanism differences between male and female patients, to eventually lead to individualized measures of intervention in the future. Factors that may affect global quality of life will be compared with captured longitudinal measures of physiologic distress in our presentation.

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FYNN—Support Program for Patients Who Have Completed Head and Neck Cancer Treatment

L. Mullis,[1] G. Dawson,[1] L. Herring,[2] B. Neff,[1] D. Salisbury,[1] C. Schinke,[1] S.E. Squire,[3] and R. Diehl[1]; [1]*Cone Health, Greensboro, NC,* [2]*Private Practice, Greensboro, NC,* [3]*Piedmont Radiation Oncology PA, Greensboro, NC*

Purpose/Objective(s): Treatment for head and neck (H&N) cancer can induce significant emotional and physical stress. Upon completion of treatment, patients are at risk for isolation, depression, and anxiety. Moreover, they cope with treatment side effects that have not resolved or are permanent, that is, a part of their "new normal". Support groups and peer mentoring can benefit those with significant oncologic issues. However, strategies for the unique population of H&N cancer patients are not well documented. Our team designed a group seminar series to address their needs in the posttreatment setting.

Materials/Methods: The program is modelled after the Finding Your New Normal (FYNN) series developed for cancer survivors at our facility. It is offered twice yearly and consists of a 5-week series, meeting once a week in the evening. Enrollment is open to patients and their caregivers who have completed treatment and limited to 16 attendees to facilitate an intimate atmosphere for sharing. Guest lecturers scheduled for specific sessions include a nurse practitioner survivorship specialist, radiation oncologist, dietician, speech language pathologist, physical therapist and psychologist. Representatives from a local YMCA and college attend and discuss, respectively, the Livestrong and Trail to Recovery programs offered by their institutions. A break-out session for patients and caregivers is included to allow them to meet in separate groups. In these safe environments, they reflect upon their respective experiences with peers. Sessions are co-facilitated by a licensed clinical social worker and the H&N oncology nurse navigator. Clinician presentations are brief to allow time for questions and round table discussions. Attendees fill out surveys following each of the 5 sessions to provide feedback and a final program evaluation.

Results: Since the initiation of H&N FYNN in 2016, 3 programs have been held with an average enrollment of 13 attendees. Survey results indicated the following rates of "strongly agree" for the four outcomes that were evaluated: Learned new information to deal with cancer experience: 83%; Better able to cope with cancer experience: 79%; Have an outlet to better handle stress: 76%; Feel that experience with H&N FYNN helps to live a better quality of life: 76%. Recurring themes of learning from each other, giving and receiving support, and an overall feeling of connection to the other participants were expressed in the comments.

Conclusion: Addressing emotional stressors, as well as treatment-related toxicities, is a key aspect of survivorship for H&N cancer patients. Our FYNN series is rated highly by patients for improving their ability to cope posttreatment. It serves as a model for H&N cancer patients and can be customized for patients with other malignancies.

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Late and Long-Term Effects Among Survivors of Head and Neck Cancer at Least 5 Years Posttreatment: A Systematic Review

M.L. Nilsen,[1,2] S. Belcher,[1] H.S. Donovan,[3] M.L. Klem,[4] A. Morrison,[1] S.M. Sereika,[3] and J.T. Johnson[2]; [1]*University of Pittsburgh, School of Nursing, Pittsburgh, PA,* [2]*University of Pittsburgh, School of Medicine, Pittsburgh, PA,* [3]*Unversity of Pittsburgh, School of Nursing, Pittsburgh, PA,* [4]*Health Sciences Library System, University of Pittsburgh, Pittsburgh, PA*

Purpose/Objective(s): The identification and management of late- and long-term treatment effects in cancer survivors has become a national priority. Little is known about the prevalence of these effects in long-term head and neck cancer survivors. The aim of this study was to review the literature on late- and long-term treatment effects among head and neck cancer survivors at least 5 years posttreatment. Reported here is a description of the body of literature identified in this study.

Materials/Methods: Head and neck cancer was defined as cancers of the oral cavity, oropharynx, and larynx. To be included, studies were required to have at least a 5-year follow-up time point. All study designs except qualitative studies were included. We queried PubMed, CINAHL, EMBASE and PsycINFO databases from inception through February 2016. Medical subject headings and text words for "head and neck cancer" and "late and long-term treatment effects" were included in the literature search. Two independent reviewers screened titles and abstracts for full-text review, evaluated studies for inclusion in the final review, assessed articles for study quality, and extracted data. When necessary, authors were contacted to obtain missing data.

Results: The search yielded 6,234 potentially relevant articles, but only 39 met inclusion criteria. Of the studies included, 24 (62%) were published within the last 10 years. Study designs included retrospective reviews (n=17, 44%), follow-up analyses of randomized controlled trials (n=12, 31%), cross-sectional studies (n=8, 21%), and a longitudinal study (n=2, 5%). The most common late- and long-term treatment effects evaluated in these studies were swallowing function/diet intake (n=20, 51%), speech/voice quality (n=12, 31%), xerostomia/salivary gland dysfunction (n=9, 23%), skin/fibrosis (n=8, 21%), and mucosal complications/mucositis (n=6, 15%). There were few studies regarding psychological symptoms (n=4, 10%), trismus (n=4, 10%), taste (n=3, 8%), oral health/dentition (n=2, 5%), pain (n=2, 5%), cranial nerve palsy (n=2, 5%), and hearing (n=1, 3%). Operationalization of terms and methods of measurement varied considerably among studies. Only a few studies employed standard toxicity grading criteria; these included RTOG CTC (n=4, 10%), LENT-SOMA (n=3, 8%), and NCI CTCAE (n=2, 5%).

Conclusion: With a burgeoning population of patients surviving head and neck cancer, there is a critical need for a more comprehensive picture of the prevalence of late- and long-term effects. We recommend that systematic and standardized operationalization of terms and measurement be implemented both in research and practice. These data are imperative to drive the development of patient-centered, evidence-based interventions for long-term care of head and neck cancer survivors.

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Use of Percutaneous Endoscopic Gastrostomy Tube Feeding Support in Head and Neck Cancer Patients

R. Kasozi,[1] A. Choudhary,[2] K. Andrus,[3] R. Wong,[1] R. Randall,[5] C. Orovets,[3] G.S. Bali,[4] L. Karapetyan,[5] M.K. Gibson,[1] P. Fu,[6] and J. Sloan[3]; [1]*University Hospitals Cleveland Medical Center, Cleveland, OH,* [2]*Henry Ford University/Wayne State University, Detroit, MI,* [3]*University Hospitals Seidman Cancer Center, Cleveland, OH,* [4]*Detroit Medical Center/Sinai Grace Hospital, Detroit, MI,* [5]*Michigan State University, East Lansing, MI,* [6]*Case Western Reserve University, Cleveland, OH*

Purpose/Objective(s): Insertion of percutaneous endoscopic gastrostomy (PEG) tubes for enteral feeding in patients with head and neck squamous cell carcinoma (HNSCC) undergoing multimodality therapy is often utilized to provide nutritional support in this at-risk population. However, controversy exists regarding pretreatment PEG placement in all patients versus placement during radiation/chemoradiation therapy. The primary objective of our study was to review data regarding PEG tube placement at our center between 2012 and 2014 in order to determine baseline factors

that could assist in choosing pre- versus during-treatment PEG placement. Maintaining a weight loss decrease of < 10% of initial body weight was deemed success from PEG use.

Materials/Methods: We reviewed charts of all HNSCC patients treated with radiation and chemoradiation therapy from January 1st, 2012 to December 31st, 2014. Data extracted: demographics, subset of HNSCC, stage, diagnosis date, treatment modality, pretreatment swallowing function, date of PEG placement (before, during, or after treatment), date of PEG tube removal, duration of PEG tube insertion, ECOG PS, weight (baseline, before PEG tube insertion and after PEG tube removal), and p16 status. Statistical associations and differences were examined using Chi-square, Fisher exact test, T-tests and ANOVA.

Results: Demographics of 54 patients: 39 M/15 F; median age 62.5yrs (range = 42-88); tumor location oropharynx 35/54 = 64.8%, oral cavity 9/54 = 16.7%, larynx 5/54 = 9.3%, nasopharynx 4/54 = 7.4%, and hypopharynx 3/54 = 5.6%. AJCC stage distribution upon diagnosis: stage 4 - 40/54 = 74.1%; stage 3 − 7/54 = 13.0%; stage 2-5/54 = 9.3%; and stage 1-2/54 = 3.7%. Treatment: chemoradiation and radiation (CRT) 27/45 = 50%, surgery plus adjuvant CRT 11/54 = 20.4%, surgery plus RT 9/54 = 16.7%, and RT alone 7/54 = 13.0%. The total rate of PEG tube usage was 87.0% (47/54) with 95% CI 0.76 -0.94. Time of PEG placement: pretreatment 28/54 = 51.9%; during treatment 17/54 = 31.5%; and after treatment 2/54 = 3.7%. Swallow function results were not frequently recorded. Based on data from 12 patients, the mean aggregate difference of weight (95% CI) (pre-PEG − post-PEG) was negative 18.5 (9.9, 27.2) lbs, which is a 10.3% (18.5/178.9) decrease. Chi-square test demonstrated statistical significance in the association between cancer type and PEG tube placement ($P = .026$).

Conclusion: We evaluated PEG use in patients who underwent different treatment modalities. Our study demonstrated in this varied population that pretreatment PEG tube placement was able to prevent treatment-related weight loss of >10% initial body weight. Although we had insufficient data on swallowing function and change in weight over time, this data suggests that prophylactic PEG use in the management of HNSCC patients treated with multimodality therapy reduced weight loss.

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HPV+ Oropharyngeal Cancer and Feeding Tube Use With Chemoradiation

C.P. Miller,[1] J.K. Russo,[2] and E. Kraft[3]; *[1]University of North Dakota School of Medicine and Health Sciences, Bismarck, ND, [2]Bismarck Cancer Center Department of Radiation Oncology, Bismarck, ND, [3]University of Minnesota Medical School, Minneapolis, MN*

Purpose/Objective(s): We sought to determine factors predicting feeding tube use and quantify measures of tube use in HPV-positive oropharyngeal cancer (OPC) patients treated with chemoradiation.

Materials/Methods: Retrospective, single-institutional analysis of patient-, disease-, and treatment-specific factors of HPV+ OPC. Eligible patients had pathologic confirmation of HPV+ OPC and received chemoradiation. Patients with unknown HPV/p16 status, <3-month follow-up, or metastatic disease were excluded.

Results: Between 2007-2015, 29 patients (28 male, 1 female) were eligible for present analysis. All patients had HPV+ OPC, median age 60 years (40-87). PEG Tubes were placed in 62% of patients for a median length of 163 days (74-1268). Seven, 17, and 5 patients had clinical stage III, IVA, and IVB cancer, with 29%, 65%, and 100% requiring PEG tube, respectively. Forty-five percent of patient with primary site resection required a PEG tube. One-hundred percent of patients initiated adjuvant chemotherapy, 17 completed their course. Fourteen, 9, 2, and 4 patients received Cisplatin (Cis) every 3rd week, IV Cis weekly, Cetuximab therapy, or other, respectively. All 18 patients with a PEG tube had Cisplatin (Table 1). All patients completed the intended course of radiation therapy (RT), with a dose range of 60-70 Gy. In pounds, -14.85 and -13, were the median values of weight change from RT start to completion for those with and without PEG tubes, respectively. Weight change from the end of RT to the 4-6-week follow-up was +1.6 and +3.1 for those with and without PEG tubes, respectively. Overall, weight change from the beginning of RT to 4-6 weeks post-RT was -17.2 and -20.7 in those with and without PEG tubes, respectively. No patient had a prior history of head/neck cancer. Of the 19 patients with a smoking history, 10 needed a PEG, 8 of which had 10+ pack-years. Of the 16 patients hospitalized 1+ times, 12 required a PEG (75%). In contrast, of the 13 patients not hospitalized, 6 required a PEG (46%). Three patients died, one treatment related, another unknown cause, and one from disease. Two patients are currently alive with disease. The other 24 patients are alive without disease. Small numbers limited statistical analysis to descriptive statistics.

Abstract 304; Table 1

	Clinical AJCC Stage (v7)			Cis q3rd week (100mg/m^{2}x3 days)	Cis IV weekly (for 6-7 weeks)
	Stage 3	Stage 4a	Stage 4b		
Median # of Days with PEG Tube	144	178	222	148	171.5

Conclusion: In HPV+ OPC treated with chemoradiation, 62% of patients require PEG tube for a median 163 days. Factors that may predispose patients to an increased likelihood and prolonged use of PEG tubes include higher clinical stage, cisplatin, 10+ pack-years, and hospitalization.

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A Model for Multidisciplinary Care of Patients With Head and Neck Cancer

S.E. Squire,[1] N. Gorsuch,[2] L. Mullis,[2] B. Neff,[2] D. Salisbury,[2] C. Schinke,[2] and R. Diehl[2]; *[1]Piedmont Radiation Oncology PA, Greensboro, NC, [2]Cone Health, Greensboro, NC*

Purpose/Objective(s): Multidisciplinary clinics (MDCs), if executed well, can foster collaboration by clinicians, minimize inconvenience for patients requiring appointments with multiple providers, and promote clarity for patients with complex treatment plans. Multiple models can be adopted for such clinics. Ideal models using provider time efficiently while serving patients have not been well-described. Our team's experience with two clinic designs demonstrates multidisciplinary care that is feasible, sensitive to patient needs, and efficient for providers.

Materials/Methods: In May 2015, our team initiated its first MDC for new H&N cancer patients referred by otolaryngology. Clinics were held during a 3-hour block twice a month. The format was modeled after well-established MDCs for breast and thoracic patients at our outpatient cancer center: patients were seen for initial consultations with a medical oncologist, radiation oncologist, dietitian, physical therapist, and social worker. Our H&N oncology nurse navigator coordinated the clinics and also met with patients. The goal was to enroll 4 patients per clinic prior to their start of treatment. In January 2017, we changed to a new model. The clinics continued to be held twice monthly with three key changes. First, physicians were eliminated from the clinics; they instead saw patients as soon as possible following referral receipt. Second, in addition to new patients, time slots were made available for patients in need of follow-up visits. Third, to reduce barriers to attending posttreatment appointments for speech and swallowing therapy, a speech-language pathologist was added to the MDC clinician team.

Results: The new model led to a 58% increase in average patient enrollment per clinic which translated to fuller clinics and better use of provider time. Patients needing follow-up with nutrition and speech-language clinicians accounted for 46% of attendees. Average patient attendance with the new model increased to 4.1 patients from 2.6 patients under the old model. Improved enrollment translated to a 39% absolute decrease in the rate of clinic cancellations. Elimination of physicians from the model allowed new patients to meet their oncologists outside the constraints of the MDC schedule. Ancillary providers could provide more concrete recommendations for patients given that treatment plans were already documented. Patient follow-ups to address quality of life, survivorship, and treatment toxicities were streamlined due to their inclusion in MDCs.

Conclusion: Our novel MDC model is well-tailored for new and established H&N cancer patients. It efficiently utilizes patient and provider time and addresses the multiple physical and psychosocial needs that are unique to this complex patient population.

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Particle Radiation Therapy of Head and Neck Malignancies at the Shanghai Proton and Heavy Ion Center

L. Kong,[1,2] J. Hu,[1] J. Gao,[1] X. Guan,[1] W. Hu,[1] J. Yang,[1] C. Bao,[1,2] Y. Dong,[1,2] Y. Huang,[1,2] and J.J. Lu[1]; *[1]Shanghai Proton and Heavy Ion Center (SPHIC), Shanghai, China, [2]Fudan University Shanghai Cancer Center, Shanghai, China*

Purpose/Objective(s): To report initial experience of particle radiation therapy for head-and-neck malignant tumor in Shanghai Proton and Heavy Ion Center.

Materials/Methods: A total of 336 patients treated between May 2014 and July 2017 were treated in the Shanghai Proton and Heavy Ion Center. Among those, 216 patients received first course radiation therapy using particles therapy (168 patients), or in combination with photon therapy (48 patients). The medians of the total dose were 66 GyE (54-72.5 GyE) and 71 Gy (67.9-74 Gy), respectively. The rest of the 120 patients with recurrent tumors were treated using carbon ion alone (111 patients), proton alone (2 patients), or a combination of carbon ion and proton (7 patients). The medians of the total dose were 60 GyE (50-65 GyE), 60 GyE (60-60 GyE), and 68 (65-68 GyE), respectively.

Results: With a median follow-up time of 13.8 months (range: 1.4-68.3 months), the 1-year overall survival of this cohort was 97.7% (95% CI: 95.8%-99.6%). Stratified analyses showed the 1-year OS of patients with tumor located in the nasopharynx, oral pharynx/larynx/hypopharynx, sinonasal region, major salivary glands, skull base, orbit, and other sites were 97.9%, 95.6%, 96.8%, 90.9%, 100%, 100%, 100%, and 97.7%, respectively, while the 1-year OS of squamous cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, chordoma, sarcoma, and other types of histology were 97.5%, 97.1%, 100%, 100%, 92.8%, and 100%, respectively. In addition, the 1-year OS of patients who received first course of RT and reirradiation were 99.5% and 94.6%, respectively.

Conclusion: Our initial results indicated that particle radiation therapy is effective in the treatment of head and neck malignant tumors.

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Methadone Use During Concurrent Chemoradiation in Patients With Head and Neck Cancer

J.Y. Bruce,[1] G. Harmon,[2] K. Woo,[3] M. Yu,[4] J. Kiltz,[5] M.E. Witek,[5] P.M. Harari,[5] and R.J. Kimple[5]; *[1]University of Wisconsin—Madison, Section of Hematology/Oncology, Madison, WI, [2]University of Wisconsin—Madison, Madison, WI, [3]University of Wisconsin—Biostatistics and Medical Informatics, Madison, WI, [4]Department of Statistics, University of Wisconsin School of Medicine and Public Health, Madison, WI, [5]Department of Human Oncology, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Among the most common toxicities of chemoradiation for head and neck cancer (HNC) are mucositis and pain. This can contribute to secondary complications including dehydration and malnutrition. Opioids are frequently beneficial for patients in this setting in addition to oral rinse medications. Methadone is a synthetic opioid with potent analgesic effects for the management of cancer pain. Using a liquid solution, we tested methadone as a first-line long-acting opioid regimen for HNC patients undergoing chemoradiation.

Materials/Methods: We conducted a retrospective chart review of new patients from July 2015 to July 2017 who were seen in the HNC medical oncology clinic. All patients who received concurrent HNC chemoradiation (adjuvant and definitive) were offered methadone as a first-line long-acting opioid for treatment of pain. Those patients who received methadone during treatment were evaluated in this study. Data were abstracted to include baseline opioid use prior to chemoradiation, dose and frequency of methadone, use of breakthrough opioid medications, duration of methadone treatment, and whether patients were weaned off opioids or returned to their baseline opioid medication.

Results: One-hundred sixteen new patient consults were evaluated for methadone use during concurrent HNC chemoradiation. Fourteen patients were treated with methadone as the first-line long-acting opioid for increasing severity of oral pain during chemoradiation. Seven patients were weaned off all opioids after completion of chemoradiation, and five patients returned to their baseline opioid medication. One patient was unevaluable due to a non-opioid related death, and one patient is receiving methadone for ongoing treatment. In these 12 patients, the median duration of methadone use was 30 days. Two patients switched to fentanyl, and the median duration of any long-acting opioid use was 50.5 days.

Conclusion: Methadone is a feasible long-acting opioid that can be utilized for mucositis and pain during concurrent HNC chemoradiation. Given the availability of a liquid solution, methadone was effective in long-acting pain control and can be administered through a gastrostomy tube when severe mucositis precludes oral intake of medication. Discontinuation of methadone after completion of HNC chemoradiation was accomplished in this patient population. We plan to study methadone in a prospective study for patients undergoing concurrent chemoradiation therapy for HNC.

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Radiobiological Analysis for Osteoradionecrosis in Patients Treated With IMRT for Head and Neck Cancer: A Department of Veterans Affairs Experience

S.P.H. Lee; *VA Long Beach Healthcare System, Long Beach, CA*

Purpose/Objective(s): Previous publications by our group regarding osteoradionecrosis (ORN) induced by head and neck (H&N) radiation therapy (RT) have focused on the total physical dose deposited at the lesion site within the mandible. Furthermore, there seems to be a volume effect predicting increasing chance of ORN with a larger proportion of mandible receiving higher total dose. As with most published results, a relatively scarce number of cases limits the validity of findings, and biological consequence of spatial variation of *dose per fraction* is often ignored. In this study, we have pooled cases of ORN from two Veteran Affairs (VA) radiation oncology facilities, and analyze the pattern of failure based on the concept of biologically effective dose (BED).

Materials/Methods: Ten patients treated with H&N radiation therapy were identified to have ORN (median time from RT completion to diagnosis of ORN was 6 months; range: 3.2 to 52.8 months). All were male veterans, with median age of 63.5 when receiving initial treatment. Five had primary oropharyngeal cancer, 3 had oral cavity cancer, and 2 were treated for unknown H&N primary. All ORN sites were localized toward the posterior portion of the mandible or retromolar area. Concurrent platinum-based chemotherapy was given to 5 patients and Cetuximab to 3. One had salvage mandibulectomy before developing ORN, the other had partial glossectomy before being treated with hypofractionated RT along with Cetuximab. Dosimetric outcomes were analyzed retroactively for 8 cases with available detailed treatment plans, using BED and linear-quadratic equivalent dose based on 2-Gy per fraction (LQED2).

Results: The average LQED2 based on the prescribed fractionation scheme was 69.3±1.4 Gy (BED of 115.6±2.4 Gy_3). At the ORN lesion site, the average LQED2 was 76.0±4.1 Gy (BED of 126.7±6.8 Gy_3), representing a 9.7% increase over the prescribed dose. For the entire mandible (average

total volume of 74.0±14.5 cc), the average percent volumes receiving minimal LQED2 of 70 (V_{70}) Gy (corresponding to BED of 116.7 Gy_3) was 12.4±15.5%, corresponding to an absolute mandibular volume of 8.3±10.1 cc. Thus, while the mandible might be considered as a serial organ as far as ORN is concerned, it might be associated with a moderate volume effect.
Conclusion: ORN can result from increased LQED2 or BED which may not be conspicuous from a dosimetric plan based solely on physical dose display. This study demonstrates the utilization of radiobiologically sound dosimetry which clinicians can use to quantify risk of late complications due to the "double trouble" arising from altered fractionation schemes. For the mandible, DVH guidelines based on BED or LQED2 might be better representations to predict true incidence of ORN, and useful when constructing the dose-response relation as a normal-tissue complication probability (NTCP) curve.
Author Disclosure: **S.P. Lee**: Officer; Southern California Radiation Oncology Society.

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A Mixed Methods Evaluation of Symptom Burden and Quality of Life After Curative Head and Neck Cancer Treatment

S. Teckie,[1] A. Marziliano,[2] C. DeCoster,[2] C. Mulvany,[2] R. Bhat,[2] and M. Diefenbach[2]; *[1]Northwell Health, New Hyde Park, NY, [2]Northwell Health, Manhasset, NY*

Purpose/Objective(s): We hypothesize that head-and-neck cancer (HNC) patients who receive multimodality treatment, especially following transoral surgery (TOS), experience treatment-related effects that negatively impact short and long-term quality of life (QoL).
Materials/Methods: A mixed methods study evaluated the effects of multimodality treatment on HNC patients. First, charts of 20 patients with oropharyngeal cancer (OPC) were reviewed; short-term scores on the MD Anderson Dysphagia and Symptom Inventories were compared among those receiving TOS followed by chemotherapy and radiation (CRT; $n=6$, 30%) and those receiving only CRT ($n=14$, 70%). Second, long-term QoL experiences were further explored through a 1.5 hour facilitated focus group (FG) with 11 HNC survivors.
Results: Chart review results: sample was mostly male ($n=16$, 80%), mean age 61 years. OPC patients who received surgery and CRT reported significantly ($P=.04$) worse dysphagia ($M=69.47$, $SD=14.61$) compared to those who received only CRT ($M=48.43$, $SD=27.63$) at 6-9 months posttreatment. FG results: Sample was 36% male and all had completed treatment >3 years ago. Three patients had surgery first, and more than half had CRT. Coders identified three themes. *Theme 1: Variability in symptoms.* Dysphagia was endorsed by a majority of patients ($n=6$), in addition to overproduction of saliva/mucus ($n=5$), loss of taste buds, loss of sense of smell (both $n=4$), neuropathy, pain (both $n=3$), fatigue, dental issues, weight loss, severe burns, muscle/throat tightness, and dry mouth (all $n=2$). Cognitive and psychological symptoms were also frequently reported: uncertainty ($n=5$), loss of control ($n=3$), feeling lonely ($n=3$), and depression/anxiety ($n=2$). *Theme 2: Long-standing negative impact on QoL.* Participants reported that treatment-related symptoms negatively and substantially impacted their QoL ($n=7$), even years posttreatment. *Theme 3: Lack of information about recovery.* All patients reported that they were unaware of the magnitude/extent of symptoms during recovery. Example: "I would at least like to know what to expect." Patients reported that providers minimized the overall impact of disease and treatment ($n=9$), or did not communicate about effects ($n=5$) or pain relief ($n=2$). One patient stated that if given a second chance, she would not pursue treatment considering what they know now. Others ($n=2$) mentioned that lack of knowledge allowed them to pursue treatment.
Conclusion: OPC and HNC survivors experience significant levels of dysphagia in the short and long-term, as well as other unanticipated effects negatively impacting QoL. More data on recovery trajectories are needed to improve communication of these effects. Supportive measures are necessary to assist patients in managing/coping with effects.
Author Disclosure: **S. Teckie**: None. **A. Marziliano**: None. **C. DeCoster**: None. **C. Mulvany**: None. **R. Bhat**: None. **M. Diefenbach**: None.

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Patients Report Less Severe Symptoms With Unilateral Radiation Therapy Than Bilateral Radiation Therapy for Tonsillar Squamous Cell Carcinomas

A. Platek,[1] M.E. Platek,[2] A.J. Iovoli,[1] L.H. DeGraaff,[3] K.E. Wooten,[3] A. Hassan,[3] V. Gupta,[3] W.L. Hicks,[3] and A.K. Singh[3]; *[1]Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [2]Buffalo State College, Buffalo, NY, [3]Roswell Park Cancer Institute, Buffalo, NY*

Purpose/Objective(s): The goal of this study was to examine the effects of radiation treatment volume on quality of life in patients with squamous cell carcinoma of the tonsil.
Materials/Methods: Clinical characteristics of patients with tonsillar squamous cell carcinoma (n=30) treated at Roswell Park Cancer institute (2013-2015) were abstracted from the medical records. Patients were either treated with radiation therapy to one side of the head and neck, unilateral radiation (n=15), or treated with radiation therapy to both sides of the head and neck, bilateral radiation (n=15). Quality of life data was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-30) and head and neck 35 (H&N 35). The EORTC survey was administered prior to the start of radiation therapy treatment, at the end of radiation therapy treatment, and at each follow-up appointment up to 1-year posttreatment. Mann Whitney U tests were used to examine differences in QOL scores between patients treated unilaterally and patients treated bilaterally at various time points posttreatment.
Results: Patients who received bilateral treatment had significantly more appetite loss six months posttreatment (55.56% vs 15.15%, t=2.92, $P=.02$), more dysphagia 3 months posttreatment (40.48% vs 13.63%, t=2.85, $P=.03$), and more xerostomia e month posttreatment (62.5% vs 33.33%, t=2.37, $P=.0486$) than patients receiving unilateral radiation. Unilateral patients reported more sticky saliva posttreatment (93.33% vs 75.56%, t=-2.12, $P=.01$) than patients who received bilateral treatment.
Conclusion: Results of this small cohort study indicate that unilateral radiation therapy in tonsillar squamous cell carcinoma may be associated with less severe symptoms than bilateral radiation therapy and more studies on a larger scale are needed to further investigate this association.
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Smoking History and Cessation Guidance in Head and Neck Cancer Patients: A Review of Practice Patterns at Consultation

J.M. Holland,[1] N. Desai,[2] E. Holland,[2] C. Defrancesco,[2] K. Bernay,[2] and M. Wade[3]; *[1]Oregon Health and Science University, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]Oregon Health & Science University, Portland, OR, United States*

Purpose/Objective(s): Smoking during head and neck (H&N) radiation therapy is associated with worse outcomes and increased toxicity. We evaluated tobacco use and tobacco cessation guidance in patients treated at an academic radiation oncology facility to improve practice.
Materials/Methods: Initial consultation notes of 135 consecutive H&N cancer patients from January 2016 through July 2017 were reviewed using the electronic medical record. These notes contained input from residents, attendings, and nurses. Descriptive statistics were used to evaluate tobacco use patterns, disease subsites, and cessation guidelines.
Results: The most common H&N subsite was oropharynx (53%), followed by oral cavity (22%) and larynx (7%). Only 80% (108/135) were asked about smoking habits. The majority of patients were former smokers (51%), with 18% quitting within the preceding year. Thirty-one percent were never smokers and only 17% were current smokers. Current users smoked an average of 0.9 packs per day (range "few" to greater than 2 packs per day). Current users reported an average of 44 pack-years smoked (range 13 to greater than 100 pack-years). Eight patients reported other

tobacco use: 6 chewing tobacco, 1 pipe, 1 cigar. Of the 19 current smokers, discussions regarding cessation were documented in only 13 (68%). Ten of these patients (77%) accepted medical cessation therapy (6 nicotine patches, 4 nicotine gum/lozenges, and 2 varenicline).

Conclusion: 1. The majority of H&N cancer patients in our practice are *former* smokers. 2. Current smokers made up 17% of our population, which is similar to the overall smoking rate of Oregon adults (17.7% in 2012). 3. All patients need to be asked about smoking history and clinic staff need to be prepared to discuss cessation strategies. The majority of current smokers are ready to discuss cessation and accept therapy.

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Only Time Can Tell. Overlapping Features of Osteoradionecrosis and Recurrent Oral Squamous Cell Carcinoma

A.M. Tufano, R. Sugarman, T. Shroff, S. Teckie, M. Ghaly, J. Pollack, D. Frank, D. Kamdar, L. Pereira, J. Fantasia, M. Lessin, G. Romeo, and N. Seetharamu; *Northwell Health, New Hyde Park, NY*

Purpose/Objective(s): Osteoradionecrosis (ORN) is a debilitating complication of chemoradiation therapy for head and neck cancer. ORN is difficult to differentiate from recurrent or progressive cancer, as they may share clinical and imaging characteristics. It is crucial, however, to distinguish between these two conditions, because management is quite different and outcomes depend on timely intervention. We performed a retrospective chart review with the goal of identifying potential clinical and radiological factors helpful in differentiating ORN from recurrent cancer.

Materials/Methods: This retrospective case series examined 10 patients (pts) treated for oral squamous cell carcinoma in the last 2 years who were clinically suspected to have ORN based on physical exam, CT and/or PET imaging. Clinical details, tobacco and alcohol history, cumulative dose of radiation, chemotherapy, radiological appearance, histopathology, final diagnosis, treatment received and outcome were collected.

Results: Of the 10 patients, 9 had locally advanced disease at presentation. Six pts were male, and 4 female. Median age was 66 years (range 22-90). Five were ultimately diagnosed with ORN (cohort A) and the rest had progressive/recurrent disease (cohort B). In both cohorts, 3 pts had mandibular involvement, and 2 maxillary. Predominant symptoms were trismus (2 pts each in A and B), oral pain (4 pts each in A and B), spontaneous teeth loss (1 pt each in A and B), and exposed bone or fistula formation (2 pts each in A and B). Median cumulative radiation dose was 6000 cGy in cohort A and 6600 cGy in cohort B. The radiation technique (SBRT, IMRT) did not appear to be associated with either outcome. Time interval between RT and suspicion of ORN was longer in cohort A (13.8 months vs. 7 months). Radiologic features were also similar in cohort A and B, with soft tissue thickening and enhancement being seen in the majority of both ORN and cancer cases. Sclerosis was noted in 1 pt in A, and 2 pts in B. Median Standardized uptake value in the bone suspected to have ORN was 6.95 in cohort A and 6.3 in cohort B. Two pts in cohort B had initial biopsies that were negative for malignancy, but were positive on subsequent biopsies. All 5 pts with ORN are alive with stable or improving clinical status but all 5 pts with recurrent cancer have expired.

Conclusion: ORN and recurrent cancer share common clinical and radiologic features. ORN symptoms occurring within a year of completion of radiation should prompt additional work up to rule out recurrence. While biopsy demonstrating malignancy can clearly help differentiate between the 2, a negative result does not rule out recurrence due to sampling issues. Repeated biopsies should be considered in pts who fail to improve with supportive care. It should be noted however that pts can have concurrent ORN and cancer and prioritization of management should be based on a discussion amongst multidisciplinary teams.

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Planned Observational Study of Hearing Loss and the Effects of Statin Drugs in Head and Neck Squamous Cell Carcinoma Patients Treated With Chemoradiation

N.C. Schmitt,[1,2] K. Fernandez,[2] B.R. Page,[3] and L.L. Cunningham[2]; *[1]Johns Hopkins University Department of Otolaryngology, Baltimore, MD, [2]NIDCD, NIH, Bethesda, MD, [3]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD*

Purpose/Objective(s): The incidence of hearing loss in head and neck squamous cell carcinoma (HNSCC) patients treated with cisplatin chemoradiation has not been well-established, particularly for low-dose, weekly (40 mg/m^2) regimens. Preclinical and retrospective clinical data suggest that statin drugs may partially mitigate cisplatin-induced hearing loss. Barriers to study of hearing loss in cancer patients include limited access to audiology services during the short window of time between cancer diagnosis and initiation of treatment. We hypothesize that a substantial proportion of HNSCC patients treated with low-dose, weekly cisplatin, and concurrent radiation therapy will develop clinically relevant hearing loss, which will be of lower magnitude in patients taking statin drugs for hyperlipidemia.

Materials/Methods: We sought to design an observational study that would facilitate the comparison of pretreatment and posttreatment audiograms on HNSCC patients treated with chemoradiation. Eligible patients will include patients with confirmed HNSCC of the oral cavity, oropharynx, larynx, or hypopharynx for whom definitive or adjuvant chemoradiation with weekly cisplatin is planned. A tympanogram and audiogram will be obtained prior to treatment and at 1 month and 6 months posttreatment. An FDA-approved software will be used with calibrated headphones for self-administered audiograms on a tablet (iPad) device. Medications, including statin drugs, will be tracked throughout treatment.

Results: This prospective observational study has been IRB approved, and preliminary results will be presented.

Conclusion: Despite lower overall toxicity, low-dose, weekly cisplatin chemoradiation regimens for HNSCC continue to cause clinically significant hearing loss. Information on the incidence and severity of the resulting hearing loss would be helpful for the counseling of patients. Statin drugs have shown promise in preliminary studies as a possible preventive intervention, but prospective clinical data are needed.

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Risk Factors Associated With Hospital Admission in Head and Neck Cancer Patients

L.A. McLaughlin and L. Hinyard; *Saint Louis University, St. Louis, MO*

Purpose/Objective(s): Oropharyngeal cancer (OPC) is a growing subpopulation of head and neck cancer (HNC) with an overall survival rate of approximately 80%. As the pool of survivors increases, it is important to evaluate treatment complications. One way to quantify complications is to examine national hospital admission rates.

Materials/Methods: The National Inpatient Sample (NIS) was used in this study. Descriptive statistics were used to characterize OPC patients hospitalized between 2008-2013. Binary logistic regression was used to assess complications among OPC and all other HNC diagnoses using crude comparisons and controlling for confounders. The OPC population was younger and more predominately male and white than the HNC group.

Results: OPC patients experience more esophagitis, nutrition, metabolic, and hematological disorders, respiratory infection, and renal failure than other HNC patients. Those with nutritional (OR 1.5 CI 1.3-1.6) and hematological (OR 1.8 CI 1.6-2.1) disorders and renal failure (OR 1.3 CI 1.14-1.5) were more likely to be OPC.

Conclusion: This analysis demonstrates greater risk for admission related to common treatment-related complications among OPC when compared to other HNC patients.

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