MULTIDISCIPLINARY HEAD and NECK CANCERS SYMPOSIUM
EXPANDING TREATMENT HORIZONS
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K. Kian Ang, MD, PhD, FASTRO, Commemorative Plenary Session

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Neoadjuvant Nivolumab +/- Ipilimumab in Patients with Oral Cavity Cancer

J.D. Schoenfeld,[1] G.J. Hanna,[2] V. Jo,[3] S. Criscitiello,[2] B. Rawal,[4] P.S. Catalano,[4] N. Chau,[5] J. Lorch,[2] J. Kass,[6] D. Annino,[6] L. Goguen,[6] B. Ross,[7] D.N. Margalit,[2] R.B. Tishler,[2] R. Uppaluri,[6] and R.I. Haddad[2]; *[1]Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, [2]Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, [3]Department of Pathology, Brigham and Women's Hospital, Boston, MA, [4]Department of Biostatistics & Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [5]BC Cancer's Vancouver Centre, Vancouver, BC, Canada, [6]Department of Surgery/Otolaryngology, Brigham & Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, [7]Brigham and Women's Hospital, Boston, MA*

Purpose/Objective(s): Preclinical/clinical data support neoadjuvant immunotherapy and PD-1/CTLA-4 inhibitor combinations. We hypothesized that a short 3-week neoadjuvant course of nivolumab (N) +/- the CTLA-4 inhibitor ipilimumab (NI) would lead to tumor response and not delay definitive surgery in patients (pts) with resectable oral cavity (OC).

Materials/Methods: This phase 2 trial enrolling pts with SCC of the OC >=T2 and/or node positive (M0), randomizing 1:1 to treatment with 2 cycles (wks 1, 3) of N (3 mg/kg) or NI (N 3mg/kg, I 1mg/kg with the 1st cycle). Surgery was performed 3-7 days following C2. Primary endpoints were safety/tolerability and volumetric response defined as any clinical, radiologic or pathologic decrease in bidirectional measurements, with the pre-specified goal of achieving a 15% response rate in either arm. Secondary endpoints included objective response per RECIST 1.1, clinical-pathologic (C-P) downstaging, pathologic response of primary tumor (determined by a head and neck pathologist blinded to treatment), DFS and OS.

Results: We treated 30 pts; 1 was subsequently found to be ineligible due to metastases at baseline and was therefore excluded. The most common subsite was oral tongue (n=16). Baseline clinical staging included pts with T2 (n=20) or greater (n=9) T-stage and 17 pts (58%) with node positive disease. There were no delays to surgery; however, 6 pts didn't receive the full C2 dose (infusion reaction n=2, toxicity n=2, pt choice n=1, concern about clinical progression n=1), and 1 pt with T4 disease with evidence of radiologic tumor shrinkage but extent of disease observed in the OR prompted a shift to definitive chemoradiation. There were toxicities at least possibly related to study treatment in 18 pts, including grade 3-4 events in n=1 (N), and n=3 (NI) pts. One pt died of toxicities unrelated to study treatment (postoperative flap failure, stroke). Responses (table 1) include 69% overall volumetric response (31% by RECIST), 61% C-P downstaging, and 39% with at least moderate (>50%) pathologic response. Four pts had major/complete pathologic response >90% (N n=1, NI n=3). With median follow up of >11 months, 90% of pts are alive and disease-free.

Abstract 1; Table 1

Treatment	Volumetric response	RECIST response*	Clinical to pathologic downstaging	Pathologic effect >50%	Pathologic effect >90%
N (n=14)	79% (11)	14% (1)	69% (9)	23% (3)	8% (1)
NI (n=15)	60% (9)	44% (4)	53% (8)	53% (8)	20% (3)

* 13 patients without measurable disease on CT and/or PET/CT, 7 in N arm, 6 in NI arm.

Conclusion: Primary endpoints were met with both N and NI demonstrating promising rates of clinical-pathologic downstaging and pathologic response, including near complete/complete responses.

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Immune Modulation in a Randomized Trial of Neoadjuvant IRX-2 Regimen in Patients with Stage II-IV Squamous Cell Carcinoma (SCC) of the Oral Cavity. INSPIRE Trial (NCT 02609386) Interim Analysis

G.T. Wolf,[1] S. Liu,[1] E. Bellile,[2] M. Sartor,[1] L. Rozek,[1] M. Shah,[3] A. Nguyen,[1] and J.B. McHugh[1]; *[1]University of Michigan, Ann Arbor, MI, [2]Department of Biostatistics, University of Michigan, Ann Arbor, MI, [3]Brooklyn ImmunoTherapeutics, LLC, New York City, NY*

Purpose/Objective(s): Immune checkpoint inhibitors have opened a new therapeutic frontier for head and neck SCC. Despite significant and long duration responses to this immunotherapy, a minority of patients benefit and methods to select optimal patients are lacking. IRX-2 is a primary-cell-derived immune-restorative consisting of human cytokines that act on multiple cell types to overcome tumor-mediated immunosuppression. Neoadjuvant perilymphatic IRX-2 provides an *in vivo* tumor vaccination designed to increase tumor infiltrating lymphocytes (TIL) and enhance the effectiveness of checkpoint inhibitors. A randomized Phase II trial was conducted of the neoadjuvant IRX-2 regimen 3 weeks prior to surgery consisting of an initial dose of Cyclophosphamide (300 mg/m^2) followed by 10 days of regional perilymphatic IRX-2 cytokine injections (115 Units subq. upper neck, bilaterally), and daily indomethacin, zinc and omeprazole (Arm A) compared to the identical regimen without the IRX-2 cytokines (Arm B).

Materials/Methods: A total of 96 patients with resectable, previously untreated, stage II-IV oral cavity cancer were randomized 2:1 to experimental (A) or control (B) arms (64:32). Paired biopsy and resection specimens from 62 patients were available for creation of tissue microarray

(TMA, n=39), and processing for multiplex T cell immunohistology (n=54)and for DNA/RNA extraction for gene methylation and NanoString immune related gene expression analyses (n=62). An increases in CD8+ TIL infiltrate score of at least 10 cells/mm^2 which was previously associated with improved overall and disease specific survival in a study of 228 oral cavity cancer patients was used to determine immune responders (IR). Paired t-tests (change), Wilcoxon and chi-square test (by regimen) and linear regression (tumor size) were employed.

Results: Arm A was associated with significant post treatment increases in CD8+ infiltrates (p=0.01) compared to Arm B which only showed a trend for higher tumor associated macrophages (CD68+, p=0.11). In patients with p16 negative cancers, significant increases in CD8+, CD20+ and overall TILs were evident in Arm A (p=0.004, 0.04, and 0.04 respectively). IRs were more frequent in Arm A (74% vs 31%, p=0.01). Multiplex immunohistology confirmed a significant correlation of increases in CD4+ (p=0.0099), and overall TILs (p=0.029) with decreases in tumor size for patients on Arm A alone.

Conclusion: The findings demonstrate significant increases in T cells infiltrating the primary tumor after perilymphatic IRX-2 injections that correlated with decreases in measured tumor size. Three quarters of patients showed significant immune responses suggesting that the IRX-2 regimen could be considered for combination with other immune modifiers such as checkpoint inhibitors. The results also suggest that p16 status could be a useful marker for patient selection.

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Spatial evolution of lymph node metastasis in Human Papillomavirus-negative head and neck cancers

R. Bao,[1,2] R.J. Cabay,[3] O. David,[3] K. Valyi-Nagy,[3] V. Macias,[3] R. Zhong,[1] and M.T. Spiotto[4,5]; *[1]The University of Chicago, Chicago, IL, [2]University of Pittsburgh Medical Center, Pittsburgh, PA, [3]University of Illinois Hospital and Health Sciences System, Chicago, IL, [4]Department of Radiation Oncology, University of Illinois Hospital and Health Sciences System, Chicago, IL, [5]Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, IL*

Purpose/Objective(s): Head and neck cancers frequently metastasize to lymph nodes, which is associated with worse survival. Transcriptional profiling of lymph node metastases (LNMs) previously identified three prognostic subtypes that were not present in primary tumors. Here, we modeled the spatial evolution of primary tumors and LNMs to define genetic mechanisms underlying this metastatic process.

Materials/Methods: We performed whole exome sequencing on primary tumors (n=22), matched LNMs (n=64) and matched non-metastatic lymph nodes (n=32) from 34 patients with HPV-negative head and neck squamous cell cancers (HNSCCs). Formalin fixed paraffin embedded samples were sequenced with 100bp paired-end reads on an Illumina HiSEQ4000 obtaining an average depth of 148±4x and 137±3x for primary tumors and LNMs, respectively. Mean estimated cellularity was 72.3±3.5% for primary tumors and 69.1±2.0% for LNMs. Non-synonymous somatic mutations (NSSMs), representing single nucleotide variants and small indels, were called by GATK4-MuTect2. Somatic copy number variations were detected by Control-FREEC, and subclones were evaluated by SciClone. Mutation frequency differences between groups were tested by two-sided Fisher's exact test with BH multiple testing correction.

Results: Two evolutionary patterns were evident: (1) a less common, sequential evolution in 36% of patients, where LNMs originated from a shared subclone in the primary tumor; and (2) a more common, early divergent evolution in 64% of patients, where primary tumors and LNMs lacked a shared subclone. The mean NSSMs between primary tumors and LNMs was 221±109 and 175±22 ($P = 0.36$), respectively, and did not differ between LNMs subtypes. LNMs shared an average of only 23.5% of NSSMs with the matched primary tumors and only 10.4% of NSSMs were shared between matched LNMs. Average ploidy did not significantly differ between primary tumors and LNMs (2.7±0.8 vs. 2.7±0.8; $P = 0.87$) or between LNMs subtypes ($P = 0.19$). The most frequently mutated genes included *TP53* (61.5% of patients), *CDKN2A*, *SYNE1* and *NOTCH1* (each 17.6% of patients). Compared to the primary tumor, the mutant genes most enriched in LNMs were *COL1A2*, *AMBRA1*, *TRO* and *OR14C36*. The poor prognostic subtype of LNMs were enriched for mutations in *TP53* ($P = 0.0003$), *BCORL1* ($P = 0.036$) and *CDKN2A* ($P = 0.036$). More favorable subtypes of LNMs were enriched for mutations in *PKD1L3* ($P = 0.035$) and *DLGAP1* ($P = 0.035$).

Conclusion: LNMs are highly divergent from primary tumors indicating that the evolution of LNM-specific subtypes is an early step in head and neck cancer. Furthermore, we identified genetic differences that were enriched in all LNMs and in LNM-specific subtypes that may partly explain the biological traits that drive these adverse subtypes.

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Exploration of Next-Generation Sequencing of Tumor Tissue and Blood in Head and Neck Squamous Cell Carcinoma

H.L. Wilson,[1] R. D'Agostino, Jr,[2] T. Lycan,[3] S. Commander,[1] U. Topaloglu,[1] and M. Porosnicu[1]; *[1]Wake Forest University School of Medicine, Winston Salem, NC, [2]Wake Forest Baptist Medical Center, Winston Salem, NC, [3]Department of Hematology & Oncology, Wake Forest School of Medicine, Winston Salem, NC*

Purpose/Objective(s): Next-generation sequencing of circulating tumor DNA (ctDNA) is a promising new tool in the analysis of tumor genomics that has traditionally been performed through sequencing of tumor tissue (tDNA). Analysis and correlation of the two platforms in each tumor type can bring valuable diagnostic, therapeutic and prognostic information. The aim of this study is to explore the genomic signature of Head and Neck Squamous Cell Carcinoma (HNSCC) in circulation and tumor tissue and understand the implications of ctDNA sequencing for prognosis and precision oncology treatments.

Materials/Methods: We retrospectively assessed 75 HNSCC patients for both tDNA performed by FoundationOne and ctDNA performed by Guardant 360 at our institution. We collected demographic and tumor diagnostic information in all patients. We collected outcome data in 67 patients who had follow up longer than 6 months. Results of ctDNA were compared and correlated with the results of tDNA to calculate concordance and with clinical outcomes to measure prognostic value. Concordance was defined as detection of matching, identical mutations in ctDNA and tDNA per gene, per patient. Standard statistical methods were applied to the analysis of categorical and continues variables and Kaplan Meier curves were generated for comparing survival curves.

Results: The 5 most frequently altered genes were TP53, CDKN2A, TERT, BRCA2, and NOTCH1. Twenty percent of patients had NOTCH1 alterations in tDNA, with none found in ctDNA. Concordance between ctDNA and tDNA was 13.03% among altered genes with 4.35 ± 2.63 tDNA alterations per patient and 2.78 ± 1.67 ctDNA alterations per patient among overlapping genes. 65.3% of patients had actionable ctDNA

alterations. ctDNA alterations were associated with decreased overall survival (OS) (p=0.042) and presence (p=0.030) and extent (p=0.039) of disease at last visit. In DNA repair genes, alterations in ctDNA alone and combined with tDNA were associated with decreased OS (p=0.0044, p=0.0055) and presence of disease at last visit (p=0.027, p=0.025). Similar significant associations were found in TP53 for ctDNA alone and combined with tDNA. DNA repair gene alterations in ctDNA (p=0.0036) and unique ctDNA alterations within partially concordant genes (p=0.014) were associated with decreased OS in multivariate analysis.

Conclusion: We demonstrate that ctDNA sequencing in HNSCC has prognostic value and concordance similar to analyses of other tumors. For the first time, total ctDNA alterations and specific ctDNA alterations in DNA repair genes, in TP53 gene as well as unique alterations within partially concordant genes were shown to be significantly associated with poor prognosis in HNSCC. Further analysis is required with larger cohorts to validate these findings in the setting of head and neck cancer.

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Multi-Institutional Randomized Double-Blind Phase II Trial of Everolimus vs. Placebo as Adjuvant Therapy in Patients with Locally Advanced Squamous Cell Cancer of the Head and Neck (SCCHN)

C.A.O. Nathan,[1] D.N. Hayes,[2] O. Harismendy,[3] J. Flores,[4] T. Moore-Medlin,[1] J.S. Gutkind,[5] P. Neupane,[6] G. Mills,[7] Z.B. Sargi,[8] T.Y. Seiwert,[9] J. Grilley-Olson,[10] T. Day,[11] M. Gillison,[12] J. Wade,[13] L. Feldman,[14] G. Jha,[15] M. Kozloff,[16] M. O'Leary,[17] F. Worden,[18] and E. Cohen[19]; *[1]Louisiana State University Health, Shreveport, LA, [2]UNC School of Medicine, Chapel Hill, NC, [3]University of California, San Diego, San Diego, CA, [4]Yale University School of Medicine, New Haven, CT, [5]University of California, San Diego Moores Cancer Center, La Jolla, CA, [6]The University of Kansas School of Medicine, Kansas City, KS, [7]Louisiana State University Health Sciences Center, Shreveport, LA, [8]University of Miami, Miami, FL, [9]Department of Medicine, Section of Hematology/Oncology, The University of Chicago Medicine, Chicago, IL, [10]University of North Carolina Hospitals, Chapel Hill, NC, [11]Medical University of South Carolina, Charleston, SC, [12]MD Anderson Cancer Center, Houston, TX, [13]Decatur Memorial Hospital, Decatur, IL, [14]University of Illinois Hospital and Health Sciences System, Chicago, IL, [15]University of Minnesota, Minneapolis, MN, [16]University of Chicago, Chicago, IL, [17]Tufts Medical Center, Boston, MA, [18]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [19]Moores Cancer Center, University of California San Diego (UCSD), La Jolla, CA*

Purpose/Objective(s): The dismal 5-year survival rate for advanced stage smoking related SCCHN of <30% has not changed in the past 30 years. Akt/mTOR is activated in most SCCHN and pathway activation in surrounding normal mucosa is associated with recurrences. Oral mTOR inhibitors appear well tolerated and effective in window of opportunity SCCHN trials. The purpose of this trial (NCT01111058) was to determine whether adjuvant everolimus improves 2-year progression-free survival (PFS) in patients with advanced SCCHN and investigate correlative biological factors associated with response.

Materials/Methods: Randomization was stratified for stage, initial therapy (IVa surgical vs. IVa non-surgical vs. IVb) and treating institution. After confirming patients were disease free with definitive curative-intent therapy, patients received either everolimus (10mg po) or placebo for a maximum of 1 year. p16 IHC and whole exome sequencing were performed on tumors. Cox proportional hazard models estimated 1- and 2-year survival. Log rank tests evaluated differences in survival.

Results: 52 patients from 13 institutions were enrolled (median age, 58 [range 37-77]). Subjects were randomized to placebo (N=24) and everolimus (N=28). There were no significant differences in demographic characteristics. Grade ≥3 toxicity was reported in 16 everolimus and 7 placebo patients, while serious adverse events were seen in 3 and 5 patients, respectively. At 1 year (duration on everolimus), 81.16% on everolimus were disease free, compared to 56.88% on placebo (P=0.039). The 2 year PFS continued to favor everolimus, but was no longer significant (P=0.36). There were no significant differences in overall survival (OS) at 1 or 2 years. Remarkably, subset analysis of *TP53* mutational status determined significantly higher survival rates in *TP53* mutated patients treated with everolimus (70.0% at 2 years) compared to *TP53* mutated patients treated with placebo (22.5% at 2 years)(Log-Rank P=0.036). This difference between placebo and everolimus was not seen in the *TP53* wt group (p=0.56).

Conclusion: There is need for adjuvant therapy in advanced SCCHN. Our study showed that patients with *TP53* mutations benefited significantly from everolimus. In addition, irrespective of p53 status, PFS and OS were significantly better while patients were on everolimus during the first year, when compared to the placebo group. Future studies with extended use of mTOR inhibitors in *TP53* mutated patients that are known to have the worst outcomes may improve survival in this group at high risk of tumor relapse.

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Long-Term Update of NRG Oncology RTOG 0522: A Randomized Phase III Trial of Concurrent Radiation and Cisplatin with or without Cetuximab in Locoregionally Advanced Head and Neck Cancer

J.J. Caudell,[1] P. Torres-Saavedra,[2] D.I. Rosenthal,[3] R. Axelrod,[4] P.F. Nguyen-Tan,[5] E. Sherman,[6] R.S. Weber,[7] J.M. Galvin,[8] A.K. El-Naggar,[7] A.A. Konski,[9] A. Trotti,[10] N.E. Dunlap,[11] G. Shenouda,[12] A.K. Singh,[13] J.J. Beitler,[14] A.A. Garsa, Jr,[15] M. Birrer,[16] A.S. Garden,[17] T.S. Herman,[18] and Q.T. Le[19]; *[1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, [2]NRG Oncology Statistics and Data Management Center, Philadelphia, PA, [3]The University of Texas MD Anderson Cancer Center Institution *, Houston, TX, [4]Thomas Jefferson University Hospital, Philadelphia, PA, [5]CHUM - Centre Hsopitalier de l'Universite de Montreal, Montreal, QC, Canada, [6]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [7]The University of Texas MD Anderson Cancer Center, Houston, TX, [8]IROC, Philadelphia, PA, [9]Chester County Hospital, West Chester, PA, [10]Mofffitt Cancer Center and Research Institute, tampa, FL, [11]University of Louisville Hospital, Department of Radiation Oncology, Louisville, KY, [12]McGill University, Montreal, QC, Canada, [13]Roswell Park Comprehensive Cancer Center, Buffalo, NY, [14]Emory University School of Medicine, Atlanta, GA,*

[15]University of Southern California Keck School of Medicine, Department of Radiation Oncology, Los Angeles, CA, [16]The University of Alabama at Birmingham, Birmingham, AL, [17]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [18]University of Oklahoma Health Science Center, Stephenson Cancer Center, Department of Radiation Oncology, Oklahoma City, OK, [19]Stanford Cancer Institute, Stanford, CA

Purpose/Objective(s): The combination of cisplatin and radiation or cetuximab and radiation improves overall survival (OS) of patients with locoregionally advanced head and neck carcinoma (HNC). The Radiation Therapy Oncology Group conducted a phase III trial to test the hypothesis that adding cetuximab to radiation and cisplatin would improve progression-free survival (PFS).

Materials/Methods: Eligible patients with AJCC 6th edition stage T2 N2a-3 M0 or T3-4 N0-3 M0 were accrued from 11/2005 – 3/2009 and randomly assigned to receive radiation and cisplatin without (arm A) or with (arm B) cetuximab. Outcomes were correlated with patient and tumor features. Late reactions were scored using Common Terminology Criteria for Adverse Events (version 3).

Results: Of 891 analyzed patients, 452 were alive at analysis (median follow up 10.1 years). The addition of cetuximab did not improve PFS [HR 1.06 (95% confidence interval (CI) 0.89 – 1.26), p=0.74), with 10-year estimates of 43.6% (95% CI 38.8 – 48.4) for Arm A and 40.2% (95% CI 35.4 – 45.0) for Arm B. Cetuximab did not reduce locoregional failure (LRF) [HR 1.21 (95% CI 0.95 – 1.53), p=0.94] or distant metastasis (DM) [HR 0.79 (95% CI 0.54 – 1.14), p=0.10], or improve overall survival (OS) [HR 0.97 (95% CI 0.8 – 1.16), p=0.36]. 10-year estimates of these secondary endpoints of arm A and B were 28.5% (95% CI 24.2 – 32.9) and 34.8% (95% CI 30.3 – 39.5) for LRF, 15% (95% CI 11.8 – 18.6) and 11.8% (95% CI 9.0 – 15.1) for DM, and 49.9% (95% CI 45.0 – 54.8) and 50.0% (95% CI 45.1 – 54.9) for OS. A differential treatment effect by p16-status on PFS was not observed (p=0.18 for interaction). Cetuximab did not appear to improve PFS in neither p16+ oropharynx [HR 1.30 (95% CI 0.87 – 1.93)] nor p16- oropharynx or non-oropharyngeal primary [HR 0.94 (95% CI 0.73 – 1.21)]. On multivariable analysis, age > 50, > 10 pack-years, p16- oropharyngeal, non-oropharyngeal, and N2c/N3 disease were associated with poorer PFS. Grade 3-4 late toxicity rates were 57.4% in Arm A and 61.3% in arm B (p=0.26). The most common late adverse event was dysphagia, which was grade 3-4 in 39.6% of Arm A and 38.2% of Arm B (p=0.72). Feeding tube use at 10 years was 14.3% in Arm A and 11.0% in Arm B (p=0.53). More than one grade 3-4 treatment related adverse event occurred in 38.7% of Arm A patients and 39.2% of Arm B patients (p=0.62 for the distribution of number of events).

Conclusion: With a median follow-up of over 10 years, this updated report confirms the addition of cetuximab to RT+cisplatin did not improve any measured outcome in the entire cohort, or when stratifying by p16-status.

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Clinical outcomes and Toxicity profile with IMRT or Brachytherapy boost in oropharyngeal malignancies: A Randomized, open label study

V. Pareek,[1] R. Bhalavat,[2] M. Chandra,[2] L. Nellore,[2] K. George,[2] D. Borade,[2] and P. Bauskar[2]; [1]All India Institute of Medical Sciences, New Delhi, India, [2]Jupiter Hospital, Mumbai, India

Purpose/Objective(s): Radical radiation therapy in oropharyngeal malignancies have a significant toxicity especially in relation to dose to dysphagia aspiration related structures (DARS), mucositis and aspiration which leads to prolonged overall treatment times, thereby, having an impact on survival outcomes. Interstitial Brachytherapy (ISBT) has significant role in reducing these toxicities, however, literature comparing Intensity modulated radiation therapy (IMRT) with Brachytherapy boost is lacking. Our study looks in to the clinical outcomes and toxicity profile while comparing the two treatment modalities.

Materials/Methods: A total of 70 patients diagnosed histopathologically as squamous carcinoma of oropharynx were randomized to receive radical radiation therapy with IMRT (n=35) or IMRT with ISBT boost (n=35). The total dose with IMRT was 70Gy and in ISBT, initial dose was 50Gy with IMRT followed by 24.5Gy dose (3.5Gy in 12 fractions). Patients were followed up as per institute protocol and assessed for a median follow-up of 36 months. Assessment of survival outcomes in terms of progression free survival (PFS) and overall survival (OS) were assessed. Toxicity profile was assessed as per CTCAE 4.0 criteria and quality of life was assessed as per EORTC-C30 and HN35 questionnaires. Dosimetric parameters for the target volumes were compared along with assessment of various important organs at risk (OAR).

Results: After a median follow up of 36 months, PFS was 86% vs 81% favoring ISBT arm (p=0.032), however, there was no difference in overall survival. On assessment of toxicities, dysphagia and xerostomia were significantly reduced with ISBT boost with Grade II and III toxicities 12% and 18% vs 18% and 24% respectively. On QoL assessment, physical (p<0.001) and social functioning (p=0.012) favored ISBT boost. On symptom assessment, fatigue, dyspnea, appetite loss, speech problems, swallowing and pain was significantly reduced with ISBT boost. Dosimetric parameters showed significant dose reduction to DARS (p<0.001) and parotid glands (p<0.001) with ISBT boost.

Conclusion: ISBT boost has shown to be effective in improving PFS, toxicity profile and quality of life outcomes in oropharyngeal malignancies in spite of technological advancements in form of IMRT. ISBT should be employed in treatment armamentarium to dose escalate and thereby improve survival especially in oropharyngeal malignancies.

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Risk of suicidal self-directed violence among survivors of head and neck cancer: A retrospective cohort analysis

S.M. Nugent,[1,2] L. Ganzini,[1,3] R. Handley,[1] E. Hooker,[4] J. Chen,[2,5] B. Morasco,[1] D. Sullivan,[1,6] and C.G. Slatore[1]; [1]VA Portland Health Care System, Center to Improve Veteran Involvment in Care, Portland, OR, [2]Oregon Health & Science University, Department of Psychiatry, Portland, OR, [3]Oregon Health & Science University, Department of Psychiatry, Porltand, OR, [4]VA Portland Healthcare System, Center to Improve Veteran Involvement in Care, Portland, OR, [5]VA Portland Health Care System, Center to Improve Veteran Involvement in Care, Portland, OR,

[6]*Oregon Health & Science University, Department of Pulmonology, Portland, OR*

Purpose/Objective(s): Head and neck cancer survivors (HNCS) suffer from high rates of chronic pain, substance use, and mental health comorbidities. HNCS have one of the highest rates of suicide among patients with cancer and are almost twice as likely to die by suicide compared to other cancer survivors. Among a national cohort of Veteran HNCS, we examined the associations between chronic pain, mental health and substance use disorder (SUD) diagnoses, and engagement in mental health services with risk of suicidal self-directed violence (SSDV), which included both suicide attempts and death by suicide.

Materials/Methods: We identified a national cohort of Veterans with a head or neck cancer diagnosis (stage I-IVB) who received any cancer treatment in the VA. We included those who did not have a recurrent head and neck or second primary cancer within the observation period (defined as 1-year prior to 2-years post cancer diagnosis). We extracted cancer diagnoses and treatment, mental health/substance use disorder (SUD) diagnoses and treatment, and pain intensity scores. We also obtained data about SSDV events from the validated Suicide Prevention Applications Network. Adjusted logistic regression models were used to determine associations between pre-cancer mental health or SUD diagnoses, number of post-cancer mental health and SUD treatment encounters) and (any SSDV event, including death by suicide) controlling for stage of cancer, cancer treatment modality.

Results: Our cohort included 10,622 Veterans who were treated from 2012-2018. Our sample was mainly comprised of males (95%) with a mean age of 65 SD 10.7; 79% identified as white non-Hispanic and 43% were married. Sixty-five percent (n=6,936) had a documented mental health or SUD diagnosis during the observation period. Thirty-six percent (n=3,771) of our cohort experienced chronic pain. One hundred and fifty (1.4%) Veterans had at least one documented suicide related event, this included suicidal ideation (n=42, 0.4%) or SSDV (n = 108, 1.0%: 17 (0.2%) of whom died by suicide). Logistic regression analyses with clinical factors and engagement in mental health services variables in the model found that chronic pain (OR = 2.00, 95% CI=1.30, 3.01), presence of pre-cancer mental health or SUD diagnoses (OR = 2.90, 95% CI = 1.78, 4.83), and number of mental health and SUD treatment encounters following the cancer diagnosis (OR= 1.01, 95% CI = 1.00, 1.01) were all significantly associated with SSDV.

Conclusion: Among HNCS, risk factors for SSDV include chronic pain, pre-cancer mental health or SUD diagnosis, and mental health and SUD treatment encounters following a cancer diagnosis. Our findings suggest an opportunity for HNCS who experience chronic pain or are already engaged in mental health services to undergo more robust suicide screening assessments and suicide prevention interventions.

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Distress Screening and Follow-Up Among Patients Within a Multidisciplinary Head and Neck Cancer Program

S. Lazaro,[1] E.R. Brauer,[2] C.L. Williams,[1] D.A. Rapkin,[1] A.B. Madnick,[3] R. Dafter,[1] G. Cheng,[4] F. Buen,[1] E. Abemayor,[1] R.K. Chin,[5] A.U. Kishan,[5] W. Chai-Ho,[6] E.G. Morasso,[5] A. Erman,[7] D.L. Jayanetti,[8] M. St John,[1] and D.J. Wong[6]; *[1]Ronald Reagan-UCLA Medical Center, Dept of Head and Neck Surgery, Los Angeles, CA, [2]UCLA School of Nursing, Los Angeles, CA, [3]Ronald Reagan-UCLA Medical Center, Department of Care Coordination & Clinical Social Work, Los Angeles, CA, [4]David Geffen School of Medicine at UCLA, Department of Physiology, Los Angeles, CA, [5]Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA, [6]David Geffen School of Medicine at UCLA, Dept of Medicine, Division of Hematology/Oncology, Los Angeles, CA, [7]Ronald Reagan-UCLA Medical Center, Department of Audiology and Speech Pathology, Los Angeles, CA, [8]UCLA School of Dentistry, Division of Advanced Prosthodontics, Los Angeles, CA*

Purpose/Objective(s): Since cancer-related distress can impact patients' quality of life, treatment compliance, and clinical outcomes, implementation of systematic distress screening is crucial to the delivery of high quality cancer care. The purpose of this study is to examine the prevalence of clinically significant distress among patients with head and neck cancer (HNC), assess common sources of distress, and report the frequency of appropriate clinical intervention made at a multidisciplinary Head and Neck Cancer Program (HNCP).

Materials/Methods: The Distress Screening (DS) was developed by the Mind Body team (MBT), a subspecialty group of psychologists and social workers within the HNCP. The DS includes the standard NCCN Distress Thermometer (DT), an adapted version of the NCCN "Problem List" relevant to HNC patients' psychosocial concerns, and screening questions for depression (PHQ-2) and anxiety (GAD-2). We hypothesized that DT scores $\geq$ 4 would correlate with positive screening scores for depression and anxiety. In September 2017 - August 2019, 245 HNCP patients completed the DS using pencil and paper in the exam room prior to consultation. Clinicians and patient navigator were also able to make direct referrals to the MBT based on their assessment of patients' anxiety, depression, anger, denial or evidence of significant delays in seeking care. A psychosocial follow-up protocol was implemented to define screening cut-off points (DT score $\geq$ 4) to trigger same-day intervention by the MBT utilizing interview-based assessment.

Results: Of the 245 patients screened for distress, 142 (58%) reported clinically significant distress [$\geq$4] on the DT, 54 (22%) screened positive for depression [$\geq$3] on the PHQ-2, and 81 (33%) screened positive for anxiety [$\geq$3] on the GAD-2. Of the patients who reported high distress, the most frequently endorsed items on the Problem Checklist were in the physical category: pain (36%), fatigue (28%), and sleep (25%). Of the 182 patients who scored [$\geq$4] or flagged for evaluation by MBT, 138 (76%) received evaluation by the MBT.

Conclusion: Patients with HNC report high levels of distress and psychosocial concerns. Psychosocial screening using brief, validated, and simple tools can identify patients who require further evaluation during their cancer care. Utilizing the DT with the PHQ-4 and the HNC-tailored Problem List moderately improved identification of distress in HNC patients. Adding further screening questions may improve the predictive validity of the DS, along with implementation of follow-up assessment. Future goals include addressing barriers to psychosocial evaluation for all patients screened for high distress, initiation of follow-up measures, and evaluation of the sensitivity, specificity, and predictive validity of the DS.

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Oral Abstract Session

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Long-Term Update of a Phase II Study of Concurrent Chemoradiotherapy Using Radiation + Bevacizumab (BV) For Locally or Regionally Advanced Nasopharyngeal Cancer (NPC): RTOG 0615

N. Lee,[1,2] J. Harris,[3] D.G. Pfister,[4] J. Kim,[5,6] A.S. Garden,[7,8] J.G. Mechalakos,[2] A.T.C. Chan,[9] K.S. Hu,[10,11] S.S. Yom,[12] B.S. Glisson,[13] G. Shenouda,[14] V. Bar Ad,[15] J.N. Waldron,[16] P.M. Harari,[17] and Q.T. Le[18]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]NRG oncology, Philadelphia, PA, [4]Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, NY, [5]Radiation Medicine Program, University Health Network and Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [6]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [7]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [8]University of Texas MD Anderson Cancer Center, Houston, TX, [9]Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China, [10]Department of Radiation Oncology, NYU Langone Health, New York, NY, [11]NYU Langone Health, Department of Radiation Oncology, New York, NY, [12]University of California, San Francisco, Department of Radiation Oncology, San Francisco, CA, [13]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [14]McGill University, Montreal, QC, Canada, [15]Thomas Jefferson University, Philadelphia, PA, [16]Department of Radiation Oncology, Princess Margaret Cancer Centre / University of Toronto, Toronto, ON, Canada, [17]Department of Human Oncology, University of Wisconsin, Madison, WI, [18]Stanford University, Palo Alto, CA*

Purpose/Objective(s): To report the long-term toxicity and treatment outcomes of a multi-center trial of combining concurrent chemotherapy and RT (CCRT) with BV in the treatment of locally or regionally advanced NPC.

Materials/Methods: Patients with NPC, WHO I-IIb/III, stage ≥IIB, ± node(s) were eligible. Concurrent BV (15mg/kg) and cisplatin (100mg/m^2) on days 1, 22, 43 were given with intensity-modulated radiation therapy or 3D conformal radiotherapy to total dose of 69.96 Gy over 33 fractions followed by adjuvant BV (15mg/kg), cisplatin (80mg/m^2) on day 1 and fluorouracil (1000mg/m^2/d) on days 1 through 4 for 3 cycles. The primary endpoint was grade 4 hemorrhage or grade 5 adverse event (AE) in the first year. Secondary endpoints were local-regional progression-free (LRPF) rates; distant metastasis-free (DMF) rates; progression-free survival (PFS) and overall survival (OS); grade 4 hemorrhage or grade 5 AE after the first year; and grade 3-5 AEs. AEs reported as definitely, probably, or possibly related to protocol treatment were included in this analysis. This report is an update of the primary endpoint results.

Results: Between 12/06 and 2/09, 46 patients were enrolled of which 44 patients were analyzable. Patients were predominantly male (65.9%), Asian (52.3%), Zubrod 0 (75%), WHO IIb or III (72.7%), and stage III/IV (88.6%) with a median age of 48.5 years. 95.5% received ≥69.96 Gy (min-max 65.72 - 70). Majority received 3 cycles of cisplatin (68.2%) and BV (70.5%) during RT. Adjuvant chemotherapy compliance was: 3 cycles of cisplatin (47.7%), fluorouracil (54.5%), and BV (52.3%). Median follow-up for surviving patients was 9.0 years (min-max 4.5 - 10.2). No grade 4 hemorrhage or grade 5 AEs were reported. The late grade 3 AE rate was 36.4% (no late grade 4-5). Late grade 3 dysphagia, hearing, and xerostomia rates were 15.9%, 13.6%, and 4.5%, respectively. 9.1% had a pre-treatment feeding tube and the rates at 1 and 2 years were 12.2% and 5.4%, respectively, with none ≥ 5 years. 19 patients have progressed/died (first event: 6 local-regional; 8 distant; 5 death without progression). The 5- and 7-year LRPF rates were 74.9% (95%CI 61.4-86.6) and 72.3% (58.4-84.7). The 5- and 7-year DMF rates were both 79.5% (66.4-90.0). The 5- and 7-year PFS rates were 61.2% (46.8-75.6) and 56.3% (41.5-71.1). 13 deaths have been reported with 61.5% due to disease. The 5- and 7- OS rates were 79.5% (67.6-91.5) and 69.7% (55.9-83.5).

Conclusion: No grade 4 hemorrhage or grade 5 AEs were reported with the addition of BV to CCRT for locally or regionally advanced NPC. The low rate of distant metastasis despite 90% of the patients presenting with stage III-IVB disease is intriguing and warrants further investigation.

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A Combination of Three Biomarkers for HNSCC Prognostication Following Chemoradiotherapy

J.W. Rocco,[1] K. Patel,[2] and E.A. Mroz[1]; *[1]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, [2]Moffitt Cancer Center, Tampa, FL*

Purpose/Objective(s): Accurate therapeutic prognostication continues to elude the head and neck oncologist, hindering de-intensification efforts and maximizing adjuvant therapy related toxicity. We examined three biomarkers: mutant allele tumor heterogeneity (MATH, a quantitative measure of intra-tumor genetic heterogeneity), and HPV and Estrogen Receptor alpha (ER-alpha) status in patients from the Cancer Genome Atlas (TCGA) treated with chemoradiotherapy (CRT). We hypothesized that this combination of biomarkers would prognosticate treatment outcome better than HPV status alone, allowing improved identification of patients at low and high risk of treatment failure.

Materials/Methods: Clinical, whole-exome sequencing (WES), and RNA sequencing (RNA-Seq) data were obtained for 528 TCGA HNSCC patients. Primary therapy received was determined from clinical data annotations. MATH was calculated from WES data, with a value > 32.7 taken as high MATH. High ER-alpha expression was taken as > 90.5 normalized reads per kilobase million (RPKM) in RNA-Seq mapped to ESR1 gene transcripts. HPV status was taken as positive if a tumor at an oropharyngeal site had > 1000 individual RNA-Seq reads mapped to HPV sequences. Relationships of these and other clinical variables to overall survival was determined by Cox proportional hazards multiple regression.

Results: Data on MATH, ER-alpha expression, and HPV status were available for 156 TCGA HNSCC patients who received CRT as primary therapy or adjuvant to surgery. Low MATH and high ER expression have known associations with HPV-positive tumors, yet they remained significantly related to overall survival in a Cox proportional hazards multiple regression that incorporated them with HPV status. Hazard ratios (with 95% confidence intervals and p-values) in a model including those 3 biomarkers were: high vs. low MATH, 2.09 (1.01-4.32; p = 0.046); high vs. low ER-alpha expression, 0.39 (0.18 - 0.84; p = 0.016); positive vs. negative HPV, 0.19 (0.05 - 0.79; p= 0.022). The hazard ratio for the combination of all three poor prognostic biomarkers (high MATH, low ER-alpha, HPV-negative) versus the combination of good prognostic biomarkers (low MATH, high ER-alpha, HPV-positive) was 28.2 (5.4 - 148; p = 0.0001).

Conclusion: The combination of ER-alpha, MATH and HPV status distinguished a wide range of overall survival outcomes in HNSCC patients from the TCGA dataset treated with chemoradiation and readily stratified patients into low and high-risk of treatment failure. Application of this marker combination based on pretreatment tumor biopsies could readily identify patients who could participate in clinical trials of de-intensification or novel therapeutic combinations to improve survival.

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Primary chemoradiotherapy or transoral robotic surgery for Stage I-II HPV-associated oropharyngeal squamous cell carcinoma

R.T. Hughes,[1] N. May,[2] J.D. Waltonen,[2] M. Porosnicu,[3] T. Lycan,[3] C.A. Sullivan,[2] H.S. Patwa,[2] R.F. Shenker,[1] B.A. Frizzell,[1] and K.M. Greven[1]; *[1]Department of Radiation Oncology, Wake Forest School of Medicine, Winston Salem, NC, [2]Department of Otolaryngology-Head and Neck Surgery, Wake Forest School of Medicine, Winston Salem, NC, [3]Department of Hematology & Oncology, Wake Forest School of Medicine, Winston Salem, NC*

Purpose/Objective(s): Clinical outcomes for patients with early-stage (AJCC 8th Edition Stage I-II) HPV-associated oropharyngeal squamous cell carcinoma are excellent. Current upfront treatment options include radiotherapy (RT) or transoral robotic surgery (TORS) followed by risk-based adjuvant therapy. We aim to compare survival, disease control and long-term gastrostomy tube (GT) presence between the two approaches.

Materials/Methods: Patients with Stage I-II (T1-3 N0-2 per the AJCC 8th Ed.) HPV-associated squamous cell carcinoma of the oropharynx diagnosed between 2010-2018 and treated with primary radiotherapy (n=64) or TORS (n=63) were identified. All patients treated with primary radiotherapy received chemoradiotherapy (CRT). RT or CRT was indicated after TORS based on pathologic risk factors. Overall survival (OS), disease-free survival (DFS) and locoregional control (LRC) were estimated using the Kaplan-Meier method and adjusted Cox proportional hazards models were performed. Factors including upfront treatment, T stage, N stage, tumor location, RT dose and neck coverage (ipsilateral/bilateral/none), any use of CRT (upfront or adjuvant), diabetes, and ≥10 pack-years were included in a multivariable backward stepwise logistic regression analysis was performed to identify predictors of GT at 1 year.

Results: In the overall cohort, mean age was 60 years, 86% were male, 99% had an ECOG performance status of 0-1, 62% had a history of smoking (46% ≥10 pack-years). After TORS, 44% underwent observation, 23% received adjuvant RT, and 33% received adjuvant CRT. Median RT dose was 70 Gy (CRT) and 60 Gy (TORS). There were significant differences in clinical stage (CRT: 48% stage I, 52% stage II; TORS: 90% stage I, 10% stage II; p<0.01) and primary tumor location (CRT: 55% BOT, 45% tonsil; TORS: 32% BOT, 68% tonsil; p=0.01). Median follow-up was 34 months. At 3 years, no significant differences between CRT and TORS were observed for OS (78% v. 85%), DFS (77%% v. 81%) and LRC (86% v. 94%). Adjusting for stage and tumor location, no difference between upfront TORS (versus CRT) was observed for OS (hazard ratio [HR] 0.75, p=0.59), DFS (HR 0.99, p=0.99) and LRC (HR 1.87, p=0.43). GT was placed in 88% of CRT and 38% of TORS patients and present at 1 year in 28% and 9%, respectively. Upon multivariable analysis, N2 (versus N0) disease was associated with increased odds of 1-year GT (OR 1.39, 95% CI 1.07-1.80, p=0.02).

Conclusion: Primary chemoradiotherapy and TORS followed by risk-adapted adjuvant therapy result in similar survival and locoregional control for AJCC 8th Ed. Stage I-II HPV-associated oropharyngeal carcinoma. Advanced nodal disease (N2) was the only identified independent predictor of late gastrostomy tube presence.

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Imaging response versus operative laryngoscopy assessment of induction chemotherapy response in an induction bioselection approach to larynx cancer

E. Jaworski,[1] L.A. Gharzai,[1] J.M. Pakela,[1] I. El Naqa,[1] C.A. Schonewolf,[1] P.G. Hawkins,[1] C.R. Bradford,[2] S.B. Chinn,[2] N. Hogikyan,[2] K. Malloy,[2] R. Kupfer,[2] M.E. Spector,[2] A. Shuman,[2] C.L. Stucken,[2] M.E. Prince,[2] A. Srinivasan,[3] P.L. Swiecicki,[4] K. Casper,[2] F. Worden,[4] and M.L. Mierzwa[1]; *[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [3]Department of Radiology, University of Michigan, Ann Arbor, MI, [4]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Bioselection with induction chemotherapy in larynx cancer is associated with excellent larynx preservation and disease-specific survival (DSS). The current approach to evaluating bioselection response consists of visual inspection of the primary tumor with operative direct laryngoscopy (DL) where ≥ 50% response to induction chemotherapy prompts continuation to definitive chemoradiation. Here, we retrospectively compare clinical and imaging response in bioselected patients.

Materials/Methods: This study is a secondary analysis of on two prospective single-institution bioselection trials at a single institution. CT response was calculated after gross tumor primary (GTVp), nodal (GTVn), and total disease burden (GTVtotal) were delineated on each scan. Imaging factors assessed included GTVtotal prior to initiation of chemotherapy, and the percent change in GTVtotal (%ΔGTVtotal) after induction. Regression was performed with regularized Cox regression (Lasso) with 10-fold cross validation to identify clinical and imaging factors predictive of dichotomized DL response of ≥50%, LR, and OS. Standard Cox regression was

further used to estimate association of predictive/prognostic factors with local recurrence (LR) and overall survival (OS).

Results: A total of 119 patients were identified, and 90 had complete data for review. 21.1% had glottic larynx tumors and 76.6% had supraglottic tumors. 44.4% had T3 tumors and 53.3% had T4 tumors, with N0, N1, and N2 representing 35.6%, 11.1%, and 53.3% respectively. Pretreatment mean GTVp was 24.3cc (range: 1.1-74.6), GTVn 5.21cc (0-41.7), GTVtotal 29.5cc (1.1-85.5). 58 patients had DL response of ≥50%, and 34 patients had CT response of ≥50%. On average, surgeons assessed DL response to be 16.8% ± 23.9% larger than %ΔGTVtotal. T-stage, tumor subsite, and pretreatment GTVtotal were not correlated with DL response, while %ΔGTVtotal was mildly correlated with DL response (Spearman rank correlation 0.5453, HR 1.019, p=0.005). T-stage, N-stage, tumor subsite, surgeon assessment, pretreatment GTVtotal, and %ΔGTVtotal were not significantly correlated with LR or OS after definitive treatment.

Conclusion: CT imaging potentially offers a non-invasive and objective opportunity to evaluate response to induction chemotherapy. CT assessment of bioselection response weakly correlated with DL response, and DL response overestimated CT response, likely due to a variety of factors including limitations of complete tumor visualization. Further investigation is needed to establish imaging markers and biomarkers that correlate with bioselection response as well as laryngectomy free survival and OS.

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Circulating Tumor Associated Cells in Head and Neck Cancers are Resistance Educated per Previous Chemotherapy Treatments

D. Akolkar,[1] D. Patil,[1] T. Crook,[2] R. Page,[3] C. Sims,[1] V. Datta,[1] R. Patil,[1] P. Fulmali,[1] S. Patil,[1] S. Apurwa,[1] S. Pawar,[1] V. Mhase,[1] A. Srinivasan,[1] and R. Datar[1]; *[1]Datar Cancer Genetics Limited, Nasik, India, [2]Royal Surrey County Hospital, Guildford, United Kingdom, [3]Worcester Polytechnic Institute, Worcester, MA*

Purpose/Objective(s): Resistance to systemic treatment agents are frequently encountered in Head and Neck Squamous Cell Carcinomas (HNSCC) and are largely undetected until symptomatic or radiological detection of disease progression. Real-time monitoring of chemoresistance in HNSCC is thus an unmet clinical need. We describe a novel approach for chemoresistance profiling (CRP) in real time in HNSCC using peripheral blood Circulating-Tumor Associated Cells (CTACs). C-TACs are defined as apoptosis-resistant cells of tumorigenic origin which are positive for Epithelial Cell Adhesion Molecule (EpCAM) and pan-cytokeratins (pan-CK) irrespective of CD45 status.

Materials/Methods: Peripheral blood was collected from 252 patients with confirmed diagnosis of HNSCC including 156 recently diagnosed and therapy naïve cases and 96 pretreated cases. Peripheral blood mononuclear cells (PBMCs) were harvested by centrifugation and treated with commercially available stabilizing agents by a proprietary protocol to stabilize apoptosis resistant C-TACs. Surviving C-TACs were confirmed by immunostaining for EpCAM, pan-CK and CD45. Harvested C-TACs were treated *in vitro* with a panel of conventional cytotoxic anticancer agents and the fraction of surviving cells estimated to determine resistance profiles.

Results: Among the recently diagnosed therapy naïve HNSCC, innate chemoresistance towards any chemotherapy agent was observed in 40.7 % cases (unique C-TAC-drug combinations), which included resistance towards platinum agents (Cisplatin + Carboplatin) in 44.2% cases, taxanes (Paclitaxel + Docetaxel) in 37.7% cases and antimetabolites (5-fluorouracil + Methotrexate + Gemcitabine) in 40.9% cases. Among the cases of previously treated HNSCC, resistance towards any of the previously administered systemic agents was observed in 91.1% cases, which included resistance towards platinum agents in 90.5% cases, taxanes in 90.5% cases and antimetabolites in 93.8% cases, respectively.

Conclusion: Chemoresistance profiling in newly-diagnosed and treatment naïve cases of HNSCC as well as in pretreated HNSCC is feasible using *in vitro* chemoresistance assay to interrogate C-TACs. Higher chemoresistance in the pretreated population, as compared to the therapy naïve sub-cohort indicates that C-TACs are resistance-educated by previous treatments and can guide treatment strategy in HNSCC cancers.

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An open-label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients (pts) with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): updated results of cohort 1 analysis

A.G. Sacco,[1] R. Chen,[2] D. Ghosh,[2] F. Worden,[3] D.J. Wong,[4] D. Adkins,[5] P.L. Swiecicki,[6] W. Chai-Ho,[4] E. Pittman,[7] K. Messer,[2] K.A. Gold,[1] G. Daniels,[1] B. Sutton,[2] A. Natsuhara,[2] and E. Cohen[8]; *[1]UC San Diego, Moores Cancer Center, Dept of Hematology/Oncology, La Jolla, CA, [2]UC San Diego Moores Cancer Center, La Jolla, CA, [3]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [4]David Geffen School of Medicine at UCLA, Dept of Medicine, Division of Hematology/Oncology, Los Angeles, CA, [5]Washington University in St. Louis, Department of Medicine, Division of Medical Oncology, St. Louis, MO, [6]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [7]Department of Family Medicine, Division of Biostatistics, University of California San Diego, La Jolla, CA, [8]Moores Cancer Center, University of California San Diego (UCSD), La Jolla, CA*

Purpose/Objective(s): Pembrolizumab (a humanized monoclonal antibody blocking programmed death receptor-1[PD-1]), and cetuximab (a chimeric monoclonal antibody inhibiting epidermal growth factor receptor [EGFR]) are both FDA-approved therapies for R/M HNSCC. This is the first trial to evaluate anti-tumor activity of anti-PD-1 therapy combined with EGFR inhibition in HNSCC. Previously reported safety and interim futility analyses demonstrated acceptable toxicity and met protocol specifications for trial continuation. Herein we present the updated analysis of cohort 1 (anti-PD-1/PD-L1 and cetuximab naïve) pts.

Materials/Methods: Pts with platinum-refractory/ineligible, R/M HNSCC were treated with pembrolizumab 200mg IV on day 1 and cetuximab 400mg/m2 loading dose followed by 250mg/m2 once weekly (21-day cycle). Primary endpoint: overall response rate (complete [CR] and partial responses [PR]) by 6 months (mo). Secondary endpoints: 12-mo progression-free survival (PFS) probability, overall survival, response duration, safety, correlative analyses.

Results: 33 pts were enrolled March 2017-July 2019. Median age 61y (range 30-86), M:F 22:11, ECOG (0:1) 12:21. Tumor sub-sites included 15 oral cavity, 13 oropharynx (11 HPV-related), 2 non-EBV-associated nasopharynx, and 3 larynx primaries. 28 pts (85%) had no prior lines of systemic therapy for R/M HNSCC (range 0-1). Of 29 pts evaluable for overall response by 6mo, there was a 41% response rate (12 pts with PR); one PR became CR after 6 mo. 6 (21%) pts had stable disease, and 11 (38%) had progressive disease (PD). Of the 11 pts classified as PD, 3 discontinued the trial prematurely (no response data) in favor of hospice. Median PFS was 252 days (range 65-599). Median duration of response was 195 days (range 53-530) for complete/partial responders and 285 days (range 63-392) for stable disease (response ongoing). There were 10 grade 3 treatment-related toxicities in 29 pts, of which 3 (1 fatigue, 2 mucositis oral) had at least possible attribution to both study drugs, resulting in cetuximab discontinuation in 2 cases with symptomatic improvement. 1 pt with grade 3 colitis related to pembrolizumab discontinued both study drugs, and 1 pt discontinued study treatment secondary to an unrelated grade 4 gastrointestinal ulceration with perforation.

Conclusion: These data suggest that pembrolizumab plus cetuximab may have promising activity for platinum-refractory/ineligible pts with R/M HNSCC. Further exploration of efficacy analysis as a function of PD-L1 expression status is warranted. NCT03082534.

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Delivering high-quality head-and-neck low-risk clinical target volumes through a fully-automated artificial intelligence-based approach

C.E. Cardenas,[1] B.M. Beadle,[2] D.J. Rhee,[1] R. McCarroll,[3] L. Zhang,[1] J. Yang,[4] and L.E. Court[1]; *[1]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Stanford University, Stanford, CA, [3]Department of Radiation Physics, University of Maryland Medical Center, Baltimore, MD, [4]The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Head and neck cancer (HNC) clinical target volume (CTV) delineation is a time-consuming task in radiotherapy that is subject to inter- and intra-observer variability. We hypothesize that we can develop a fully automated artificial intelligence tool to produce high quality CTV contours for patients undergoing definitive radiotherapy.

Materials/Methods: CT scans from 71 patients with HNC were retrospectively collected for this study. All cases had lymph node levels Ia-V, Ib-V, II-IV, and retropharyngeal (RP) node contours; these were previously manually drawn or approved by a radiation oncologist specializing in HNC and deemed "clinically acceptable without requiring edits." The patients' scans were split into train (n = 51), cross-validation (n = 10), and test (n = 10) datasets. Regions of interest (ROIs) about each patient's nodal levels were automatically identified using computer vision techniques. The ROI (CT image crop) and approved contours were then used to train a U-net autosegmentation model. Each lymph node level was trained independently with model parameters being optimized by assessing each model's performance on the cross-validation dataset. Once the best model was identified, overlap and distance metrics were calculated to compare differences between ground truth and autosegmentations on the final test set. Lastly, this final model was on used on 18 additional patient scans (not included in original 71 cases) and their auto-segmentations were visually inspected and rated by a radiation oncologist as being "clinically acceptable" (no edits required), "requiring minor edits" (less than 3mm edit), or "requiring major edits."

Results: The auto-segmentation model took 17.5 minutes on average to autosegment all lymph node level combinations. When comparing the ground truth to the autosegmentations on the test dataset, the median Dice Similarity Coefficients were 0.90, 0.90, 0.89, and 0.81 and the median mean surface distance values were1.0 mm, 1.0 mm, 1.1 mm, and 1.3 mm for node levels Ia-V, Ib-V, II-IV, and RP nodes, respectively. Qualitative evaluation showed that 93% of auto-segmentations were rated as "clinically acceptable" and the remaining 7% were rated as "requiring minor edits". No autosegmentation required "major edits".

Conclusion: We developed a fully automated artificial intelligence approach to auto-delineate nodal CTVs for patients with intact HNC. A majority of autosegmentations were found to be clinically acceptable after qualitative review. This work is promising in that it automatically delineates high quality CTVs in a robust and reliable manner; this approach can be implemented in ongoing efforts for fully automated radiation treatment planning for HNC.

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Research Feature

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De-Escalated Adjuvant Therapy after Transoral Robotic Surgery for HPV related Oropharyngeal Carcinoma: The SiRS Trial

B. Miles,[1] M. Posner,[1] M.S. Teng,[2] M. Yao,[2] R. Chai,[2] K. Misiukiewicz,[1] V. Gupta,[3] R.L. Bakst,[3] S. Sharma,[3] D. Zhang,[2] F. Ye,[2] W.H. Westra,[4] S. Kim-Schulze,[2] S. Sobotka,[2] A. Sikora,[5] P. Som,[2] and E. Genden[1]; *[1]Department of Otolaryngology − Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, [2]Icahn School of Medicine at Mount Sinai, New York, NY, [3]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [4]Department of Anatomic and Clinical Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, [5]Baylor College of Medicine, Houston, TX*

Purpose/Objective(s): Improved survival rates after treatment ofHPV related oropharyngeal SCChave resulted in "de-escalation" strategies to preserve survival while limiting toxicity. We hypothesized that transoral robotic surgery (TORS) for early T-stage disease withpathologic stratification andreduced dose adjuvant therapy would result in equivalent PFS and OS while reducing toxicity and preserving long term quality of life.

Materials/Methods: This study is a non-randomized Phase II trial for early stage (AJCC 8thT1-2, N1, AJCC 7thT1-T2, N2b) HPVOPC treatedwith upfront TORS and reduced dose radiotherapy. Patients with p16+ HPVOPC, previously untreated, and ≤20 pack years smoking history were enrolled. After TORS and confirmation of HPV status via PCR, patients were assigned to: Group 1: No poor risk features − surveillance; Group 2: intermediate pathologic risk factors (PNI,LVI) postoperative radiotherapy (50 Gy); Group 3: poor prognostic pathologic factors (ECE, >3+LNs, + margin) - postoperative concurrent chemoradiotherapy (56 Gy) with weekly cisplatin. The endpoints of the study were LRC, DSS, DFS, OS, patterns of failure and survival after salvage. QOL endpoints were assessed via EORTC HNQLQ35/C-30, MDADI, and a xerostomia questionnaire.

Results: 76 patients were enrolled, 21 subjects withdrew from the trial (primarily geographical issues with radiotherapy), leaving 54 subjects evaluable. There were 25 subjects in Group 1, 15 subjects in Group 2, and 14 subjects in Group III. Median follow up was 26.8 months (6.4-51.3). DSS was 100%, and PFS was 92.5%. Progression free survival probability via Kaplan-Meier was 91.3% for Group 1, 90.9% for Group 2, and 92.86% for Group 3. There was one death of unrelated cause (late MI). Four locoregional failures (LRF) and no distant metastases occurred. Average time to LRF was 21.2 months (9.6-28.8). All 4 LRFs were successfully salvaged and remain disease free(10.5-42.7months). Mean HNQLQ35 scores for Group I were 1.16 (1-2.17) with no significant changes over time. Baseline QOL scores for Groups 2 and 3 peaked at day 100, 1.40 (1.00-2.29) 1.79 (1.00-2.93) respectively, with a decrease over time (p=.003) Dysphagia scores were low at day 725, 1.82(1.20-2.80) and higher for xerostomia, 3.37 (.25-7.75) Group 2 had similar findings.

Conclusion: The results of this trial indicate that transoral robotic surgery and pathologic criteria driven adjuvant therapy with reduced dose radiation for T1-2, N1 (AJCC 8th) stage HPV OPSCC results in favorable survival with excellent ability for salvage. Functional and QOL outcomes utilizing this approach are excellent. Mean QOL, dysphagia, and xerostomia scores were low in all groups and improved over time, with statistically higher rates of dysfunction in Groups 2 and 3 as expected. These results support radiation dose reduction after TORS with appropriate pathologic staging as a de-escalation strategy.

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Low risk HPV associated oropharyngeal squamous cell carcinoma treated with induction chemoimmunotherapy followed by TORS or radiotherapy

A.J. Rosenberg,[1] N. Agrawal,[2] A. Pearson,[1] T.Y. Seiwert,[3] Z. Gooi,[2] E.A. Blair,[2] M.T. Spiotto,[4] M. Jones,[1] D.J. Haraf,[5] and E.E. Vokes[3]; *[1]University of Chicago, Chicago, IL, [2]Department of Otolaryngology, The University of Chicago Medicine, Chicago, IL, [3]Department of Medicine, Section of Hematology/Oncology, The University of Chicago Medicine, Chicago, IL, [4]Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, IL, [5]Department of Radiation and Cellular Oncology, The University of Chicago Medicine, Chicago, IL*

Purpose/Objective(s): The incidence of HPV-associated OPSCC is rising rapidly. Patients with HPV-positive tumors have excellent prognosis, and we may be overtreating this patient population. Strategies to de-escalate therapy are being investigated, but the optimal strategy is not defined. Response to induction chemotherapy indicates favorable prognosis and may identify candidates for de-intensified locoregional therapy. Here we describe a low-risk subset of patients from the OPTIMA 2 de-escalation trial with a deep response to induction chemoimmunotherapy.

Materials/Methods: The OPTIMA 2 trial (NCT03107182) is enrolling locoregional HPV-positive OPSCC. Carboplatin, nab-paclitaxel, and nivolumab combination are administered for 3 cycles. Patients with low risk, small volume tonsillar primary (T1-T2, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) or BOT primary (T1-2 with lateralized primary ≤3 cm, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) with >50% reduction by RECIST underwent TORS and selective nodal dissection with de-intensified adjuvant radiation or radiation alone to 50Gy.

Results: Since 2017, 41 patients have enrolled on this ongoing trial. Of these, 11 low-risk patients achieved >50% response by RECIST and are analyzed. Median age was 60 years (range 40-75), eight (72.7%) were male. Primary tumor sites were tonsil (n=8) and BOT (n=3). T-stage T1 (n=4), T2 (n=4), T3 (n=0). N-stage N0 (n=1), N1 (n=3), N2a (n=4), N2b (n=3). Median response was 57% (45.5%-87.5%). Five patients underwent TORS and six patients received radiation alone to 50Gy. Of patients who underwent TORS, three (60%) achieved a pathologic CR in both primary and lymph nodes. After a median follow-up of 22 months (range 13-23), there has been no disease recurrence.

Conclusion: Induction chemoimmunotherapy followed by TORS or radiation alone in low-risk HPV-positive OPSCC was feasible. Pathologic complete responses were noted in TORS surgical specimens. The anticipated full enrollment goal is 74 patients with complete analysis of OPTIMA 2 upon study completion.

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Risk Factors for Disease Progression Following Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma (HPV-OSCC)

D.J. Ma,[1] E.J. Moore,[2] K. Van Abel,[3] C.M. Lohse,[4] K.R. Bailey,[4] K. Price,[5] S.H. Patel,[6] M.L. Hinni,[7] J.J. Garcia,[8] M.A. Neben-Wittich,[1] Y. Garces,[1] A.V. Chintakuntlawar,[5] D.L. Price,[9] K.D. Olsen,[3] J.L. Kasperbauer,[9] J.R. Janus,[3] L.A. McGee,[6] S.C. Lester,[1] J.C. Rwigema,[6] and R.L. Foote[1]; *[1]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, [2]Department of Otolaryngology, Mayo Clinic, Author contributed equally to this work, Rochester, MN, [3]Mayo Clinic, Rochester, MN, [4]Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, [5]Division of Medical Oncology, Mayo Clinic, Rochester, MN, [6]Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, [7]Department of Otorhinolaryngology, Mayo Clinic, Phoenix, AZ, [8]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, [9]Department of Otolaryngology, Mayo Clinic, Rochester, MN*

Purpose/Objective(s): Our group has previously reported on treatment outcomes following a phase II trial utilizing 30-36 Gy of adjuvant radiotherapy (RT) for selected patients with HPV-OSCC. The goal of this study is to evaluate the patterns of disease progression following aggressive dose de-escalation in comparison with historical controls.

Materials/Methods: The phase II cohort consisted of HPV-OSCC patients with ≤10 pack-year smoking history and negative surgical margins. Intermediate risk patients received 30 Gy delivered in 1.5 Gy fractions b.i.d. over 2 weeks along with 15 mg/m^2 docetaxel weekly. ENE+ patients received a simultaneous integrated boost to ENE+ levels to 36 Gy in 1.8 Gy fractions b.i.d. The comparison cohort consisted of 112 consecutively treated HPV-OSCC patients with margin negative transoral resection and ≤10 pack-year smoking history who received standard adjuvant therapy from 2007 − 2015. Cohorts were analyzed by pathologic tumor stage, # involved nodes, and extent of ENE. 2 year survival rates free of locoregional progression (LRFS) and distant metastases (DMFS) were estimated using the Kaplan-Meier method.

Results: For ENE- cohorts, only one de-escalated (n=36) and only two historical patients (n=39) experienced disease progression. Analysis therefore focused on the ENE+ cohorts. 54 of the 72 historical ENE+ patients received concurrent cisplatin. Among the 42 de-escalated ENE+ patients, all had at least two years of follow-up. 9 patients had disease progression (3 local, 1 regional, 5 distant.) Of these patients, 8/9 (89%) had ENE >1mm, 5/9 (55%) had ≥5 involved nodes, and 5/9 (56%) had pT4 disease. Of the 3 local site recurrences, 66% had pT4 disease and 33% had ≥5 involved nodes. Of the 5 distant metastases, 60% had pT4 disease and 80% had ≥5 involved nodes. Demographics for ENE+ cohorts were similar for stage, although patients in the de-escalation cohort were older (62 yrs vs 53 yrs p=0.005) and more likely to be have ENE >1mm when compared to the historical cohort (95% vs 56%, p<0.001). 2 year LRFS for ENE+ de-escalated vs historical cohorts were 93% (95% CI 85%-100%) vs 97% (93-100) while two year DMFS were 90% (82-100) vs 89% (82-97). For patients with >1mm ENE, 2 year LRFS were 92% (84-100) vs 95% (87-100) while 2 year DMFS were 89% (80-100) vs 84% (72-97). Only 2 patients in the historical cohort had pT4 disease. For patients with ≥5 involved nodes, 2 year LRFS (de-escalated vs historical) were 90% (73-100) vs 85% (67-100) and 2 year DMFS were 60% (36-100) vs 60% (38-96).

Conclusion: Allowing for risk factors, oncologic outcomes were qualitatively similar between de-escalated and standard cohorts. Regardless of received treatment, patients with pT4 disease and ≥5 involved nodes remain at risk for disease progression, particularly distant metastases, and may benefit from novel therapies. These findings are currently being validated in an ongoing phase III trial.

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Is Upfront Surgical Resection in HPV-Mediated Oropharyngeal Cancer Associated with Improved Outcomes?

A.M. Torgeson,[1] K. McComas,[2] S. Lloyd,[3] and V. Avizonis[4]; *[1]Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT, [2]University of Utah School of Medicine, Salt Lake City, UT, [3]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, [4]Intermountain Medical Center, Murray, UT*

Purpose/Objective(s): The incidence of HPV-Mediated Oropharyngeal Cancer (HPV-SCC) is increasing and associated with improved survival compared to HPV-negative disease. Advanced surgical techniques may decrease toxicity without diminishing local control in low-risk patients and improve outcomes in higher-risk patients. To examine the effect of upfront surgical resection, we conducted a multi-institutional study to compare outcomes from patients with HPV-SCC treated with either upfront oncologic surgery (Surg) or radiotherapy (RT).

Materials/Methods: We analyzed 281 patients with non-metastatic HPV-SCC treated definitively from 2010-2017. Chi-square analysis was used to compare demographic, clinical, treatment, and outcomes data between Surg and RT patients. The primary outcome was event-free survival (EFS), with event being defined as local recurrence, distant metastases, or death from any cause. Secondary outcomes were overall survival (OS), loco-regional recurrence-free survival (LRFS), distant metastases-free survival (DMFS), and major complications (eg: feeding tube >1 year, osteoradionecrosis, spinal cord injury). Cox-proportional hazards modeling followed by Kaplan Meier analysis were used and univariate (UVA) and multi-variate (MVA) analyses done. Patients were then divided into low-risk (7th edition T0-2, N0-1) and high-risk (N2b-N3, >10 pack-year smoking history) groups and analyzed in a similar fashion.

Results: Of the 281 patients (55 with Surg versus 226 with RT first), median age was 60 and median follow-up was 37 months. Patients in the RT group tended to be older with poorer performance status and more advanced T and N stages. RT patients had fewer major complications (11% versus 18%, p<0.01) but more loco-regional failures (11% versus 0%, p=0.04). Overall, 44% of Surg patients required adjuvant chemoradiotherapy and 24% high-dose RT (>66Gy RT). On UVA there was a trend for poorer EFS in the RT group (HR 2.06, p=0.07) which did not persist on MVA (HR 1.07, p=0.91). Former smoking status (HR 2.64, p=0.02) and cetuximab compared to no chemotherapy (HR 6.13, p=0.02) were associated with poorer EFS and OS on MVA. On subgroup analysis, neither subgroup appeared to benefit from upfront surgical resection for either EFS or OS. Patients in the high-risk group experienced significantly fewer major complications with RT than Surg (10% versus 25%, p=0.02).

Conclusion: Upfront surgery was not associated with improvements in EFS, OS, LRFS, or DMFS, in either the overall cohort or subgroups. It was associated with improved loco-regional control at the expense of more major complications. The likelihood of major complications in the Surg group increased with more advanced disease. Almost half of Surg patients required tri-modality therapy, including a 24% who required high-dose RT.

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Semiquantitative analysis of tumor microenvironment from window of opportunity trial with nivolumab +/- Tadalafil in patients with Squamous Cell Carcinoma of the Head and Neck

R. Ganti,[1] U. Nwagu,[1] M. Stewart,[1] R. Stapp,[1] L. Harshyne,[2] and A. Luginbuhl[1]; [1]*Thomas Jefferson University Hospital, Philadelphia, PA,* [2]*Thomas Jefferson University, Philadelphia, PA*

Purpose/Objective(s): Searching for biomarker profiles of responders v non-responders to immunotherapy has become a high priority. Our window of opportunity trail (WOT) with nivolumab +/- tadalafil provides pre/post treatment pathologic samples allowing for grading of pathologic treatment effect. In conjunction with this trial, it was hypothesized that patients have predictive factors in immunohistochemistry (IHC) that predispose certain individuals to better response with these treatments as well as tracking changes from pre to post treatment.

Materials/Methods: We conducted a two-arm multi-institutional WOT RCT in patients with SCCHN of any stage, who were complete surgical resection candidates (NCT03238365). Subjects in the two cohorts received nivolumab 240 mg IV on day 1 and 15 followed by surgery on day 28, and the combination cohort received tadalafil 10 mg p.o. once daily. IHC markers CD163, CD8, FoxP3, and PD-L1, were recorded. Pre and post treatment samples were obtained and 3 zones were sampled: tumor, tumor-stroma interface, and stroma. Counts of CD163, CD8, FoxP3 and PD-L1 were taken for each patient in each zone, and this count was divided by the area sampled for standardization. Further categorization based on their primary tumor pathology into complete responder (100 %, n = 4), responder (20-99%, n=8), minimal responder (1-20%, n=7), and non-responder (0%, n=10) was done. Biopsy cell counts and differences in cell counts between areas were analyzed for trends between the responder and treatment groups.

Results: Results in semiquantiative analysis of pretreatment specimens showed stroma had a higher density of CD163, Foxp3 and CD8+ cells as compared to the intratumoral compartment and tumor/stromal interface. Oropharyngeal tumors had a greater number of immune cells in the 3 compartments but in the correlation to response this is not predictive considering an even distribution of responders to non-responders in HPV + and - patients. HPV - tumors infiltrated with higher number of immune cells overall trend towards a better response (p=0.07). Post treatment samples demonstrate a trend in patients receiving tadalafil with nivolumab with a lower number of CD163 in the stroma/tumor interface as compared to nivolumab alone (p=0.07). CD8+ cells at the tumor interface and within the stroma trend towards a larger infiltrate after treatment in both treatment groups as compared to non-responders (p = 0.08, p=0.06).

Conclusion: Currently, no clear pretreatment profile emerges from IHC utilizing these basic markers that would predict response the nivolomab +/- tadalafil WOT. However, we do see trends pointing to an increase in CD8 after treatment as a potential predictor of response. The increase in immune cells in the oropharynx does not translate to an improvement in pathologic response contrasting to HPV negative tumors with an higher immune infiltrate as trending to better response.

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Survival Benefit of Postoperative Radiotherapy in Pathological N1 Oral Cavity Squamous Cell Carcinoma

M. Xiang, F.C. Holsinger, M.F. Gensheimer, V. Divi, E. Pollom, A.D. Colevas, Q.T. Le, and B.M. Beadle; *Stanford University, Stanford, CA*

Purpose/Objective(s): In patients with pathological N1 oral cavity squamous cell carcinoma, the role of postoperative radiotherapy (PORT) in the absence of other PORT indications is controversial. We analyzed survival of such patients, with and without PORT, compared to similar patients with pathological N0 or N2 disease.

Materials/Methods: The National Cancer Database was queried for patients over 18 years of age with non-metastatic squamous cell carcinoma of the oral cavity, diagnosed 2010-2015, and treated by surgical resection with pathological stage of T1-2 N0-2 (AJCC 7th edition), negative surgical margins, no extranodal extension, and no lymphovascular invasion. Status of perineural invasion was unavailable. Patients who received systemic therapy were excluded. The primary outcome was overall survival (OS). Multivariable Cox proportional hazards modeling was used to adjust for variables that could confound the association between receipt of PORT and OS, including Charlson comorbidity index and age.

Results: In total, 5,018 pN0, 530 pN1, and 253 pN2 patients were identified, of whom 9%, 35%, and 64% received PORT respectively. Median follow-up was 3 years in living patients. The median number of lymph nodes resected was 24 (interquartile range, 14-35). Within the pN1 patient cohort, PORT was associated with increased OS (adjusted hazard ratio for death [HR] 0.67, 95% confidence interval [CI] 0.46-0.97, $P = 0.03$), which persisted in subgroup analysis of 30 or more lymph nodes resected. Moreover, among patients not receiving PORT, survival of pN1 was similar to pN2 (adjusted HR 0.98, 95% CI 0.68-1.42, $P = 0.92$) and inferior to pN0 (adjusted HR 2.14, 95% CI 1.77-2.60, $P < 0.0001$). In the absence of PORT, pN1 remained a significantly poor prognostic factor relative to pN0 in sensitivity analyses stratified by depth of invasion, lymph node size, and lymph node location (level I vs other). In contrast, among patients receiving PORT, survival of pN1 was similar to pN0 (adjusted HR 1.16, 95% CI 0.82-1.64, $P = 0.39$) and superior to pN2 (adjusted HR 0.60, 95% CI 0.40-0.89, $P = 0.01$).

Conclusion: PORT was associated with an overall survival benefit among patients with pathological N1 oral cavity squamous cell carcinoma without other indications for adjuvant therapy. However, PORT is administered to only one-third of such patients. When PORT is omitted, the prognosis of pN1 patients is similar to pN2; with PORT, their prognosis is similar to pN0. Our results suggest that pN1 by itself may be an indication for PORT after resection of oral cavity primary tumors; further study is warranted to understand the risks and benefits of this approach.

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Circulating Hybrid Cells as a Marker of Nodal Metastases in Oral Cavity Squamous Cell Carcinoma

Y. Anderson,[1] M.H. Wong,[2] and D. Clayburgh[3]; [1]*Oregon Health & Science University, Portland, OR,* [2]*Oregon Health & Science University, Portland, OR, United States,* [3]*VA Portland Health Care System, Department of Otolaryngology, Portland, OR*

Purpose/Objective(s): The current standard of care for clinically N0 patients at risk for cervical lymph node metastases is to undergo neck dissection for completion of staging, as the status of the cervical lymph node basins at the time of diagnosis provides important information about prognosis and treatment planning. However, up to 70% of cN0 patients have no nodal disease and thus underwent unnecessary surgery. The aim of this study is to identify an easily available peripheral blood biomarker that could serve as a marker of occult nodal metastases in cN0 patient with oral cavity squamous cell carcinoma (OCSSCa). We previously identified a novel cell type in peripheral blood that displays characteristics of both a leukocyte and a tumor cell, and sought to determine whether the level of these cells correlates with the presence of occult cervical lymph node

metastases. This novel cell type (circulating hybrid cell, CHC) was first described in a mouse model as a fusion cell that contains genetic material of both a tumor cell and a host leukocyte. These cells have been demonstrated to be more tumorigenic and more numerous than conventional circulating tumor cells (CTCs). They have been shown in a variety of other human cancers to be predictive of disease stage and progression. We hypothesize that the level of CHCs found in the peripheral blood of patients with cN0 OCSCCa will correlate with the presence of occult nodal metastases.

Materials/Methods: Peripheral blood samples were obtained from 20 cN0 OCSCCa patients undergoing resection of the primary tumor and neck dissection for staging. We performed immunohistochemistry on the samples to identify cells co-expressing both cytokeratin (tumor cell marker) and CD45 (macrophage marker), indicating a circulating hybrid cell. The pathological results of the neck dissection were then compared to the level of CHCs identified in the blood sample. Patients with clinically obvious nodal burden were used as positive controls, and volunteers with no cancer were used as negative controls.

Results: There was a statistically significant difference between CHC levels of cN0 patients who remained pN0, and those that converted to pN1+ ($p=0.005$). The level of CHCs in the peripheral blood correlated with the presence of both overt ($p= 0.002$, positive controls) and pathologically identified occult cervical nodal metastases ($p=0.0001$).

Study group	CHCs per 50k nuclei (median)	P value compared to positive control	P value compared to negative control
cN0→pN0	14	0.06	0.03
cN0→pN1+	173	0.25	0.0001
Positive control (pN1+)	119	n/a	0.002
Negative control	1	0.002	n/a

Conclusion: These data show promise for development of a blood-based biological assay that provides non-invasive insight into the status of the cervical lymph nodes in OCSCCa. Further development and characterization of these cells may aid in risk stratification of patients to help aid in treatment decision making.

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nab-paclitaxel Monotherapy followed by Cetuximab and Radiation in Cisplatin-Unsuitable Patients with Locally Advanced Head and Neck Cancer: A Single-Arm, Multicenter Phase 2 Trial

P. Oppelt,[1] J. Ley,[2] H.A. Gay,[3] M.D. Daly,[3] R.S. Jackson,[4] J. Rich,[4] P. Pipkorn,[4] R.C. Paniello,[5] K. Palka,[2] P. Neupane,[6] S. Powell,[7] W. Spanos,[8] M. Gitau,[9] J. Liu,[2] J. Zevallos,[4] W.L. Thorstad,[3] and D. Adkins[10]; *[1]Washington University in St. Louis, Department of Medicine, Division of Medical Oncology, St. Louis, MO, [2]Washington University School of Medicine, St. Louis, MO, [3]Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO, [4]Washington University School of Medicine, Department of Otolaryngology, St. Louis, MO, [5]washington university school of medicine, st. louis, MO, [6]The University of Kansas School of Medicine, Kansas City, KS, [7]Sanford Health, Sioux Falls, SD, United States, [8]Sanford Health, Sioux Falls, SD, [9]Sanford Roger Maris Cancer Center, Fargo, ND, [10]Washington University, Villigen PSI, Aargau, Switzerland*

Purpose/Objective(s): Many patients with locally advanced head and neck squamous-cell carcinoma (HNSCC) are not suitable candidates for cisplatin. Cetuximab is the most common drug combined with radiation therapy (CetuxRT) in patients not given cisplatin. The IMCL-9815 trial showed that CetuxRT improved locoregional control (LRC) and overall survival (OS) compared to RT alone. The LRC rate after CetuxRT was 50%. Persistent or recurrent locoregional disease was the most common cause of treatment failure. Prior studies showed that disease control after RT inversely correlated with tumor volume. This observation supports the hypothesis that tumor volume reduction before CetuxRT could improve LRC. Macropinocytosis promotes internalization of albumin into cells to serve as a nutrient supply and is driven by signaling pathways that are frequently hyperactivated in HNSCC. *nab*-paclitaxel is a nanoparticle albumin-bound formulation of paclitaxel that improves drug delivery into tumor compared to paclitaxel. The primary aim of this phase 2 trial was to determine the tumor response of locally advanced HNSCC to *nab*-paclitaxel monotherapy, given before CetuxRT.

Abstract 107; Table

Characteristic	% of Patients (n=40)
ECOG PS	
0	40
1	33
2	28
ACE Co-morbidity Score	
0	8
1	58
2	23
3	13
Reason for No Surgery	
Extent/Morbidity	58
Organ Preservation	28
Unresectable	11
Patient declined	3

Materials/Methods: Eligibility criteria included SCC of the larynx, hypopharynx or oropharynx, stage III-IV disease (excluded T_1), and unsuitable candidates for cisplatin (GFR 30-75 cc/min, ECOG PS 2, moderate/severe COPD, hepatic dysfunction, and/or severe hearing loss). After two cycles (one cycle=3 weeks; 100 mg/m^2/week) of *nab*-paclitaxel, patients with tumor response at the primary site (assessed by clinical examination) received one additional cycle of *nab*-paclitaxel followed by CetuxRT. Patients without response proceeded directly to CetuxRT. The primary endpoint was complete clinical response (CCR) at the primary site after two cycles of *nab*-paclitaxel. Assuming a CCR rate of $\geq$58% with *nab*-paclitaxel, 40 patients provided a power=0.80 with a one-sided $\alpha=0.05$ to conclude similarity vs historical reference (*nab*-paclitaxel and cisplatin-based regimen).

Results: Forty patients enrolled (Table). Patient characteristics: mean age 66 and smoking history in 80%. Tumor characteristics: $T_{3/4}$ (83%), HPV-unrelated (58%), and HPV-related (43%). After two cycles of *nab*-paclitaxel, CCR at the primary site occurred in 8 of 37 evaluable patients (22%), partial response in 26 (70%) and stable disease in 3 (8%). Median follow-up was 17 mos (IQR: 11 − 26). The overall LRC rate was 80%; 78% in HPV-unrelated HNSCC and 82% in HPV-related OPSCC.

Conclusion: The CCR rate after *nab*-paclitaxel monotherapy was less than a *nab*-paclitaxel and cisplatin-based regimen. However, the LRC rate in these patients was higher than expected with CetuxRT alone.

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Redefining Patients at Risk of Contralateral Neck Disease for HPV-positive Oropharyngeal Cancer: A Pathologic Study of Patients with Bilateral Neck Dissection

A.W. Smith,[1] M. Gallitto,[1] I. Wasserman,[2] V. Gupta,[1] S. Sharma,[1] W.H. Westra,[3] E. Genden,[4] M.S. Teng,[4] Y. Haidar,[2] M. Yao,[2] B. Miles,[4] and R.L. Bakst[1]; *[1]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [2]Icahn School of Medicine at Mount Sinai, New York, NY, [3]Department of Anatomic and Clinical Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, [4]Department of Otolaryngology – Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY*

Purpose/Objective(s): HPV positive oropharynx squamous cell carcinomas (OPSCC) have a better prognosis than HPV negative OPSCC. Standard radiation volumes cover at risk nodal regions draining the primary tumor, and avoidance of the contralateral neck may improve morbidity. However, optimal volumes are still undetermined, especially for base of tongue (BOT) tumors, and few studies have used surgical series to risk stratify HPV positive patients. We reviewed all patients who received trans-oral robotic surgery (TORS) of OPSCC and bilateral neck dissection to determine risk of contralateral nodal disease (CND).

Materials/Methods: After IRB approval, patients with cT1-T3 SCC of the tonsil or BOT who received resection and bilateral neck dissection were identified with HPV positive disease by PCR between 2010 and 2018. Pre-surgical PET and CT scans, and physician notes were reviewed for clinical staging by AJCC 8th edition, and well lateralized primary disease was defined as lack of soft palate or midline structure involvement. Fisher's exact test evaluated associations of CND with pre-surgical clinical information. Univariate and multivariate odds ratios were constructed with logistic regression.

Results: Of 120 cases, there were 11 (9%) with positive contralateral lymph nodes on pathology, including 7.1% (4/56) of tonsil and 10.9% (7/64) of BOT cases. Tumor crossing midline ($p=0.03$) and cN2 disease ($p<0.01$) were both significantly associated with pathologic CND. Patients with a well lateralized BOT primary and without bilateral clinical nodal disease (cN0/N1) were not likely to have pathologic CND (OR 0.05; 95% CI:0.007-0.298), which was present in only 4% of such patients. Among the whole cohort, presenting without bilateral clinical nodal disease was the strongest predictor of lack of pathologic CND (adjusted OR 0.03; 95% CI:0.005-0.19). Of the 9 patients with a clinically N0 neck, none had pathologic CND. Radiographic extranodal extension, smoking history, and >1 clinically suspicious nodes were not associated with pathologic CND.

Conclusion: HPV-related OPSCC cancers that are clinically and radiographically N0-N1 have exceedingly low rates of contralateral disease on pathology. This is the first pathologically driven study to suggest that well lateralized HPV positive BOT primaries with limited clinical nodal disease may be able to receive elective nodal irradiation to the ipsilateral neck only. Future prospective trials should determine if such BOT primaries can be treated with unilateral neck irradiation in a manner akin to some tonsil primaries, thereby expanding opportunities for HPV-related treatment de-intensification.

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De-escalation with Definitive Unilateral Neck Radiation for T3 or N2b/N3 p16+ Tonsil Squamous Cell Carcinoma Using Prospectively Defined Criteria

S.X. Yan,[1] J. Mojica,[2] D. Barbee,[1] L.B. Harrison,[3] M.E. Gamez,[4] M. Tam,[1] C.M. Concert,[1] Z. Li,[5] B. Culliney,[6] A. Jacobson,[2] M. Persky,[7] M. DeLacure,[7] M. Persky,[2] T. Tran,[2] B. Givi,[2] and K.S. Hu[1]; *[1]Department of Radiation Oncology, NYU Langone Health, New York, NY, [2]Department of Otolaryngology, NYU Langone Health, New York, NY, [3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, [4]Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, OH, [5]Department of Medical Oncology, NYU Langone Health, New York, NY, [6]Department of Medicine, Mount Sinai at Beth Israel, New York, NY, [7]NYU Langone Health, Department of Otolaryngology, New York, NY*

Purpose/Objective(s): American College of Radiology recommends unilateral neck radiation (RT) for small lateralized tonsillar cancer with low-volume nodal disease. Safety of unilateral RT for larger primary or advanced nodal disease remains to be explored but provides an important opportunity for treatment de-escalation. We report oncologic and functional outcomes of patients with advanced-stage p16+ oropharyngeal cancer treated with unilateral RT using prospectively defined criteria.

Materials/Methods: Patients (pts) with T3 or N2b/N3 (AJCC 7th; N1/N3 AJCC 8th) lateralized oropharyngeal tumors >1cm from midline and functional imaging confirmation of unilateral nodal disease were reviewed. Initial cohort was treated on a prospective trial; subsequent pts who met criteria were treated accordingly. Post-RT flexible endoscopic evaluation of swallowing function (FEES) was performed and swallowing outcome measured with Yale Pharyngeal Residue Severity and Penetration Aspiration Scale ratings. Patient reported functional outcome was assessed with Functional Oral Intake Scale (FOIS).

Results: Thirty-five pts (6 T3, 33 N2b, 1 N3) received unilateral RT with concurrent chemotherapy. Four pts received 60 Gy on a prospective de-escalation protocol; all others received 70 Gy. At median follow-up of 31.2 months, 3-yr actuarial estimates were disease free survival 93%, local control 100%, ipsilateral neck control 96%, distant metastasis-free survival 93%, and overall survival 97%. No contralateral neck failures were observed. No failures were noted in pts treated with dose de-escalation. Median weight loss after RT was 8.1% (range, -1.3%—20.3%). One patient required temporary PEG placement due to severe weight loss. Of 14 pts who underwent FEES, exam revealed impaired volitional clearing in 79% pts (up to 26 months from RT) and airway penetration in 14% pts (up to 22 months from RT). No patient treated with dose de-escalation scored PAS >3 during follow up. Of 12 pts with baseline FOIS, 92% reported at least 1-point decrease in score at median of 1 month after RT. FOIS scores improved or stabilized over time. Mean doses to organs at risk were superior constrictor 52 Gy, middle constrictor 37 Gy, inferior constrictor 23 Gy, larynx 30 Gy, proximal esophagus 26 Gy, contralateral submandibular gland 18 Gy and parotid gland 11 Gy.

Conclusion: In one of the largest series of p16+ advanced-stage oropharyngeal cancer, definitive unilateral neck RT using prospectively defined criteria resulted in excellent oncologic outcomes. Objective and patient reported measures reveal mild to moderate acute swallowing dysfunction in majority of pts and low rates of severe chronic swallowing dysfunction despite meeting dose constraints for optimal swallowing function. Further treatment de-escalation with dose reduction remains important to improve function preservation using the unilateral RT approach.

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Examining the Prognostic Impact and Therapeutic Implications of Adjuvant Chemotherapy for Patients with Oral Cavity Squamous Cell Carcinoma and Extranodal Extension

M. Khan,[1] A. Spreafico,[2] S. Huang,[3] D. Goldstein,[4] A. Hansen,[5] A. Hosni,[6] I. Weinreb,[7] B. Perez-Ordonez,[7] T. Truong,[3] W. Xu,[3] and J. de Almeida[8]; *[1]Mount Sinai Medical Center, New York, NY, [2]Department of Medical Oncology, Princess Margaret Cancer Centre/ University of Toronto, Toronto, ON, Canada, [3]Princess Margaret Cancer Center, Toronto, ON, Canada, [4]Department of Otolaryngology - Head & Neck Surgery,*

University Health Network-University of Toronto, Toronto, ON, Canada, [5]Department of Medical Oncology, Princess Margaret Cancer Centre-University of Toronto, Toronto, ON, Canada, [6]Radiation Medicine Program, University Health Network and Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [7]Surgical Pathology, University Health Network-University of Toronto, Toronto, ON, Canada, [8]Department of Otolaryngology – Head and Neck Surgery, University of Toronto, Toronto, ON, Canada

Purpose/Objective(s): Extranodal extension (ENE) in lymphatic metastases from oral cavity squamous cell carcinoma is an adverse prognostic feature that portends a poor prognosis and adverse outcomes. In a pooled analysis of two randomized controlled trials, a therapeutic benefit with the addition of chemotherapy to adjuvant radiotherapy was demonstrated in patients with ENE. The College of American Pathologists have recently recommended classification of ENE by extent of capsular invasion into minor (<= 2 mm) and major (>2mm) ENE. Currently little is known about whether this classification has prognostic and therapeutic implications.

Materials/Methods: Data was collected from 388 patients with oral cavity squamous cell carcinoma (T1-T4) and at least one positive node treated between 2005 and 2014 at one tertiary care institution. Pathologic specimens were reviewed and patients with ENE were reclassified by extent of capsular invasion. Clinical, pathologic and demographic information was collected. Local control (LC), regional control (RC), and distant control (DC) were assessed with competing risks and disease free survival (DFS), and overall survival (OS) with Kaplan Meier method. Oncologic outcomes were compared for patients with no ENE, minor ENE, and major ENE in univariable (UVA) and multivariable analysis (MVA). The impact of chemotherapy in patients with minor and major ENE was similarly assessed in UVA and MVA.

Results: A total of 388 patients were included in the study with a median age of 62.9. One hundred and seventy six (45%) had ENE with 62 (16%) minor ENE and 114(29%) major ENE. Adjuvant chemotherapy was given in 15%, 34%, 39% of patients with no ENE, minor ENE, and major ENE respectively. Patients with no, minor, and major ENE had 5 year DFS of 49%, 42%, and 15% respectively and 5 year OS of 55%, 45%, and 16%. Major ENE was associated with significantly poorer DFS ($p=0.004$) and OS ($p=0.002$) than minor ENE. Patients with minor ENE receiving chemotherapy had significantly better 5 year DFS than those not receiving chemotherapy (55% vs. 34%, $p=0.011$) on MVA. Patients with major ENE receiving adjuvant chemotherapy had significantly better 5 year DFS than those not receiving adjuvant chemotherapy (32% vs 5%, $p<0.001$). There was no therapeutic benefit for chemotherapy in the patients with no ENE on UVA or MVA.

Conclusion: In patients with oral cavity squamous cell carcinoma, major ENE is associated with a worse prognosis than minor ENE. Regardless of the extent of ENE, the addition of chemotherapy to adjuvant radiotherapy improves survival.

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Concurrent ChemoRadiation (CCR) is better than Accelerated Radiation Alone (ARA) in Patients with Moderate Advanced Head and Neck Squamous Cell Carcinoma (MAHNSCC). Mature results of HN08 Polish Trial

D. Księżniak-Baran,[1] M. Stankiewicz,[2] A. Wygoda,[3] T. Rutkowski,[3] B. Pilecki,[3] P. Polanowski,[3] U. Dworzecka,[3] M. Kentnowski,[3] A. Bieleń,[3] A. Brewczyński,[3] K. Dębiec,[3] D. Leś,[3] and K. Skladowski[4,5]; *[1]I Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Slaskie, Poland, [2]Brachytherapy Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Slaskie, Poland, [3]I Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [4]I Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute, Gliwice, Poland, [5]I Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute in Gliwice, Gliwice, Poland*

Purpose/Objective(s): Literature data of locally advanced HNC treatment confirm one week accelerated radiation could be biological equivalent to one course of high dose cisplatin given concurrently with conventional radiation. We have wondered if in less (moderately) advanced HNC patients ARA could replace the toxic CCR. This is report of long term outcomes of CCR and ARA of patients treated in MSC Cancer Centre and Institute in Gliwice over 2008-2013 within randomised clinical trial (HN08 PT).

Materials/Methods: Re-evaluate data analysis of 101 patients with MAHNSCC (T2-T4aN0-N2) treated by ARA (54 pts) and CCR (47 pts). Most patients were male (77). Mean and median age were 59, in range 37-81 years. Tumor sites were as follow: 46 OPC, 30 LXC, 13 HPC and 12 tumors invading both larynx and pharynx. ARA was delivered by 7 fractions of 1.8 Gy, 7 days per week to 72 Gy in 40 fractions over 40 days. In CCR 70 Gy in 35 fractions over 47-49 days was combined with 3 courses of cisplatin (100 mg/m2/d on day 1, 22 and 43).

Results: Median follow up was 86 months (2–132 months). Local and nodal recurrence was described in 18,5% and 9,3% of patients in ARA arm. In CCR arm local and nodal recurrence appeared in 14,9% and 12,8% of cases respectively. Five-year LRC was 69% in ARA and 79% in CCR group. After CCR 24 patients had died, 35 cases died after ARA. Five-year OS was 35% in ARA group and 51,5% in CCR arm. Second neoplasms (mostly - 54% - lung cancer) were diagnosed in 13 patients in ARA and in 11 in CCR. Late treatment related toxicity deteriorated QL were observed in 24% of ARA patients and 11% of CCR patients.

Conclusion: The results of our trial directly confirm that concurrent, platinum-based chemoradiation remains the best therapeutic option for majority patients with HNC. The hypothesis that moderately advanced HNSCC could be safely and effectively cured by one treatment modality, i.e. altered radiation alone is false in the light of our findings, especially in aspect of QL restricted late morbidity, which were twice times more presented after ARA treatment.

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The Role of Concomitant Chemoradiotherapy on Survival in AJCC 7th Edition T1-2N1 Oropharyngeal Carcinoma in the HPV Era

D.J. Lu, M. Luu, A.T. Nguyen, S.L. Shiao, K. Scher, A. Mita, J. Mallen-St Clair, A.S. Ho, and Z.S. Zumsteg; *Cedars-Sinai Medical Center, Los Angeles, CA*

Purpose/Objective(s): Radiotherapy (RT) without chemotherapy is considered a standard of care for management of American Joint Committee on Cancer (AJCC) 7th edition (7E) T1-2N1 oropharyngeal squamous cell carcinoma (OPSCC). However, very few studies have actually compared RT to concomitant chemoradiation (CCRT) in this population. In the only comparative effectiveness study we are aware of, we showed CCRT was associated with improved survival versus RT alone for patients with AJCC 7E T1-2N1 head and neck cancer. However, this prior study included a variety of anatomic subsites and did not have HPV data for OPSCC patients. Given the radiosensitivity of HPV-positive OPSCC, it is plausible that CCRT would have less benefit in this subgroup. In this study, we compared survival outcomes in AJCC 7E T1-2N1 OPSCC patients with known HPV status undergoing RT versus CCRT.

Materials/Methods: This study analyzed patients in the National Cancer Database between 2010 to 2015 with AJCC 7E stage cT1-2N1M0 OPSCC with known HPV status undergoing definitive RT or CCRT. Cox regression and propensity score matching were used to adjust survival analyses for

clinical and demographic covariates. Statistical interactions between HPV status and T stage, and the effect of CCRT on survival were assessed using tests of interaction.

Results: Overall, 1964 patients with AJCC 7E T1-2N1 OPSCC were included, including 1297 (66%) HPV-positive and 667 (34%) HPV-negative patients. 1299 patients (66%) received CCRT and 665 (34%) received RT alone. In multivariate analysis, CCRT was associated with improved survival compared with RT alone (hazard ratio [HR] = 0.70, 95% confidence interval [CI] 0.57-0.87), P=0.001). In propensity-score matched cohorts, 4-year overall survival was 87.4% vs 80.4% in patients receiving CCRT and RT alone, respectively (P=0.002) for HPV-positive patients, and 58.9% vs 65.5%, respectively, for HPV-negative patients (P=0.2). There was no evidence that HPV-positivity was associated with less of an effect of CCRT on survival. In fact, a larger magnitude of benefit was associated with HPV-positive patients (HR=0.57, 95% CI 0.42-0.81) versus HPV-negative patients (HR= 0.86, 95% CI 0.64-1.16) (interaction P=0.06). In addition, there was no interaction between T stage and the impact of CCRT on survival (interaction P=0.65).

Conclusion: Our study shows that CCRT is associated with improved survival in AJCC 7E stage T1-2N1 OPSCC compared to RT alone. Despite the radiosensitivity of HPV-positive OPSCC, the association of CCRT with improved survival for T1-2N0 HPV-positive OPSCC was at least as strong, if not stronger, as what was observed in HPV-negative tumors. Our study supports consideration of CCRT for all OPSCC with AJCC 7E T1-2N1 OPSCC healthy enough to tolerate this therapy.

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Clinical Translation and Optimization of Dynamic Optical Contrast Imaging for Intraoperative Surgical Margin Assessment

P. Pellionisz,[1] Y. Hu,[2] A.S. Moon,[2] Y.M. Alhiyari,[3] K. Kwan,[4] A. Miller,[2] and M. St John[5]; *[1]University of California, Los Angeles, Los Angeles, CA, [2]UCLA, Los Angeles, CA, [3]Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [4]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [5]Ronald Reagan-UCLA Medical Center, Dept of Head and Neck Surgery, Los Angeles, CA*

Purpose/Objective(s): Head and Neck cancers are debilitating diseases where patient prognosis depends on complete tumor extirpation. Currently, preoperative imaging is used to assess tumor size and extent but intraoperative margin detection relies solely on visual and tactile feedback during surgical resection. Recently, our team published a novel method, termed dynamic optical contrast imaging (DOCI), to generate functional tissue contrast in a surgically relevant field of view via lifetime imaging. Prior ex-vivo images demonstrated remarkable contrast between tissue types and head and neck squamous cell carcinoma (HNSCC). Our work herein was to further optimize our imaging system into a tool for real time intraoperative use.

Materials/Methods: We used *ex vivo* tissue samples correlated with histology and subsequently generated images *in vivo* to demonstrate the capability of the system to produce useful contrast for the operating surgeon toward identifying tissue and determining boundaries. Fluorescence calibration and decay images were generated using a gated and intensified CCD camera coupled to a high-speed motorized filter wheel containing ten bandpass filters. For illumination, a new LED board was manufactured for increased light intensity with robust pulse shape at 370nm to allow for increased resolution and tissue delineation. Mean relative fluorescence decay signatures were calculated for tumor, fat, muscle and collagen tissues. Statistical analyses were performed using the Wilcoxon signed rank test.

Results: We have now quantified the temporal resolution of our system (and capacity to delineate HNSCC) by recording the difference between known standards at nanosecond separation and ex vivo tissue. Ex-vivo and initial promising in-vivo results have been registered to our images with histology where the specimen is sectioned horizontal en-face, and evaluated by independent pathologist for morphological significance. Qualitative analysis of DOCI images revealed microscopic characterization sufficient for tissue type identification comparable to histology. Quantitative analysis of the 55 HNSCC specimens and surrounding tissues collected from the tumor bed revealed a statistically significant difference ($p < 0.05$) between HNSCC and collagen among ten of ten spectral bands analyzed, between HNSCC and muscle in ten bands, and between fat and HNSCC in two bands.

Conclusion: We present promising results from our ongoing clinical study to translate preclinical results into a real time intraoperative imaging system capable of rapid tissue differentiation by imaging large, surgically relevant fields of view. The presented results support our ongoing efforts of adapting our algorithm into an imaging technology enabling intraoperative guidance through the ability to characterize HNSCC and different tissues in situ.

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PET Imaging Biomarkers and Clinical Features to Predict Locoregional and Distant Failures in HPV-Associated Oropharyngeal Squamous Cell Carcinoma

J.R. Wilkie,[1] B.S. Rosen,[1] K. Casper,[2] T. Chotchutipan,[3] A. Eisbruch,[1] F. Worden,[4] J. Miller,[5] and M.L. Mierzwa[1]; *[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [3]Chulabhorn, Bangkok, Krung Thep, Thailand, [4]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [5]University of California Los Angeles, Los Angeles, CA*

Purpose/Objective(s): Identification of patients at higher risk of locoregional (LR) or distant metastatic (DM) recurrences may allow for personalization of treatment for patients with p16+ oropharyngeal squamous cell carcinoma (OPSCC). In this study, we investigated whether PET imaging biomarkers could improve prediction models for LR and DM survival outcomes over clinical features alone for patients treated with definitive chemoradiotherapy (CRT).

Materials/Methods: 274 patients with p16+ OPSCC treated with definitive CRT in our department from 2005-2016 with evaluable pre-treatment PET scans were included in the study. PET and CT scans were reviewed in order to determine quantitative imaging metrics: metabolic tumor volume (MTV), total lesion glycolysis (TLG), GTV size and qualitative imaging metrics: retropharyngeal lymph node involvement (RPN), radiographic extracapsular extension (rECE), matted nodes (MN), and positive inferior cervical nodes (ICN). Clinical characteristics (age, AJCC8 stage, smoking status) were obtained from the medical record. Univariate analysis with Cox regression was used to assess associations between clinical/imaging features and LR recurrence free survival (LRRFS), DM free survival (DMFS) and overall survival (OS). Multivariate analysis (MVA) was applied for clinical features only and clinical/imaging features using penalized logistic regression for feature selection and generation of predictive models using the LASSO technique.

Results: There were 28 LR and 33 DM recurrences as first failures in our dataset. Imaging biomarkers were significantly associated with LRRFS, DMFS and OS. PET metrics outperformed CT and clinical metrics for LRRFS, with MTV having the strongest association: C-index = 0.69 (0.59-0.79). CT and PET metrics performed better than clinical metrics for DMFS, with TLG having the strongest association: C-index = 0.73 (0.64-0.81). On MVA, the C-index increased to 0.74 from 0.63 for LRRFS and to 0.85 from 0.77 for DMFS with the addition of imaging metrics compared to clinical features alone. The increases in prediction accuracy were robust to repeated 10-fold cross-validation. Qualitative CT features were the dominant predictors in DMFS models, while PET features were often selected for LRRFS prediction.

Conclusion: Imaging biomarkers are significantly associated with LRRFS, DMFS and OS for p16+ OPSCC treated with definitive chemoRT, and improved prediction models over those based on clinical metrics alone. PET biomarkers may help identify patients at higher risk of LRR, for whom dose de-escalation may not be appropriate, while CT features are superior for identification of patients at higher risk for DM who may benefit from intensified systemic therapy.

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The Role of SPECT-CT in Addition to PET for Lymphatic Drainage Mapping in Patients with HPV+ Oropharyngeal Squamous Cell Carcinoma

A. Rosko,[1] M.E. Spector,[1] D.B. Chepeha,[2] T. Glazer,[3] and A. Eisbruch[4]; *[1]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [2]Department of Otolaryngology - Head & Neck Surgery, University Health Network-University of Toronto, Toronto, ON, Canada, [3]University of Wisconsin, madison, WI, [4]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Most patients presenting with HPV+ oropharyngeal carcinoma (OPSCC) have a good prognosis. Therefore, survivorship and late effects are particularly relevant for both surgical and radiation oncologists. It is important to know what the "target volume" should be, whether the disease is treated surgically or with radiation. We employed SPECT-CT to map lymphatic drainage in conjunction with PET-CT to identify regional disease for target delineation. This effort is similar to the SUSPECT trial with the addition of long term 5-year follow-up. It should be noted that lymphatic mapping is customarily used for the clinically and radiologically negative neck. This represents a novel and application or lymphatic mapping in the N+ neck. The objective was to describe the lymphatic flow in OPSCC and observe the difference with respect to PET avid disease.

Materials/Methods: Twenty patients with previously untreated AJCC 7 stage III and IV p16+ OPSCC treated between 2011-2014 were included. Subsites were base of tongue (11/20), tonsil (9/20) and pharyngeal wall (1/20.) During endoscopy under general anesthesia, Technetium-99m−labeled sulfur colloid was administered peritumorally at the primary site per sentinel node protocol. Postoperative SPECT-CT and a PET scans were performed. The primary outcome was the lymphatic drainage pattern on SPECT-CT compared to PET-CT avid regional disease.

Results: Nine patients had tumors that extended to within 1 cm of midline and 7 of these crossed the midline. All patients had a clinically/radiologically positive nodal disease. 19/20 demonstrated lymphatic drainage on SPECT-CT as one patient with bulky disease did not have nodal drainage on SPECT-CT. 3/20 patients exhibited the same levels of involvement on SPECT-CT and PET-CT. SPECT-CT co-labelled 50% (19/38) of nodal stations that were PET avid an there was FDG avidity in 45% (19/42) of nodal stations with SPECT-CT drainage as 15 patients had drainage on lymphoscintigraphy to additional levels in the neck that were not PET avid including 4 patients with drainage to level 5 (3 ipsilateral, 1 contralateral). 1 patient had mapping to an ipsilateral retropharyngeal node that was not involved on the PET-CT while 2 additional patients had ipsilateral retropharyngeal involvement on PET-. All levels that were identified on PET-CT and SPECT-CT were covered in the radiation field. Recurrence free survival at 5 years was 75% as 2/20 patients recurred distantly and 3/20 has in field recurrences.

Conclusion: Lymphoscintigraphy with SPECT-CT does delineate lymphatic drainage in a N+ neck and potentially identifies additional at risk levels. This technique potentially supplements PET-CT in determining at risk nodal basins that should be given additional consideration prior to considering surgery or radiation treatment to the.

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HPV/p16 status of cervical lymph node metastases in oropharyngeal squamous cell carcinoma by molecular testing of FNA samples

C. Pingree,[1] N. Hales,[2] C. Guzman,[3] J. Christal,[3] and T. Kardos[3]; *[1]San Antonio Uniformed Services Health Education Consortium, San Antonio, TX, [2]ENT Clinics of San Antonio, San Antonio, TX, [3]Pathology Reference Laboratory, LLC, San Antonio, TX*

Purpose/Objective(s): Detection of HPV/p16 status of oropharyngeal squamous cell carcinoma (OPSCC) is necessary in staging patients with OPSCC. OPSCC has a propensity for metastasizing to cervical lymph nodes which provides a ready target for both establishing a diagnosis and staging disease by fine needle aspiration biopsy (FNA). Because of the cystic/necrotic nature of the metastases establishing the p16 status of the tumor in aspirate sample is often problematic. It has been suggested that molecular HPV assays may be a better alternative for determining the tumors HPV status in lymph node FNAs. In this study material from lymph node FNAs was tested using a molecular assay which detects E6/E7 viral mRNA from HPV. We hypothesize that adequate assessment of the HPV status of cervical node metastases can be made using this test.

Materials/Methods: A retrospective review over the past 10 years in a community-based head and neck oncologic surgery practice was conducted in which patients who were diagnosed with OPSCC and who also had cervical lymph node FNA with a diagnosis of squamous cell carcinoma and in whom tissue from the primary had been tested with p16 by IHC was conducted using archived stained slides. Aspirated material was harvested and prepared for assay with the molecular platform. Test results were compared to the primaries p16 findings. Information was used to calculate sensitivity, specificity, positive and negative predictive values.

Results: A total of 63 patients were identified in our files who had an OPSCC with p16 status on a surgical specimen determined by IHC with a diagnosis of SCCA in a cervical lymph node FNA. The results of the molecular testing of FNA samples compared with p16 status of the primary tumor are illustrated in the table below.

	p16 Positive	p16 Negative	Total
HPV Positive	54	0	54
HPV Negative	1	8	9
Total	55	8	63

From this data, sensitivity was calculated 1, specificity 0.9818, PPV 1 and NPV 0.8889.

Conclusion: This analysis shows that molecular testing for HPV is a viable option in determining HPV status of OPSCC in patients with nodal metastases. The cases represented a wide range of tumor cellularity on the tested slides, some cases containing a very low burden of tumor cells. In most cases even with a low tumor burden accurate HPV status could be determined, however, the one false negative HPV case one was in which there was low tumor cellularity. For this reason, it is recommended that cases which have very limited tumor load and negative results be retested if additional material becomes available.

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Exceptional Responders to Immunotherapy in Head and Neck Cancer

M. Porosnicu,[1] A.H. Song,[1] T. Lycan,[2] K.M. Greven,[3] R.T. Ng,[1] R. Kinney,[1] R. Petro,[1] H.S. Patwa,[4] and J.D. Waltonen[4]; *[1]Wake Forest*

University School of Medicine, Winston Salem, NC, [2]Department of Hematology & Oncology, Wake Forest School of Medicine, Winston Salem, NC, [3]Department of Radiation Oncology, Wake Forest School of Medicine, Winston Salem, NC, [4]Department of Otolaryngology-Head and Neck Surgery, Wake Forest School of Medicine, Winston Salem, NC

Purpose/Objective(s): The approval of immunotherapy (IO) with checkpoint inhibitors brought great advancements in the treatment of the HNC. Response rates, however, remain suboptimal. Tremendous effort has been invested in finding predictors of response that would allow a better patients' selection. Continuing the model of Exceptional Responders Initiative organized by NCI represents an opportunity to capture and organize information for future analysis. We present a case series of 14 patients with HNC who displayed exceptional response to single agent PD-1 inhibitors.

Materials/Methods: We evaluated retrospectively all patients with cancers developed in the head and neck area, of any pathology, treated at our institution with single agent PD-1 inhibitors in the last 5 years. Patients with an exceptional response as defined by the NCI Exceptional Responders Initiative were identified. We obtained PD-L1 level and next generation sequencing evaluation of the tumor with Foundation One (F1) in all patients with available tumor tissue.

Results: We identified 14 out of 87 patients treated with single agent PD-1 inhibitors Nivolumab or Pembrolizumab who met the exceptional responders NCI criteria. 8 patients have Squamous Cell Cancer (SCC) of the Head and Neck (SCCHN), 2 patients have salivary gland cancers, 3 patients have cutaneous SCC (CSCC) developed in the head and neck area and one patient has anaplastic thyroid cancer. Patients received between 3 and 33 administrations of IO. Treatment was well tolerated. One patient developed asymptomatic hypothyroidism resistant to treatment. Two patients developed unusually aggressive infections while on treatment. 8 of the 14 patients are in complete remission (CR). 4 of the 8 patients with SCCHN and 1 patient with salivary gland tumor developed CR that has been maintained for more than 2 years despite having metastatic cancers at the beginning of IO. Two other patients with CSCC and one patient with recurrent SCCHN are currently in CR. Interestingly, 4 of the 14 patients developed other primary cancers while on immunotherapy. 12 patients had available tissue and PD-1 and genomics were tested with F1. 5 patients had PD-1 expressed on more than 60 % of the tumor cells. One patient with metastatic salivary gland adenocarcinoma, now in CR for more than 2 years, had PD-L1 of 0. All patients had stable MS. 6 patients had low TMB, 3 patients had intermediate TMB and 3 patients had high TMB. 10 out of the 12 tested patients had TP53 mutations. Further genomic analysis is ongoing and will be presented.

Conclusion: There are limited reports in the literature of exceptional responders to immunotherapy, particularly amongst head and neck cancer patients. We present the largest such series of exceptional responders and provide PD-1 level and genomic analysis for majority of patients.

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Predictors of Immunotherapy Response in Head and Neck Cancer: Per Lesion Analysis of a Prospective Randomized Trial with Nivolumab

Y. Yu,[1] L. Chen,[1] N. Riaz,[1] C.J. Tsai,[2] J.J. Kang,[1] E. Sherman,[3] N. Lee,[2] and S. McBride[2]; *[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*

Purpose/Objective(s): The capacity for radiation and checkpoint inhibitors to elicit clinical responses is impacted by tumor immunogenicity and the immune microenvironment. We sought to determine whether head and neck primary site and metastatic tumor location was associated with response in non-irradiated lesions.

Abstract 118; Table 1

Primary Tumor Subsite	Oropharynx Nasopharynx Larynx/Hypopharynx Oral cavity Other	Unadjusted Likelihood of Early Progression (p=0.050)
	Total (n=59) 23 10 13 7 6	30% 32% 31% 82% 33%
Metastatic Tumor Sites	Lung LN Liver Soft Tissue Bone	Unadjusted Likelihood of Early Progression (p=0.001)
	Total (n=144) 57 46 23 16 2	40% 15% 74% 37% 0%

Materials/Methods: We evaluated response in 144 non-irradiated lesions from 59 patients with metastatic head and neck cancer enrolled on a phase II randomized controlled trial of nivolumab with stereotactic body radiotherapy (n=30) vs. nivolumab alone (n=29). Nivolumab was administered 3 mg/kg intravenously every 2 weeks. Radiated lesions were treated with 27 Gy / 3 fractions within 14 days of the first nivolumab dose. Non-target lesion progression was defined ≥30% increase in the greatest axial diameter 8 weeks after enrollment. Fisher's exact test with nested bootstrap resampling was used for univariate analysis. Logistic regression with a mixed random effects term was used for multivariate analysis. Differences in progression-free and overall survival were evaluated using log-rank test.

Results: Primary tumor site, metastatic tumor organ sites, and the unadjusted likelihood of progressive disease by site are listed in Table 1. On multivariate logistic regression controlling for PD-L1 status (p=0.66) and viral status (p=0.29), lymph node metastases (OR 0.79, p=0.0064) were associated with decreased risk of progression, while liver metastases (OR 1.39, p=0.014) and oral cavity primaries (OR 1.56, p=0.018) were associated with increased risk of progression at 8 weeks, using lung metastases and larynx/hypopharynx primaries as reference. Presence of liver metastases at trial enrollment was associated with worse progression-free (p=0.0047) and overall survival (p=0.00032).

Conclusion: Primary tumor subsite and metastasis location were predictors of response or stable disease following treatment with nivolumab. Metastases from oral cavity primaries and metastases to the liver were at increased risk of initial progression. Table 1:

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Health-Related Quality of Life of Pembrolizumab for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma in KEYNOTE-629

B.G.M. Hughes,[1,2] R. Mendoza Gonzalez,[3] N. Basset-Seguin,[4] O. Vornicova,[5] J. Schachter,[6] A. Joshi,[7] N. Meyer,[8] F. Grange,[9] J.M. Piulats,[10] J. Bauman,[11] D. Chirovsky,[12] P. Zhang,[12] B. Gumuscu,[12] R. Swaby,[12] and J.J. Grob[13]; *[1]Royal Brisbane and Women's Hospital, Herston, QLD, Australia, [2]University of Queensland, Brisbane, QLD, Australia, [3]Centro Estatal de Cancerologia de Chihuahua, Chihuahua, Mexico, [4]Hôpital Saint-Louis, Paris, France, [5]Rambam Health Care Campus, Haifa, Israel, [6]Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel, [7]Townsville Cancer Centre, Townsville, QLD, Australia, [8]IUCT—Oncopole, Toulouse, France, [9]CHU Reims—Hôpital Robert Debre, Reims, France, [10]Hospital Duran i Reinals ICO de Hospitalet, Barcelona, Spain, [11]Fox Chase Cancer Center, Philadelphia, PA, [12]Merck & Co., Inc., Kenilworth, NJ, [13]AIX-Marseille University, Marseille, France*

Purpose/Objective(s): In the recurrent or metastatic (R/M) cohort (n = 105) of KEYNOTE-629 (NCT03284424), pembrolizumab (200 mg every 3 weeks for up to 24 months) yielded a clinically meaningful objective response rate (ORR) and durable benefit in patients with R/M cutaneous squamous cell carcinoma (cSCC), whose median age was 72 years. Here we present results of the prespecified exploratory objective to evaluate changes from baseline in health-related quality of life (HRQoL).

Materials/Methods: The EORTC QLQ-C30 and EQ-5D-5L questionnaires were administered electronically at baseline; at weeks 3 and 6; then every 6 weeks through the first year; then every 9 weeks through the second year until end of treatment; and at the 30-day safety follow-up visit. HRQoL was analyzed in patients who received ≥1 dose of pembrolizumab and had both baseline and ≥1 postbaseline HRQoL assessments. Mean changes from baseline in HRQoL scores were evaluated primarily at week 12. Changes from baseline in EORTC QLQ-C30 global health status/quality of life (GHS/QoL) and physical functioning scores were also analyzed through week 48. The overall improvement rate for GHS/QoL and physical functioning scores, defined as ≥10-point increase from baseline at any time point with confirmation at the next consecutive visit, was assessed using the exact binomial method. Analyses were conducted without imputation for missing data. Database cutoff was April 8, 2019.
Results: HRQoL analyses included 99 patients for EORTC QLQ-C30 and 100 patients for EQ-5D-5L. The compliance rate was >80% at week 12 and >75% at each postbaseline time point except week 42. At week 12, mean changes from baseline for GHS/QoL (mean change, 4.95 points; 95% CI, −1.00, 10.90), physical functioning scores (mean change, −3.38 points; 95% CI, −8.80, 2.04), and EQ-5D-5L visual analog scores (mean change, 1.97 points; 95% CI, −3.85, 7.79) were stable; the trend in stable GHS/QoL and physical functioning scores was maintained through week 48. Patients consistently exhibited stable functioning and symptom scores at week 12. The proportion of patients with improved postbaseline scores was 29.3% (95% CI, 20.6, 39.3) for GHS/QoL and 17.2% (95% CI, 10.3, 26.1) for physical functioning.
Conclusion: The clinically meaningful benefit, as assessed by ORR, observed in patients with R/M cSCC receiving pembrolizumab was obtained without clinically meaningful impact on overall HRQoL. These findings support the benefit of pembrolizumab monotherapy in this elderly patient population.
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CD26 in checkpoint blockade-induced tumor immunity

H.M. Knochelmann, D. Arhontoulis, A. Rivera-Reyes, M. Wyatt, D. Neskey, and C. Paulos; *Medical University of South Carolina, Charleston, SC*

Purpose/Objective(s): Immunotherapy targeting PD-1/L1 has revolutionized clinical medicine by mediating durable responses in a small cohort of patients. Mechanisms permitting patient response remain incompletely understood, which limits ability to bolster efficacy of these therapies in those who are non-responsive. We have reported that CD26, a novel, multifunctional ectoenzyme, marks T cells with potent antitumor function and posited that CD26 expression correlates with productive immune responses post checkpoint blockade. To address this, we studied patients with oral cavity squamous cell carcinoma (OCSCC) to elucidate CD26 expression profiles in the context of response to nivolumab. We further assessed CD26 expression using syngeneic murine models to determine the impact of CD26 on therapy and outcome.
Materials/Methods: A Phase II single-arm trial of presurgical nivolumab was conducted at our institution. CD26 expression in tumor-infiltrating lymphocytes (TILs) expanded *ex vivo*from surgical specimens post treatment was determined for 8 of 9 patients in the first stage of the trial. For preclinical modeling, murine oral cancers that were responsive (Moc22) and non-responsive (Moc2) to PD-1 blockade were used to determine CD26 expression in T cells directly isolated from tumors with and without PD-1 therapy.
Results: Responding OCSCC patients expressed higher frequencies of $CD26^+$ TILs versus non-responders. CD26 expression in $CD8^+$ T cells from these patients was significantly correlated with CXCR3 expression. In mice, the frequency of $CD26^+$ TIL populations was augmented by PD-1 therapy, but only in responding tumors. Conversely, the frequency of $CD26^+$ T cells was diminished in the peripheral blood with PD-1 therapy in responding animals, yet was unchanged in the blood of non-responding animals.
Conclusion: Expression of CD26 in TILs correlates with response to PD-1 therapy in both clinical and preclinical settings. Preclinical evidence suggests CD26 is upregulated over the course of PD-1 therapy only in T cells from responding tumors. Ongoing and future studies will determine the mechanism of CD26 upregulation in T cells and whether functional activity of CD26 is critical to a productive immune response. These findings are important to discern qualities of T cells capable of response to checkpoint blockade in order to promote antitumor activity in patients non-responsive at baseline.
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A Multidimensional Gene Expression Model that Accurately Predicts Tumor Response to Pembrolizumab or Nivolumab

D. Adkins,[1] J. Ley,[2] N. LaFranzo,[3] J. Hiken,[4] I. Schillebeeckx,[3] P. Oppelt,[1] K. Palka,[2] and B. LaFleur[5]; *[1]Washington University in St. Louis, Department of Medicine, Division of Medical Oncology, St. Louis, MO, [2]Washington University School of Medicine, St. Louis, MO, [3]Cofactor Genomics, San Francisco, CA, [4]Cofactor Genomics, St. Louis, MO, [5]The University of Arizona, Tucson, AZ*

Purpose/Objective(s): There is an important unmet need for better tools for immunotherapy response prediction for patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (RM-SCCHN). Current on-label diagnostics, namely PD-L1 immunohistochemistry (IHC), have poor accuracy in predicting tumor response. In this study, we demonstrate that a new approach to characterizing pre-treatment tumor tissue, where multiple RNA signals are combined into a multidimensional biomarker, delivers improved predictive performance over individual analytes.
Materials/Methods: An initial cohort of 18 patients with RM-SCCHN treated with pembrolizumab (16) or nivolumab (2) were evaluated for this exploratory study. Total RNA was extracted from pre-treatment FFPE tumor tissue and sequenced following targeted capture to enrich for predetermined immune related genes. Data was analyzed using multidimensional models of immune cells built from gene expression, resulting in robust and sensitive estimation of immune cell percentages. Immune escape, coinhibitory, and costimulatory genes were also quantified and reported. The immune profiles of individual samples were used for downstream biomarker discovery and statistical analysis. A multidimensional biomarker was generated using supervised clustering and a machine-learning based approach. The predictive accuracy of this biomarker was determined using K-fold/leave-one-out cross validation and compared to the individual analytes in the assay.
Results: Patients were stratified based on tumor response to pembrolizumab or nivolumab. Best tumor response was complete or partial response in 6 patients, and progression in 12. Traditional statistical analyses including recursive partitioning and hierarchical clustering demonstrated that multi-collinear relationships and a subset of features predicted

tumor response. In addition, a machine-learning derived multidimensional biomarker showed high predictive performance (83%), positive predictive value (100%), and negative predictive value (80%). The multidimensional marker had superior ability to predict tumor response, with 15 of 18 patients characterized correctly. The predictive performance of this approach was compared to the tumor proportion score (TPS) with the on-label PD-L1 IHC assay in 15 of the 18 patients, which showed only 33% success in predicting tumor response.

Conclusion: This retrospective study, using a well-defined patient cohort, demonstrates that new methods employing RNA expression and immune health expression models generated a comprehensive multidimensional biomarker model resulting in significant improvements in predicting tumor response, compared to PD-L1. Additional patients will be analyzed to increase the cohort to at least 100 patients, and this data will be presented alongside the preliminary data described above.

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Profiling the Spatial Composition of the Hypoxic Tumor-Immune Microenvironment through Multiplex Immunohistochemistry in a Prospective cohort of HPV Associated Oropharynx Cancer

L. Chen,[1] T. Hollmann,[2] Y. Li,[2] N. Katabi,[2] R. Shah,[2] Y. Yu,[1] J.J. Kang,[1] C.J. Tsai,[2] S. McBride,[2] N. Lee,[2] and N. Riaz[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Hypoxia is associated with radio-resistance and an immunosuppressive tumor microenvironment (TME). In a prospective trial using hypoxia as biomarker for radiation dose de-escalation to 30 Gy, we aimed to interrogate the spatial relationships between tumor and immune cells in the microenvironment of human papilloma virus (HPV) associated oropharyngeal carcinoma. We hypothesized that the presence of hypoxia impacts the composition of immune infiltrates as well as the spatial relationships of tumor and immune cells.

Materials/Methods: 21 immuno-histochemical markers were used to evaluate the pre-treatment TME in a cohort of n=10 HPV-associated oropharynx squamous cell carcinoma patients enrolled on a prospective trial (n=19) of hypoxia-guided radiation dose de-escalation. Hypoxia negative status was determined by the absence of uptake of Flurorine-18 labeled Fluoro-Misonidazole (18F-FMISO) PET/CT imaging. Formalin fixed paraffin embedded resected primary tumor was reviewed in conjunction with a pathologist. Slides were stained using the Vectra Opal Multiplex immunohistochemistry system. Tumor and immune cell populations were phenotyped and quantified using semi-automated cell segmentation with the Halo digital pathology platform. Spatial analysis was conducted by evaluating immune cells within 50 micrometers of tumor cells. Two-sided student's T-test was used for statistical analysis between hypoxic and non-hypoxic primary tumors.

Results: 50% (n=5) of patients were initially hypoxia negative, 30% (n=3) converted from hypoxia positive to hypoxia-negative after 10 fractions of radiation, and 20% (n=2) remained persistently positive. TME of initially hypoxia negative and patients who converted to hypoxia-negative was associated with an increased density of exhausted CD8+/PD1+/EOMES+ T-cells ($p=0.027$), lower density of CD68+/CD163+ M2-macrophages ($p=0.032$), and a lower density CD4+/FOXP3+ T-regulatory cells ($p<0.001$). There were no significant differences in tumor PDL1 expression, as well as density of CD8+, proliferating CD8+/Ki67, or activated CD8+/Ki67+/granzyme B+ T cells.

Conclusion: Absence of hypoxia in the TME of HPV associated oropharynx carcinoma is associated with a decreased density of immunosuppressive T-regulatory cells, M2 macrophages, and an increased density of infiltrated exhausted T-cells. Insight into tumor-immune cell relationships, may increase understanding for treatment resistance in hypoxic TMEs is being investigated in a larger prospective study.

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Viable Circulating Ensembles of Tumor Associated Cells Persist in Patients with No Radiologically Detectable Disease after Treatment in Head and Neck Cancer

P. Fulmali,[1] D. Akolkar,[1] D. Patil,[1] T. Crook,[2] S. Limaye,[3] R. Page,[4] A. Ranade,[5] C. Sims,[1] V. Datta,[1] R. Patil,[1] P. Fulmali,[1] A. Ainwale,[1] A. Srinivasan,[1] and R. Datar[1]; *[1]Datar Cancer Genetics Limited, Nasik, India, [2]Royal Surrey County Hospital, Guildford, United Kingdom, [3]Kokilaben Dhirubhai Ambani Hospital, Mumbai, India, [4]Worcester Polytechnic Institute, Worcester, MA, [5]Avinash Cancer Clinic, Pune, India*

Purpose/Objective(s): Advanced (metastatic) Head and Neck Squamous Cell Carcinomas (HNSCC) have limited systemic treatment options and such patients are often referred for palliative care. Response evaluation in HNSCC is determined by clinical and radiological parameters with FDG PET-CT being the modality of choice. However, recurrence or emergence of new metastases are frequently encountered in cases where radiological scans previously implied complete response to systemic treatments. To explore the mechanistic basis of disease recurrence in spite of apparently effective systemic therapy, we hypothesized that Circulating Metastatic Disease (CMD) in the form of viable tumor cells or clusters might be a feature of persisting HNSCC.

Materials/Methods: We obtained 15 ml blood from 762 known and previously treated HNSCC, which included 635 (83.3%) males and 127 (16.7%) female patients just prior to a PET-CT scan. Peripheral blood mononuclear cells (PBMCs) were harvested by centrifugation. Circulating Ensembles of Tumor Associated Cells (C-ETACs) which are clusters of heterotypic apoptosis resistant cells of tumorigenic origin were enriched by a novel process using combination of commercially available stabilizing agents. C-ETACs were characterized by immunostaining for EpCAM, pan-CK and CD45.

Results: Out of 762 patients who underwent PET-CT scan 142 patients (18.6%) had no detectable disease. Astonishingly, in this cohort of 142 patients C-ETACs were detected in 133 (93.7%). There appeared to be no association between metastatic status and presence of C-ETACs.

Conclusion: The presence of CMD in a significant proportion of cases with no evidence of metabolically active disease implies that the majority of patients in whom conventional parameters of disease are negative have viable residual systemic disease and are not biologically cured.

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Encyclopedic Tumor Analysis Guided Treatments with Conventional Drugs Outperform Available Alternatives in Refractory Head and Neck Cancers

D. Akolkar,[1] D. Patil,[1] T. Crook,[2] C. Sims,[1] V. Datta,[1] R. Patil,[1] P. Fulmali,[1] P. Devhare,[1] S. Apurwa,[1] A. Srinivasan,[1] and R. Datar[1];

[1]Datar Cancer Genetics Limited, Nasik, India, [2]Royal Surrey County Hospital, Guildford, United Kingdom

Purpose/Objective(s): Patients with advanced, refractory Head and Neck Squamous Cell Carcinomas (HNSCC) are often considered for immunotherapy with checkpoint inhibitors subject to PD-L1 expression. We hypothesized that such HNSCC would have unexplored vulnerabilities that could be identified using integrative molecular and cellular investigations (Encyclopedic Tumor Analysis, ETA) and targeted using conventional agents in a label- and organ-agnostic manner. We present findings from the HNSCC sub-cohort of the pan-cancer RESILIENT trial where patients with advanced refractory disease were treated with ETA guided treatments regimens.
Materials/Methods: Freshly biopsied tumor tissue was obtained from all patients. As part of ETA, Tumor Molecular Profiling (TMP) identified druggable gene alterations and dysregulated metabolic pathways. Immunohistochemistry (IHC) identified hormone receptors (HR) that could be targeted with endocrine agents. Chemoresistance and response (CRR) profiling of viable tumor derived cells (TDCs) identified functional vulnerabilities of the tumor against a panel of systemic anticancer agents. Integration of MP, IHC and CRR datasets (i.e., ETA) generated patient-specific, label- and organ-agnostic drug priority lists with projected efficacy and safety. Patients who received such ETA-guided treatments were evaluated radiologically to determine treatment response as well as Objective Response Rate (ORR), Disease Control Rate (DCR) and Progression Free Survival (PFS).
Results: ETA-guided regimens were administered to 30 patients with HNSCC who were evaluable for response *per protocol*. PR was observed in 14 patients (ORR = 46.7%) and 29 patients continued to exhibit PR or SD at study termination (DCR = 96.7%). Median PFS was 147 days at study completion with several patients continuing to remain progression free. Median PFS rate at 90 days was 100%. There were no significant or grade IV therapy related adverse events (AEs) or treatment related mortalities. Most patients reported stable to improved Quality of Life (QoL) in terms of disease-related symptoms and functional status.
Conclusion: ETA-guided treatments outperformed available alternatives such as checkpoint inhibitors in this heavily pretreated HNSCC cancer population by offering meaningful survival benefit.
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Withdrawn

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Prognostic Significance of Cell Differentiation and Immune Pathway Mutations in Recurrent Laryngeal Squamous Cell Carcinoma

M.E. Heft-Neal,[1] A. Bhangale,[1] A. Birkeland,[1,2] J.B. McHugh,[1] A. Rosko,[3] M.E. Spector,[3] and J.C. Brenner[1]; [1]University of Michigan, Ann Arbor, MI, [2]University of California, Davis, Sacramento, CA, [3]Department of Otolaryngology, University of Michigan, Ann Arbor, MI

Purpose/Objective(s): Organ preservation protocols are commonly used as first line therapy for advanced laryngeal squamous cell carcinoma (SCC). Disease free survival after radiation or chemoradiation ranges from 30-60% and recurrent tumors often display an aggressive phenotype resulting in poor patient outcomes. The aim of this study is to identify genetic alterations associated with overall and disease specific survival in patients with recurrent laryngeal SCC undergoing salvage laryngectomy.
Materials/Methods: Sixty-two tumors from patients treated at a single NCI designated cancer center were obtained and sequenced using a targeted panel of 250 genes which were identified as being mutated at >1% frequency in the original head and neck squamous cell carcinoma TCGA project. Alterations were grouped based on the pathways defined in Go-lists curated by MSigDB. Disease specific and overall survival were stratified by mutation status for each pathway and outcomes were compared using log rank analysis and multivariate cox regression.
Results: Patients with alterations in the *Cell Differentiation/Epigenetic* and *Oxidation* pathways had significantly worse five-year disease specific survival compared to patients without alterations in these pathways (47.5%, 95% CI 25.2 − 66.9, vs. 82.3%, 95% CI 61.3 - 92.6, p = 0.007 and 32.3%, 95% CI 4.78 − 64.1, vs. 74.9%, 95% CI 59.8 − 85.6, p = 0.023). Conversely, alterations in the *HN-Immunity* pathway were associated with improved five-year disease specific survival (100% vs. 60.0%, 95% CI 42.2 - 73.8, p = 0.019) and overall survival (80.0%, 95% CI 40.8 - 94.6, vs. 38.2%, 95% CI 22.7 − 53.6, p = 0.048). On multivariate cox regression analysis, the *Cell Differentiation/Epigenetic* pathway remained an independent predictor of disease specific survival (HR 4.38, 95% CI 1.04 − 18.4, p = 0.044). The *HN-Immunity* pathway remained significantly associated with improved overall survival (HR 0.269, 95% CI 0.079 − 0.915, p = 0.035) while the *Oncogenic Kinases* pathway was significantly associated with worse overall survival (HR 3.46, 95% CI 1.26 − 9.45, p = 0.016).
Conclusion: Patients with alterations in the *Cell Differentiation/Epigenetic* pathway had significantly worse disease specific survival and patients with alterations in the *HN-Immunity* pathway had significantly improved overall survival in multivariate analysis. Identification of these prognostic genetic biomarkers may serve to help both identify patients at risk for poor outcomes and identify targetable pathways to improve survival.
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Sentinel Node Status to Guide Adjuvant Radiation Therapy in Patients with Merkel Cell Carcinoma

T. Ahmad,[1] H. Vasudevan,[2] A. Lazar,[2] J. Chan,[2] J. George,[3] M.D. Alvarado,[4] S.S. Yu,[5] A. Daud,[6] and S.S. Yom[2]; [1]University of California, San Francisco, School of Medicine, San Francisco, CA, [2]University of California, San Francisco, Department of Radiation Oncology, San Francisco, CA, [3]University of California, San Francisco, Department of Otolaryngology-Head & Neck Surgery, San Francisco, CA, [4]University of California, San Francisco, Department of Surgery, San Francisco, CA, [5]University of California, San Francisco, Department of Dermatology, San Francisco, CA, [6]University of California, San Francisco, Department of Oncology, San Francisco, CA

Purpose/Objective(s): Wide local excision (WLE) with sentinel lymph node biopsy (SLNB) followed by adjuvant radiation therapy (aRT) to the primary tumor site is the preferred initial management approach for Merkel cell carcinoma (MCC). However, management of the draining lymph node basin is less clear, with some studies suggesting nodal aRT can be omitted if SLNB is negative, but other studies documenting nodal recurrence rates as high as 33%. Here, we report a 20-year experience treating MCC with aRT adapted to SLNB findings, specifically to evaluate whether nodal aRT can be safely omitted in SLNB-negative MCC.
Materials/Methods: We retrospectively identified patients who underwent WLE and SLNB for MCC from 1996-2015. SLNB-positive patients underwent completion lymphadenectomy. aRT to the primary tumor site was routinely recommended. The draining lymph node basin was included in the aRT target volume for SLNB-positive patients but omitted if SLNB was negative. Endpoints included overall survival (OS), disease-specific survival (DSS), locoregional recurrence-free survival (LRRFS), and distant recurrence-free survival (DRFS). Survival rates were estimated using the Kaplan-Meier methodology. Differences were assessed using the log-rank test.
Results: 55 patients underwent WLE and SLNB, including 41 (75%) who had a negative SLNB and 14 (25%) who had a positive SLNB. 33 (80%) SLNB-negative patients underwent aRT to the primary site only and 8 (20%) were observed. 11 (79%) SLNB-positive patients underwent aRT to the primary site plus nodal basin and 3 (21%) were observed. Median follow-up was 43.1 months (range: 5-182). 4-year DSS was 100% for SLNB-negative patients irradiated to the primary site only and 75% for

SLNB-positive patients irradiated to the primary site plus nodal basin (p = 0.010). 4-year LRRFS was 100% for patients irradiated to the primary site only and 73% for patients irradiated to the primary site plus nodal basin (p = 0.005). 4-year DRFS was 100% for patients irradiated to the primary site only and 83% for patients irradiated to the primary site plus nodal basin (p = 0.037). Tumor site and size, number of involved nodes, age, sex, and TNM group were not associated with survival outcomes.

Conclusion: After WLE and negative SLNB, aRT to the primary tumor site alone provided excellent disease control without the need for nodal aRT. For these patients, there was zero risk of regional recurrence from omission of nodal aRT. Patients with a positive SLNB experienced higher rates of both locoregional and distant failure. For these patients, nodal aRT is recommended and additional systemic interventions are needed.

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Immune Status and the Efficacy of Adjuvant Radiotherapy for Patients with Localized Merkel Cell Carcinoma of the Head and Neck

M.B. Yusuf,[1] J. Gaskins,[2] M.E. May, Jr,[1] S. Mandish,[1] W. Wall,[3] W. Fisher,[4] P. Tennant,[5] J. Jorgensen,[5] J.M. Bumpous,[5] and N.E. Dunlap[1]; *[1]University of Louisville Hospital, Department of Radiation Oncology, Louisville, KY, [2]University of Louisville School of Public Health, Department of Bioinformatics & Biostatistics, Louisville, KY, [3]Medical College of Georgia, Department of Dermatology, Augusta, GA, [4]University of South Florida Morsani College of Medicine, Tampa, FL, [5]University of Louisville Hospital, Department of Otolaryngology Head Neck Surgery and Communicative Disorders, Louisville, KY*

Purpose/Objective(s): Immunosuppressed (IS) patients are at increased risk for developing Merkel Cell Carcinoma (MCC) of the head and neck and have worsened clinical outcomes compared to immunocompetent (IC) patients. Although adjuvant radiotherapy (RT) is associated with improved survival for select patients with MCC, the effects of immune status on the efficacy of adjuvant RT regarding overall survival (OS) are unclear. We sought to determine the effects of immune status on the efficacy of adjuvant RT regarding OS for patients with stage I, II or III (localized) MCC of the head and neck.

Materials/Methods: The National Cancer Database (NCDB) was queried for patients with localized MCC of the head and neck with known immune status diagnosed from 2010 to 2014. Patients who did not undergo surgical resection were excluded from this analysis. Patients with < 1 month of follow up from resection were also excluded to minimize immortal time bias. Kaplan-Meier methods were used to describe OS for the overall cohort and subgroups categorized by patient and treatment factors including immune status and adjuvant RT receipt. Log-rank tests, multivariable Cox regression models and interaction effect testing were used to compare OS by subgroup.

Results: A total of 892 (89.6%) IC patients and 104 (10.4%) IS patients with MCC of the head and neck were included in the cohort. Etiologies for immunosuppression included solid organ transplantation (n=28), chronic lymphocytic leukemia (CLL , n =29), Non-Hodgkin lymphoma (NHL , n =19) and other including HIV/AIDS (n =28). IS patients had worsened 3-year OS rates (43.6%) compared to IC patients (64.5%, p <.0001) and immunosuppression was associated with increased adjusted hazard of death (HR 2.43, 95% CI 1.84 − 3.20) in multivariable modeling controlling for RT, chemotherapy, stage, age, sex, insurance status, facility type, comorbidity score, lymph node examination, and surgical margins. Adjuvant RT was associated with improved 3-year OS rate for both IS patients (49.4% vs 35.5%, p =0.0467) and stage I/II IC patients (72.4% vs 62.9%, p =0.0092). Adjuvant RT was also associated with decreased adjusted hazard of death (HR 0.77, 95% CI 0.62 − 0.95). Interaction effect testing did not demonstrate a significant difference in the efficacy of adjuvant RT on OS between IC and IS status (p = 0.191). Interaction effect testing of the etiology of immunosuppression suggested solid organ transplantation, CLL or NHL may be associated with increased hazard of death (p =0.013) relative to other IS (including HIV/AIDS).

Conclusion: In this analysis of a large national database, adjuvant RT was associated with decreased hazard of death for patients with localized MCC of the head and neck regardless of immune status and should be considered for both IS and IC patients.

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Systematic Review and Meta-analysis of Quality of Life Outcomes Based on Type of Treatment for HPV-associated Oropharyngeal Cancer

D. Quan[1] and J. Cramer[2]; *[1]Wayne State University School of Medicine Detroit, MI, [2]Wayne State University School of Medicine, Department of Otolaryngology, Detroit, MI*

Purpose/Objective(s): In the era of HPV-associated oropharyngeal cancer survival outcomes are generally good and functional outcomes after treatment are critical. The literature is limited with a paucity of randomized trials. In this study, we synthesize existing studies to examine the impact of treatment modality on functional outcomes in HPV-associated oropharyngeal cancer.

Materials/Methods: We performed a systematic literature review using Pubmed, Embase, and Cochrane databases and identified 1,107 unique entries, 217 of which were in English and reported functional outcomes on patients after treatment for HPV-associated oropharyngeal cancer. From these, we reviewed full-texts and performed meta-analysis using a fixed-effects model with inverse variance method.

Results: 22 articles met inclusion criteria, reporting on 3,092 patients who had been treated for HPV-associated oropharyngeal cancer. G-tube dependence at 24-36 months was significantly worse with surgery plus adjuvant radiation/chemoradiation (S-a[C]XRT) 9.5% [95% confidence interval (CI) 5.9-14.2] compared to 3.8% [1.1-8.6] with surgery alone, 0% [0.0-3.0] with surgery plus de-intensified adjuvant, 3.3% [2.0-5.0] with chemoradiation (CRT) and 0.9% [0.1-3.4] with de-intensified CRT. S-a[C]XRT similarly resulted in worse swallow function than CRT at 12 months as measured by UW-QOL Swallowing (84 [CI 80-88] *v* 89 [87-90]) and HNQOL Eating (65 [60-69] *v* 85 [83-86]), but equal function in the MDADI (80.1 [75.5-84.4] *v* 79.5 [77.3-81.8]) and EORTC QLQ-HN35 Swallowing (12.7 [7.3-18.1] *v* 11.8 [10.1-13.4]). Surgery alone resulted in similar swallow function as CRT, but preserved saliva, outperforming CRT and S-a[C]XRT on the XQ (surgery alone − 15 [CI 6-24]; S-a[C]RT - 37 [27-47]; CRT − 34 [29-40]), HN35 Dry Mouth (surgery alone − 16 [4-27]; S-a[C]RT - 46 [36-56]; CRT − 49 [37-60]) and UW-QOL Saliva (surgery alone − 94 [90-98]; S-a[C]RT - 62 [58-66]; CRT − 53 [46-59]). De-intensified CRT and surgery with de-intensified adjuvant both outperformed CRT in measures of overall function, including the EORTC QLQ-C30 (de-intensified CRT − 82 [CI 80-85]; CRT − 77 [76-78]), and FACT (de-intensified CRT − 123 [118-128]; surgery plus de-intensified adjuvant - 128 [125-131]; CRT − 112 [112-113]).

Conclusion: Upfront surgery and CRT result in differential quality of life effects. Surgery with adjuvant therapy leads to worse swallow function than surgery alone or CRT. Surgery alone leads to superior saliva function. In comparing CRT versus upfront surgery, as the proportion of surgical patients requiring adjuvant therapy increases, swallow function decreases. De-intensified CRT and de-intensified adjuvant therapy result in better overall function than CRT, necessitating further study.

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Poster Presentations

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De-intensified approach for HPV p16-positive oropharyngeal carcinoma using concurrent chemo-radiotherapy and 60 Gy IMRT

C. Nguyen[1] and T. Dobleman[2]; [1]*Radiation Oncology Creighton University Medical Center, Omaha, NE,* [2]*Head and Neck Surgery, Creighton University, Omaha, NE*

Purpose/Objective(s): To report our experience with de-intensified chemo-radiotherapy (CRT) for patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).
Materials/Methods: Our inclusion criteria were: i) T1-T3, N0-N2c,M0, ii) minimal smoking history , and iii) HPV p16 positive. Staging was performed using AJCC 7th version, prior to implementation of the 8th version. Treatment was limited to 60-62 Gy intensity modulated radiation therapy (IMRT) with mean dose of 60 Gy. Minor or remote smoking history was present in 15% of the patients. The majority of the patients received concurrent CRT. Only 3 patients received induction chemotherapy with TPF regimen, followed by definitive concurrent CRT. All patients were treated by the same team of head and neck surgeon, medical oncologist and radiation oncologist. Concurrent chemotherapy was weekly intravenous cisplatin 40 mg/m^2. For the 5 patients treated with TPF (docetaxel, cisplatin and 5-fluorouracil) for bulky disease, all 5 achieved a complete clinical response prior to definitive CRT. All patients underwent post-treatment PET-CT at 10-12 weeks to assess response and to determine the need for planned neck dissection. The study endpoint was 2-year progression-free survival (PFS), local regional control (LRC). Data analysis was performed for patients with a minimum of 2 years of follow-up.
Results: Thirty five (35) patients were treated. All patients had pathology slides immunostain positive for p16. Three (3) patients had planned neck dissection with one (1) having minimal pathological residual disease in sternocleidomastoid muscle. Two-year PFS, LRC were: 94% and 97% respetively. The feeding tube requirement was 35%, which were subsequently removed a few months post-treatment once adequate oral intake was achieved. No grade III late adverse events were observed. No significant esophageal swallowing or stricture was observed. The rate of slight hearing loss was 30%.
Conclusion: Our study adds to the body of literature on de-intensified CRT showing excellent LRC in OPSCC with p16-positive pathology with reasonable quality of life, with no cases of permanent tube feeding or significant hearing loss.
Author Disclosure: **C. Nguyen**: None. **T. Dobleman**: None.

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A phase 1b trial of prexasertib in combination with chemoradiation in patients with locally advanced head and neck squamous cell carcinoma (HNSCC)

E.S. Yang,[1] E. Deutsch,[2] A. Mehmet,[3] J. Fayette,[4] L. Nabell,[5] S.A. Spencer,[1] M.C. Dobelbower,[1] C.D. Willey,[1] J.A. Bonner,[1] X. Wang,[6] A. Lin,[6] and W.N. William[7]; [1]*University of Alabama at Birmingham, Birmingham, AL,* [2]*Gustave Roussy, Université Paris-Saclay, Villejuif, France,* [3]*MD Anderson, Houston, TX,* [4]*Clinical Oncology, Cancer Center "Centre Léon Bérard," University of Lyon, Lyon, France,* [5]*Clinical Studies Unit, University of Alabama at Birmingham, Comprehensive Cancer Center, Birmingham, AL, United States Minor Outlying Islands,* [6]*Eli Lilly and Company, Indianapolis, IN,* [7]*The University of Texas MD Anderson Cancer Center, Division of Cancer Medicine, Houston, TX*

Purpose/Objective(s): The CHK1/2 inhibitor prexasertib enhanced the efficacy of chemoradiation in HNSCC in pre-clinical trials. Previous phase 1b trials of prexasertib with cetuximab or cisplatin assessed the safety of the combinations. The primary objective of this study was to determine the RP2D of prexasertib with radiation (RT) and cisplatin or cetuximab. Secondary objectives included safety, toxicity, and preliminary efficacy.
Materials/Methods: Study JTJI is a Phase 1b study of prexasertib with RT and cisplatin (Part A) or cetuximab (Part B) for previously untreated patients with locally advanced HNSCC. . Patients received prexasertib every 14 days with 70 gray (Gy) radiation given over 7 weeks and weekly cisplatin given 1 day before prexasertib or weekly cetuximab given same day as prexasertib. Starting dose of prexasertib was 20mg/m^2. Dose escalation was driven by safety using a modified Time-to-Event Continual Reassessment Method (TITE-CRM).
Results: In Part A, 7 patients were treated with a prexasertib dose of 20 mg/m^2. Three of these patients experienced a dose limiting toxicity (DLT) (febrile neutropenia in each case). The maximum tolerated dose (MTD) could not be determined due to toxicities. The most frequent treatment emergent AEs (TEAE) deemed related to study treatment were thrombocytopenia (85.7%, G3/4:0%), neutropenia (71.4%, G3/4 57.1%), and dysphagia (71.4%, G3/4: 42.9%). The hematologic toxicity was transient. Of the 7 patients enrolled in Part A, 3 complete responses (CRs; 42.9%) and 2 partial responses (PRs; 28.6%) were observed for the objective response rate (CR+PR) of 71.4%. One patient (14.3%) had stable disease. The observed duration of response ranged from 0.03- 24.2 (censored) months. In Part B, 18 patients were treated with prexasertib dose of 20 mg/m^2 (n=4) 30 mg/m2 (n=6) or 40 mg/m^2 (n=2). No patient in cohort 1 (20 mg/m^2) experienced DLTs. Three of 8 patients in cohort 2 (40 mg/m^2), experienced the DLT, febrile neutropenia and 1/6 patients in cohort 3 (30 mg/m^2) experienced the DLT, febrile neutropenia. The 30 mg/m^2 dose was determined to be the MTD. The most frequent TEAEs deemed related to study treatment were stomatitis (66.7%, G3/4: 38.9%), dysphagia (61.1%, G3/4 44.4%), and dermatitis acneiform (61.1%, G3/4: 22.2%). In part B, 9 CRs (50.0%) and 6 PRs (33.3%) were observed for an ORR of 83.3%. One patient (5.6%) had SD. The observed duration of response (DoR) ranged from 0.03 to 26.3 months. Because patients were censored for the DoR analysis, the median DoR was not evaluated.
Conclusion: Prexasertib can be safely combined with the dose/schedule of RT used in this study in combination with cetuximab. This increases the possibility that the combination of RT and a CHK1 inhibitor like prexasertib could be explored in future clinical studies.
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Efficacy and safety of Apatinib and Tegafur Gimeracil Oteracil as Induction Chemotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck

W. Jiang, S. Dou, MD, R. Li, L. Zhang, and G. Zhu; *Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China*

Purpose/Objective(s): Pre-clinical and clinical evidence suggests that apatinib, a novel orally small-molecule tyrosine kinase inhibitors which can decrease the effect of vascular endothelial growth factor (VEGF), has a potential antitumor activity in a wide range of advanced solid tumors. This

study evaluated the efficacy and safety of induction chemotherapy using apatinib plus tegafur gimeracil oteracil in patients with head and neck squamous cell carcinomas (HNSCCs).

Materials/Methods: In this single-arm phase II study, patients with locally advanced HNSCCs who were judged surgically unresectable or appropriate for non-surgical definitive therapy were recruited. Apatinib and tegafur gimeracil oteracil were used jointly in a regimen of induction chemotherapy. Apatinib was administered orally at a dose of 500mg daily d1-21 and tegafur gimeracil oteracil at 20 mg twice daily d1-14, repeated every 3 weeks. Definitive concurrent chemoradiotherapy was performed after 2-4 cycles of this regimen. The primary endpoint was the objective response rate (ORR) after induction chemotherapy. 1-year progression-free survival (PFS) and adverse events were also assessed. This study is registered with ClinicalTrails. gov: NCT03267121.

Results: Between October 2017 and May 2019, 31 patients with locally advanced HNSCCs were screened, 25 patients were enrolled. 23 patients (92%) were male, and the median age was 61 years (range 40-75). Seven patients (28.0%) were p16-positive oropharyngeal cancer. With a median follow-up period of 10 months (range 3-22), the objective response rate after induction chemotherapy was 96% (95%CI 79.6%-99.9%). The median progress-free survival had not been reached. 1-year PFS rate was 71.3% (95%CI 47.1%-86.8%). The most common adverse events were grade I-II hypertension (56.0%) and hand-foot syndrome (28.0%), which were manageable. Only one patient had grade III hypertension and apatinib was reduced to 250mg daily. One patient had grade IV thrombocytopenia and another patient reported grade III oral pain, therefore they didn't complete this regimen and refused further chemoradiotherapy. One patient died due to progress of disease. No drug-related mortality occurred.

Conclusion: The regimen of apatinib and tegafur gimeracil oteracil may be used as induction chemoradiotherapy in patients with advanced HNSCCs, which can lead to a high ORR before definitive concurrent chemoradiotherapy. Most of the toxicities were manageable.

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Risk factors for failure in the contralateral neck after adjuvant radiotherapy for squamous cell carcinoma of the oral cavity (SCCOC)

C.C. Hansen, K. Ruth, D.Y. Lee, M. Lango, J. Liu, J. Bauman, J.A. Ridge, and T.J. Galloway; *Fox Chase Cancer Center, Philadelphia, PA*

Purpose/Objective(s): Bilateral adjuvant neck radiation (BLRT) is frequently employed for patients with oral cavity cancer due to proximity to midline and/or pathologic features. Can BLRT be safely omitted in select groups at low risk of contralateral neck failure (CF)?

Materials/Methods: This single-institution retrospective review includes patients from 2010 to 2018 with SCCOC who underwent appropriate primary resection with neck dissection(s) and then adjuvant radiotherapy. All received primary site radiation; the decision to irradiate either the ipsilateral or bilateral neck was based on the anticipated recurrence risk. Risk groups were assigned based on the presence of select pathologic features: PNI, LVI, ENE, and more than 1 positive ipsilateral lymph nodes (>1LN). Group 1 had no risk factors, Group 2 had only one, and Group 3 had more than one factor or midline < 1cm. CF was described within these risk groups, and time to CF compared using logrank tests.

Results: Of 114 patients meeting inclusion criteria, 52 (46%) were treated with BLRT. Median follow-up from end of RT was 19.1 mo. Oral tongue primary accounted for 40% and were more likely to receive BLRT ($p=0.006$). Factors predictive for the administration of BLRT are ENE ($p=0.008$), PNI ($p=0.004$), LVI ($p<0.001$), and >1LN ($p<0.001$). The percentage of patients with each factor treated by BLRT is ENE, 76%; PNI, 57%; LVI, 78%; and >1LN, 81%. During follow-up, 26 patients had locoregional failure including 10 patients with CF, of which 40% had CF only. Most patients in Group 1 (31/36, 86%) received unilateral/no neck RT, while most patients in Group 3 (30/38, 79%) received bilateral therapy. In group 2, 23/40 patients (57%) received unilateral/none, with 5 of 6 CFs in this group (18 mo. freedom from CF = 77% (95%CI=49%-91%) for unilateral vs 100% for bilateral, $p=0.14$). CF by extent of radiation field and risk group is listed below. The most common risk factor in a group 2 patient was PNI (n = 28/40, 70%). Of the 28 patients radiated only for PNI, 5 (18%) had CF and all received unilateral therapy. By contrast none of the patients managed unilaterally with either LVI or >1LN had a CF.

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	Failure by Risk Group			
	Local	Ipsilateral neck	CF with BLRT	CF with Unilateral/ none
Overall	19/114 (16.7%)	11/114 (9.6%)	4/52 (7.7%)	6/62 (9.7%)
Group 1 (no risk factors)	2/36 (5.5%)	0/36 (0%)	0/5 (0%)	1/31 (3.2%)
Group 2 (PNI or LVI or 2+LN)	8/40 (20%)	3/40 (7.5%)	1/17 (5.9%)	5/23 (21.7%)
Group 3 (Multiple risk factors or ENE)	9/38 (23.7%)	8/38 (21.1%)	3/30 (10%)	0/8 (0%)

Conclusion: Even with a single risk factor engendering the need for adjuvant radiation, the failure rate in the contralateral neck is unacceptably high when elective contralateral neck radiation is not delivered. This was strongly associated with PNI, and less clearly with LVI or multiple nodes.

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Continued Tobacco Use and Survival in Patients with Carcinoma of the Larynx

A. Srivastava,[1] W.R. Kennedy,[1] H.A. Gay,[1] W.L. Thorstad,[1] and A.J. Apicelli III[2]; [1]*Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO,* [2]*VA St. Louis Health Care System, Saint Louis, MO, United States*

Purpose/Objective(s): Laryngeal preservation (LP) with chemoradiation is an alternative to total laryngectomy (TL) in patients with advanced larynx cancers. However, recent studies suggest that patients with T4a disease have inferior outcomes when treated with LP. These studies, though, have not controlled for confounders such as tobacco use during radiotherapy (RT), which affects disease control in other malignancies such as lung cancer, though this relationship is less clear in larynx cancers. In this study, we evaluated the relationship between continued tobacco use (CU) and outcomes in patients undergoing RT, hypothesizing that CU would result in impaired outcomes. Next, we studied individuals with T4a tumors to determine whether TL and LP are comparable when controlling for this confounder, hypothesizing that TL and LP would be equivalent when controlling for CU.

Materials/Methods: An institutional database was reviewed for patients with a history of tobacco use treated with RT between 2008-2017. Patients were divided into two cohorts based on tobacco use: tobacco cessation (TC, documented cessation prior to LP), or CU. The Kaplan-Meier method was used to calculate estimates of disease control and the Cox proportional hazards model to identify predictors of outcomes. For the second part of this analysis we limited the population to patients with T4a disease and used an inverse probability of treatment weighting (IPTW) adjusted Cox proportional hazards regression to compare survival by treatment modality.

Results: 195 patients were eligible with a median follow-up of 30 months. At two-years' follow up, overall survival (OS) was higher in patients who stopped smoking (87% v. 63%, $p<0.01$). On multivariable analysis, lower KPS (Adjusted Hazard Ratio [aHR]: 3.87, 95% CI: 1.95 − 7.66, $p<0.01$), higher N-stage (aHR: 2.61, 95% CI: 1.31 − 5.20, $p=0.01$), and CU (aHR: 3.31, 95% CI: 1.69 − 6.44, $p<0.01$) predicted for OS. On evaluation of T4a patients (n=75), CU (HR=6.13, 95% CI: 2.84 − 36.19, $p<0.01$), GTV (HR=1.04, 95% CI: 1.00 − 1.10, $p=0.048$), and treatment modality

(HR for TL: 0.72, 95% CI: 0.55 − 0.98, p=0.04) all predicted for mortality in the univariable analysis (UVA). Unadjusted survival at two years was 64% for LP patients and 84% for TL patients. However, on IPTW-weighted analysis, 2-year OS was 76% v. 72% (log-rank p=0.75) with an aHR for mortality of those undergoing TL of 1.07 (95% CI: 0.88− 1.47, p=0.74). IPTW analyses adjusted for tobacco use alone yielded an aHR of 0.82 (95% CI: 0.64 − 1.13, p=0.29).

Conclusion: Tobacco use during RT was associated with inferior disease control and survival for patients with carcinoma of the larynx. Adjusting for this confounder in patients with T4a disease demonstrated comparable survival in patients undergoing TL and LP thus underscoring the importance of tobacco cessation and equivalence of these treatments in patients with advanced laryngeal carcinomas.

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Genetic and micro-environmental factors influencing response to definitive 30Gy chemo-radiotherapy (chemoRT) in HPV Positive Oropharyngeal Cancer (OPC)

N. Riaz,[1] E. Sherman,[2] X. Pei,[3] H. Schoder,[3] R. Paudyal,[4] N. Katabi,[3] D.J. Ma,[5] C.J. Tsai,[3] S. McBride,[3] L.G. Morris,[6] J.O. Boyle,[7] B. Singh,[8] R.L. Foote,[5] A. Ho,[9] R.J. Wong,[7] J. Humm,[3] A. Dave,[3] D.G. Pfister,[9] J. Reis-Filho,[3] and N. Lee[3]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [3]Memorial Sloan Kettering Cancer Center, New York, NY, [4]MSKCC, New York, NY, [5]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, [6]Memorial Sloan Kettering Cancer Center, Department of Head and Neck Surgery, New York, NY, [7]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, [8]memorial sloan kettering cancer center, new york, NY, [9]Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, NY*

Purpose/Objective(s): We previously reported outcomes for de-escalated chemoRT in HPV+ OPC by assessing tumor hypoxia with pre and intra-treatment (rx) dynamic 18F-FMISO (fluoromisonidazole) PET. Patients with absence of hypoxia on pre- or intra-rx scan were de-escalated to 30Gy, whereas those who remained hypoxic received 70Gy. Here, we sought to define genetic and/or micro-environmental factors that may influence clinical outcomes to de-escalated therapy.

Materials/Methods: 19 patients enrolled on trial and in de-escalated patients, a 4-month neck dissection assessed pathologic response. Whole-genome sequencing (WGS) was performed on DNA from pre-therapy tumor and paired normal samples, along with RNA sequencing. A subset of cases (N=19; 9 of whom recurred) from a Mayo Clinic study of low-dose adjuvant radiotherapy to 30Gy (NCT: NCT01932697) were obtained to validate findings from the genomic analyses. Longitudinal functional imaging with FMISO PET and serial MRIs were used to assess changes in the tumor microenvironment. Compartmental analysis on dynamic FMISO scans was performed as previously described. MRI including diffusion-weighted (DW-) and dynamic contrast-enhanced (DCE-) images were obtained pre-rx and weekly during therapy. Mann-Whitney U-test was used for group comparisons.

Results: As previously reported, 15 of 19 patients underwent de-escalation based on FMSIO PET, 11 of which had a pathologic complete response (pCR). The 2-year LRC and OS was 94% and 95% for the entire cohort. WGS identified typical alterations associated with HPV-related OPC, including *PI3KCA* (29%) & *TRAF3* (18%), although none associated with response. Mutational signature analysis identified a significant enrichment in the proportion of small deletions with sequences of micro-homology, indicative of a defect in double strand break DNA repair, in patients de-escalated to 30Gy who did not recur as compared to others (p = 0.018). A similar analysis of the Mayo Clinic cohort confirmed the observation that patients who responded to 30Gy had a significantly higher proportion of deletions with micro-homology than those who recurred (p=0.028). Pre-rx DCE-MRI analysis identified a perfusion/permeability difference in cases with residual disease vs. pCR (p=0.076). Tumor volume on serial MR Imaging demonstrated slow regression during rx, which did not correlate with pCR, but changes in micro-structure (kurtosis, measured by DW-MRI) did (p=0.01).

Conclusion: WGS analysis revealed a mutational signature consistent with a DNA-repair defect correlated with response to de-escalated chemoRT in two independent prospectively collected cohorts of HPV+ OPC patients. Longitudinal imaging analysis identified changes in the micro-environment but not tumor burden correlated with pCR. Both pre-rx characteristics and changes during therapy may help guide precision chemoRT in HPV+ OPC.

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Proton Therapy for Nasopharyngeal Cancer: A Matched Case-control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy

X. Li,[1] A. Lee,[1] and N. Lee[2]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): There is a paucity of published data on the outcomes of nasopharyngeal cancer (NPC) treated with proton therapy (PT). Here we report the dosimetry parameters, treatment-related toxicities and clinical outcomes of NPC treated with intensity-modulated proton therapy (IMPT) and in matched NPC cases treated with intensity modulated photon therapy (IMRT) from the same single institution.

Materials/Methods: Patients with newly diagnosed non-metastatic NPC treated with IMPT between January 2016 and December 2018 were matched in 1:1 ratio to patients treated with IMRT in the same date range using the following matching variables in descending order: T-stage, N-stage, chemotherapy regimen, WHO classification, EBV status, age and sex. Patient characteristics, treatment details and treatment related toxicities were compared between IMPT and IMRT groups. Treatment outcomes including local control (LC), regional control (RC), distant metastasis free survival (DMFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Acute and late toxicities were graded using CTCAE version v5.0.

Results: Eleven patients with newly diagnosed non-metastatic NPC were treated with IMPT from 2016 to 2018. Eleven NPC cases treated with IMRT were matched to the IMPT cases with criteria described as above. After matching, there's no significant difference between the two groups in distribution of staging, WHO classification, EBV status, age and sex. All patients were treated with concurrent chemotherapy except for one patient who was treated with IMPT alone for T1N0 disease. All IMPT cases received dose of 69.96 CGE in 33 fractions. All IMRT cases received 69.96 Gy in 33 fractions. IMPT group had significantly lower mean parotid dose (median 19.5CGE vs 24.9Gy, p<0.00001), lower mean larynx dose (median 17.7CGE vs 29.7Gy, p=0.0035) and lower mean oral cavity dose (median 17.4CGE vs 33.1Gy, p=0.00008) compared to IMRT group. The

dosimetry parameters for spinal cord, brain stem, temporal lobes, optic chiasm, optic nerves and cochlea did not differ significantly between IMPT and IMRT groups, IMPT group had lower grades of acute oral mucositis (0% vs 27.3% grade 3 or above), acute dysphagia (27.3% vs 72.7% grade 2 or above) and acute weight loss (9.1% vs 90.9% grade 2 or above) compared to IMRT group. There were no significant differences in other acute or chronic toxicities between the IMPT and IMRT group. There were no grade 4-5 toxicities. With a median follow up of 25 months (IQR 16-33), the 2-year LC, RC, DMFS and OS were all 100% in the IMPT group while the IMRT group also had 2-year LC, RC and OS of 100% with DMFS of 90.9% (1 distant metastasis to liver).

Conclusion: In this largest reported single institution series of matched IMPT vs IMRT cases of NPC, IMPT showed dosimetry advantages over IMRT and lower rates of acute toxicities while both had comparable treatment outcomes.

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Improved Outcomes by proton beam radiation for nasal cavity and paranasal sinus malignances

M. Fan,[1] N. Lee,[1] A. Lee,[2] J.J. Kang,[2] D. Fan,[2] C.J. Tsai,[1] and L. Chen[2]; [1]*Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): To perform a retrospective analysis of patients with nasal cavity and paranasal sinus (PNS) malignancy treated with proton therapy (PT) at Memorial Sloan-Kettering Cancer Center and Procure Proton therapy center.

Materials/Methods: Between October 2013 and November 2018, 88 patients with PNS and nasal cavity malignance underwent PT. Most patients had squamous cell carcinoma (39.8%; n=35), T3-4 tumors (65.9%; n=58), and the nasal cavity or ethmoid sinus (61.3%; n=54) as the primary disease site. 45 patients (51.1%) had surgery and received adjuvant PT. 21 patients (23.8%) had recurrent tumors and 20 patients (22.7%) had prior full course of radiation therapy. 70 patients (79.5%) had proton therapy only while others (20.5%) received proton therapy as a boost after photon radiation. The median radiation dose was 70Gy (RBE) for all patients and RT-naïve patients, and 67.4Gy (RBE) for patients with re-RT.

Results: With a median follow-up of 23.4months (range 1.7-68.2 months) for all patients and 28.4 months (range 2.3-68.2months) for surviving patients, the 2-year estimates of local control (LC), distant metastasis-free (DMFS), and overall survival (OS) for all patients was 88.6%, 85.2%, and 80.7%, respectively. For treatment-naïve patients, 2-year LC, DMFS, OS was 91.0%, 88.1%, 83.6%, respectively. For patients with recurrent tumors, 2-year LC, DMFS, OS was 80.9%, 76.2%,71.4%, respectively. Univariate analysis indicated a significant worse RPFS for lymph node involvement ($p=0.029$), and a worse OS for non-operable patients and squamous cell histologic ($p=0.035$, $p=0.027$, respectively). On multivariate analysis, borderline significance was presented for squamous cell histologic and recurrent tumor in predicting for worse overall survival, and lymph node involvement for increased risk of regional failure.

Conclusion: Proton beam therapy offers durable local control and survival in patients with nasal cavity and paranasal sinus malignancy. Even patients with recurrent tumors or with prior radiation history could achieve encouraging outcomes. PT is a promising treatment option and worth further investigation.

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Five-year follow-up for head-and-neck cancer of unknown primary origin treated with intensity-modulated radiotherapy

S.W. Dutta, R.C. Bliley, C. Luminais, and P.W. Read; *University of Virginia, Charlottesville, VA*

Purpose/Objective(s): To determine long term survival, failure patterns, and toxicity in patients with head-and-neck carcinoma of unknown primary origin (HNCUP) treated with intensity-modulated radiotherapy (IMRT).

Materials/Methods: Medical records from 55 consecutive patients with non-metastatic HNCUP treated with IMRT from years 2002-2018 were reviewed. Staging was per the 7th edition of the American Joint Committee on Cancer staging manual. Limited (cN1-N2a) and advanced (cN2b-N3) disease was present in 47.3% (n=26) and 52.7% (n=29) of patients, respectively. Planned neck dissection was performed after a median preoperative dose of 56 Gy to Waldeyer's ring and gross nodal disease (including 50.4 Gy to the cN0 bilateral neck), in 50.9% (n=28) of patients. Chemotherapy was given to 30.9% (n=17) for advanced disease. Late toxicities were scored according to Common Terminology Criteria for Adverse Events version 5.0. The Kaplan–Meier (KM) procedure was utilized to estimate survival at five years. Univariate (UVA) and multivariate (MVA) analyses were performed to generate hazard ratios (HR) with 95% confidence intervals (CI) for overall (OS) and progression-free (PFS) survival.

Results: The median follow-up was 5.33 years. P16 status was positive in 78.9% (n = 15) of specimens analyzed (n = 19). The pathological complete response rate among planned neck dissection patients was 64.3% (n=18) after a median dose of 56 Gy. The mucosal, regional, and distant recurrent rates were 1.8%, 12.7%, 12.7%, respectively. The single mucosal recurrence occurred outside Waldeyer's ring in the floor of mouth. The majority (n = 6/7, 85.7%) of locoregional recurrences had simultaneous distant metastases. Among patients with pathological extranodal extension (ENE) status, which was positive in 11/25 neck dissection specimens where it was described, only those with positive ENE recurred regionally or distantly. Among all patients, the KM estimated OS at 5 years was 79.8%. KM estimated PFS at 5 years was 76.8%. WHO Performance status >0 (HR 3.77, 95% CI 1.17-12.10, p = 0.027) and advanced nodal disease was associated with decreased PFS on MVA (HR 4.05, 95% CI 1.13-14.55, p = 0.032). Patients eligible for neck dissection experienced improved PFS on MVA (HR 0.264, 95% CI 0.084-0.831, p = 0.023). The late grade 3 toxicity rate was limited to fibrosis (n=3, 5.5%). Five (9.1%) patients developed subsequent metachronous malignancies.

Conclusion: Radiation treatment of HNCUP results in impressive long term survival with minimal late toxicity. Neck dissection appears to play a valuable role in improving outcomes for eligible patients. Dose de-escalation of Waldeyer's ring, particularly in light of zero Waldeyer's ring recurrences treated to 56 Gy and the possibility for transoral robotic surgery for salvage, should be explored in the treatment of non-smoking patients with p16 positive disease.

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The Rise of HPV in the Elderly: A Changing Landscape of Oropharyngeal Carcinoma

D.R. Dickstein,[1] M. Egerman,[2] J. Doucette,[3] S. Sharma,[1] J.T. Liu,[1] V. Gupta,[1] B. Miles,[4] M. Posner,[5] W.H. Westra,[6] K. Misiukiewicz,[5] E. Genden,[4] and R.L. Bakst[1]; [1]*Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY,* [2]*Icahn School of Medicine at Mount Sinai, New York, NY,* [3]*Environmental Medicine and*

Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, [4]Department of Otolaryngology − Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, [5]Department of Medicine, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [6]Department of Anatomic and Clinical Pathology, Icahn School of Medicine at Mount Sinai, New York, NY

Purpose/Objective(s): As the human papillomavirus (HPV) epidemic continues to grow, the number of elderly patients with oropharynx squamous cell carcinoma (OPSCC) is rapidly increasing. Despite this observation, this cohort remains understudied as they are often excluded from clinical trials. We aimed to determine HPV prevalence in this cohort and its impact on disease outcomes.

Materials/Methods: We identified patients aged ≥ 70 with nonrecurrent, nonmetastatic OPSCC treated with curative intent at our institution from 2007-2018 and analyzed demographics, treatment characteristics, and outcomes. Survival analyses were used for outcome-specific endpoints.

Results: In total, 88 patients were identified with a median age of 73 (interquartile range [IQR]:71-78). The majority was male (78%), white (66%), former smokers (61%), and non- or moderate drinkers (80%). The median Charlson Comorbidity Index (CCI) was 6 (IQR: 5-7) and 82% of patients were ECOG 0 or 1. Of note, 70% of the cohort was HPV positive (HPV+), and of these patients, 68% had PCR subtype confirmation, with 83% serotype 16. Fifty one percent of patients were AJCC 8th edition stage I/II and 49% were stage III/IV. Thirty-six percent of patients underwent surgery and 24% received adjuvant RT. Of those receiving definitive RT (n=57), 88% were treated with concurrent chemotherapy and of those, 50% underwent induction chemotherapy (n=25). Twenty-three percent of patients experienced a treatment interruption with no statistical difference between HPV+ and HPV- patients (P=0.24). Two patients (both HPV-) died on treatment due to an unrelated health condition. Median follow-up time was 2.5 years (IQR: 0.9-4.7). At 5 years, overall survival (OS) was 79.2% for HPV+ patients and 34.8% for HPV- patients (P=0.002); and disease specific survival (DSS) was 86% for HPV+ and 45.7% for HPV- patients (P=0.004). Estimated locoregional control (LRC) at 5 years was 83.0% for HPV+ and 58.0% for HPV- patients (P=0.013). By multivariable analyses adjusting for age, race, gender, alcohol use, smoking history, CCI, and ECOG, HPV+ status was significantly associated with improved OS, DSS, LRC (OS: HR 0.27, [95% CI: 0.11, 0.64], P=0.003; DSS: HR 0.22, [95% CI: 0.072, 0.67], P=0.008; LRC: HR 0.26, [95% CI: 0.082, 0.82], P=0.021).

Conclusion: In our cohort of elderly patients with OPSCC, the majority was HPV+. Consistent with prior studies in younger populations, positive HPV status was associated with improved survival and disease outcomes in elderly patients. There are many challenges when managing elderly patients with OPSCC, but as the population ages and the HPV epidemic evolves, clinical trials should include elderly patients with HPV+ OPSCC to explore the role of de-intensification treatment regimens in treating this growing, complex population.

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Low neutrophil to lymphocyte & high lymphocyte to monocyte ratios associated with improved overall survival & response to induction chemotherapy when selecting patients with locally advanced squamous cell of the larynx for combined chemoradiation

Z. Risch,[1] E. Bellile,[2] R. Townsend,[1] P.L. Swiecicki,[3] K. Casper,[4] K. Malloy,[4] N. Hogikyan,[4] M.E. Spector,[4] A. Shuman,[4] C.L. Stucken,[4] S.B. Chinn,[4] D. Chepeha,[1] S. Jolly,[5] M.L. Mierzwa,[5] C.R. Bradford,[4] A. Eisbruch,[5] T. Carey,[6] M.E. Prince,[4] G.T. Wolf,[4] and F. Worden[3];
[1]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]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [6]Departments of Pathology and Otolaryngology, University of Michigan, Ann Arbor, MI

Purpose/Objective(s): A single institution protocol (9520) treated patients (pts) with stage III/IV locally advanced squamous cell carcinoma of the larynx (LSCC) with 1 cycle of cisplatin & 5-FU (PF) to select pts for definitive therapy. Pts whose tumors attained a ≥ 50% response after 1 cycle of PF underwent combined chemoradiation (CRT). Those who had a < 50% response to induction chemotherapy (IC) were treated with total laryngectomy + RT. Correlative science from 9520 demonstrated that an increased percentage of CD4+ cells predicted response to PF & suggested improved survival. Published retrospective data also has demonstrated that lower neutrophil to lymphocyte ratios (NLR) & higher lymphocyte to monocyte ratios (LMR) are associated with improved prognosis in p16-SCC of the oropharynx & pyriform sinus, while cancers with higher NLR & lower LMR have a worse prognosis. Similar to our previous correlative analysis, this study is also a secondary analysis of the predictive value of NLR & LMR in a prospective trial of bio-selective IC.

Materials/Methods: NLR & LMR were calculated from pre-treatment CBC for all pts (N=87) enrolled onto 9520.

Results: All 87 pts received IC with PF. 65/87 (75%) responded to IC & received CRT. Results of response to IC compared the NLR & LMR ratios by logistic regression analysis & was used to create NLR & LMR cut points. Among pts with LMR ≥ 3, the response rate (RR) was 89% while the RR was 64% with LMR < 3 (p=0.008). Among pts with NLR ≤ 4.7, the RR was 79% while the RR of pts with > 4.7 was 58% (p=0.06). Overall & disease specific survivals were greater in pts with LMR ≥ 3, (log rank p=0.04, p=0.03, respectively).

Conclusion: Higher LMR & lower NLR are associated with favorable responses to IC & LMR ≥ 3 is associated with improved survival. This data correlates strongly with our published results from 9520, whereby elevated circulating CD4+ lymphocytes predict response to IC & survival. This important information may help direct the design of future laryngeal preservation protocols.

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Clinical Outcomes Using Reduced Target Volume Expansions for Patients with Laryngeal Cancer

A. Burr,[1] P.M. Harari,[1] A. Haasl,[2] R.J. Kimple,[3] G.K. Hartig,[4] M.E. Witek,[3] A. Wieland,[5] J.Y. Bruce,[6] and T.M. McCulloch[7];
[1]Department of Human Oncology, University of Wisconsin Hospital and Clinics, Madison, WI, [2]Univeristy of Wisconsin, Madison, WI, [3]Department of Human Oncology, University of Wisconsin, Madison, WI, [4]University of Wisconsin, Madison, WI, [5]Department of Surgery, Division of Otolaryngology and Head and Neck Surgery, University of Wisconsin, Madison, WI, [6]University of Wisconsin - Madison, Section of Hematology/Oncology, Madison, WI, [7]University of Wisconsin, Milwaukee, WI, United States

Purpose/Objective(s): To evaluate patterns of failure, toxicities, and dosimetric impact on dysphagia/aspiration risk structures (DARS) using a

direct gross tumor volume (GTV_{70}) to planning target volume expansion ($dPTV_{70}$) in patients treated for laryngeal squamous cell carcinomas.

Materials/Methods: We performed a retrospective review of patients with laryngeal squamous cell carcinomas treated between 2003-2018 with primary radiotherapy with or without concurrent systemic therapy. Overall survival, local, and regional control, and gastrostomy tube rates were analyzed with the Kaplan-Meier method. Factors associated with local control and overall survival were assessed by univariate and multivariate analyses. Dosimetric comparisons between $dPTV_{70}$ and consensus guideline-generated PTV ($cPTV_{70}$) was performed with the paired *t*-test.

Results: Seventy-three patients with laryngeal squamous cell carcinoma were identified with a median follow-up of 58.8 months among surviving patients. Overall survival at 5-years was 57.9% (95% CI: 43.7%-69.7%). Five-year primary tumor control was 79.6% (95% CI: 67.3%-87.7%) and regional control was 88.1% (95% CI: 76.5%-94.2%). A total of 18 patients experienced a locoregional recurrence, of which 15 had treatment plans available. Of these, 80% (n=12) experienced failures that were 95% contained within the high-dose treatment volume. One patient experienced a marginal failure of the primary tumor in the intermediate risk primary tumor region. One patient failed in the intermediate risk nodal region, and one patient failed in the low risk nodal region. There were no factors associated with overall survival or local control on multivariate analysis. Metastatic only failure occurred in 2.7% of patients (n=2). The gastrostomy tube rate at 2-years was 5.1%. A total of 6.8% of patients required permanent tracheostomy tube placement. Aspiration pneumonia occurred in 20.6% of patients and 13.7% required esophageal dilation. Dose (V65) to DARS was significantly lower for $dPTV_{70}$ compared to $cPTV_{70}$.

Conclusion: Management of patients with laryngeal squamous cell carcinoma using definitive radiotherapy and a high-dose planning target volume created without a gross tumor volume to clinical tumor volume expansion resulted in high locoregional control with the vast majority of failures occurring within the high-dose field. Long-term toxicity was generally favorable. Dosimetric data support a reduction in the high-dose volume of radiation to dysphagia/aspiration risk structures. Distant metastatic-only failure was a rare event suggesting the potential benefit of evaluating local therapy intensification techniques to further improve control. These data suggest that judicious reduction in high-dose target volumes can preserve high tumor control rates while diminishing normal tissue toxicity profiles.

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Does Age Impact Outcomes of Oropharyngeal squamous cell carcinoma?

A.I. Ghanem,[1,2] M.A. Schymick,[3] S. Bachiri,[4] R. Khalil,[5] C. Burmeister,[5] J. Sheqwara,[6] S. Chang,[5] T. Ghanem,[5] and F. Siddiqui[1]; *[1]Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI, [2]Alexandria Clinical Oncology Department, Alexandria University, Alexandria, Egypt, [3]Department of Radiation Oncology, Detroit, MI, [4]Radiation Oncology Department, Henry Ford Health System, Detroit, MI, [5]Henry Ford Health System, Detroit, MI, [6]Henry Ford Hospital, Detroit, MI, United States*

Purpose/Objective(s): It is well-established that human papilloma virus (HPV) positive (+ve) oropharyngeal (OP) squamous cell carcinoma (SCC) carries a better overall prognosis than HPV negative (-ve) tumors. We sought to investigate the impact of age upon survival endpoints for HPV +ve and -ve OP SCC as well as the differences in acute radiotherapy (RT) toxicity.

Materials/Methods: We included all OP SCC cases treated definitively between 2010-2017. All cases underwent either surgery ± adjuvant RT; or definitive RT; ± chemotherapy according to the multidisciplinary tumor board decision. After determining p16 status we dichotomized each HPV group by age at diagnosis into old (> or = 65 years) and young (<65 years) sub-groups. Patients' demographics, clinico-pathological data and treatment modalities were compared across age groups for both HPV subtypes. Log-rank test and Kaplan-Meier curves were utilized to measure effect of age on overall (OS), local recurrence free (LRFS) and distant metastases free (DMFS) survival for HPV +ve and -ve. For patients receiving RT we compared weight loss, feeding tube insertion, treatment breaks and hospitalization during RT as parameters for acute toxicity across age groups.

Results: We identified 217 OP SCC who fit our inclusion criteria. Seventy percent were HPV+ve, males were 82%, mean age at diagnosis was 61 years, 75% were white, 67% were ever smokers and 54% were frequent/heavy alcohol drinkers. According to AJCC 7th edition, Stages III and IVA formed 87%; however, these were regrouped as stage I (51%) and stage IVA (62%) as prevalent stages for HPV+ve and -ve respectively as per AJCC 8th version. Definitive CRT was utilized in 58% and surgery ± adjuvant therapy in 31% of the study cohort. For HPV+ve sub-group, 31% were old (n=47); whereas they constituted 40% (n=27) of HPV-ve cases. Clinicopathological and treatment characteristics were generally equivalent among age groups except that HPV +ve younger patients had more adequate surgical margins (≥5mm) (78% vs 36%; p=0.03) than old; and HPV-ve old cases had a trend towards more utilization of concomitant cetuximab (30% vs 13%; p=0.09) than younger ones. All endpoints were not significantly different between old vs young HPV+ve cases with 2-year OS and LRFS of (64% vs 59%; p=0.41 and 88% vs 87%; p=0.98 for both respectively). Similar outcomes were observed between study age groups for HPV-ve cases (p>0.05 for all endpoints). Hospitalization during RT was more frequent in old patients (44% vs 28%; p=0.03). Median weight loss during RT was 9.5% (0-22%) vs 9.3% (0-17%) for old vs young (p=0.35) and RT breaks were also non-significant (39% vs 27%, p=0.8). Feeding tubes were inserted after RT initiation in 41% of old and 36% in young (p=0.5).

Conclusion: Older patients with OP SCC have equivalent outcomes compared to younger ones irrespective of HPV status. Optimal treatments must be offered following standard of care as determined by a multidisciplinary group of providers.

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Comparison of clinical outcomes in patients with squamous cell carcinoma of the oral tongue treated with adjuvant bilateral vs. unilateral neck radiation

R.I. Chin,[1] W.R. Kennedy,[1] M.D. Daly,[1] H.A. Gay,[1] P. Oppelt,[2] D. Adkins,[2] P. Pipkorn,[3] R.S. Jackson,[3] J. Rich,[3] R.C. Paniello,[3] J. Zevallos,[3] and W.L. Thorstad[1]; *[1]Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO, [2]Washington University in St. Louis, Department of Medicine, Division of Medical Oncology, St. Louis, MO, [3]Washington University School of Medicine, Department of Otolaryngology, St. Louis, MO*

Purpose/Objective(s): The role of adjuvant radiation therapy (RT) is well-established for squamous cell carcinoma (SCC) of the oral tongue cancer with high-risk pathohistological features. However, it remains controversial whether adjuvant RT can be omitted for the contralateral elective neck. This study reports the clinical outcomes of patients with oral tongue cancer treated with adjuvant unilateral vs. bilateral elective neck RT.

Materials/Methods: 95 patients with newly diagnosed SCC of the oral tongue treated with adjuvant IMRT between 1998 and 2017 at were

identified from a single institutional database. Exclusion criteria included incomplete RT (<60 Gy). Staging was completed using AJCC 7th edition. The pT classification for this group was pT1 (15, 16%), pT2 (45, 47%), pT3 (24, 25%), and pT4 (11, 12%). The pN classification was pNX (4, 4%), pN0 (23, 24%), pN1 (19, 20%), pN2a (2, 2%), pN2b (36, 38%), pN2c (10, 11%), pN3 (1, 1%). The AJCC group stage was I (5, 5%), II (10, 11%), III (26, 27%), IVA (53, 56%), and IVB (1, 1%). Of the 95 patients, 85 (89%) patients had no or ipsilateral-only nodal involvement, and 59 (62%) received bilateral neck RT and 26 (27%) received unilateral neck RT. Ten (11%) patients had bilateral neck disease (pN2c) and all of them received bilateral neck RT. Prescribed radiation doses were 60-70 Gy to the postoperative bed and involved neck and 52-54 Gy to the elective neck in 30-33 fractions using simultaneous integrated boost. Chemotherapy was delivered to 41 (44%) patients. Neck dissection was performed in 90 (95%) patients, 55 (58%) in the ipsilateral neck and 35 (37%) in the bilateral neck. Survival outcomes were compared using Kaplan-Meier method with log-rank test.

Results: The median age was 55 (22-87). The unilateral RT group had less advanced pT ($p<0.001$), pN ($p=0.04$), and group stage ($p<0.001$) compared to the bilateral RT group. More bilateral neck dissections were performed in the bilateral RT group (45% vs. 15%, $p=0.014$). The median follow-up for living patients was 2.9 (0.5-16.9) years. Comparing the unilateral and bilateral RT groups, there was no difference local recurrence-free survival (2-year: 84% vs. 89%, $p=0.36$), distant metastasis-free survival (2-year: 66% vs. 88% $p=0.12$), or overall survival (2-year: 60% vs. 76%, $p=0.80$). The unilateral RT group had worse regional recurrence-free survival compared to the bilateral RT group (2-year: 62% vs. 89%, $p=0.001$). There were more failures in the contralateral neck in the unilateral RT group (23% vs. 5.7%, $p=0.01$). Of the 11 regional tumor recurrences that occurred in the unilateral RT group, 5 (45%) occurred in the contralateral neck and 1 (9%) occurred in the bilateral neck.

Conclusion: Omission of adjuvant elective neck RT to the contralateral neck in unselected patients with squamous cell carcinoma of the oral tongue was associated with a high risk of tumor recurrence in the contralateral neck.

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Human Papillomavirus in Sinonasal Squamous Cell Carcinoma

J.R. Oliver,[1] S.M. Lieberman,[2] M.M. Tam,[3] C.Z. Liu,[4] Z. Li,[5] K.S. Hu,[3] L.G. Morris,[6] and B. Givi[7]; *[1]NYU School of Medicine, New York, NY, [2]NYU Langone Health, Department of Otolaryngology-Head and Neck Surgery, New York, NY, [3]NYU Langone Health, Department of Radiation Oncology, New York, NY, [4]NYU Langone Health, Department of Pathology, New York, NY, [5]Department of Medical Oncology, NYU Langone Health, New York, NY, [6]Memorial Sloan Kettering Cancer Center, Department of Head and Neck Surgery, New York, NY, [7]Department of Otolaryngology, NYU Langone Health, New York, NY*

Purpose/Objective(s): The role of Human Papillomavirus (HPV) in oropharyngeal cancers and its impact on survival has been well described. Whether HPV association is influential in other sub-sites of head and neck is not as well studied at this time. We investigated the patterns of HPV testing and its association with survival in sinonasal squamous cell carcinoma (SNSCC) utilizing the National Cancer Database (NCDB).

Materials/Methods: We selected all SNSCC cases between 2010-2016. HPV testing rates, clinicodemographic factors, treatments, and survival were analyzed. Multivariable regression was used to identify factors associated with HPV-positive tumors and overall survival.

Results: We identified 6010 SNSCC cases during the study period. Only 1274 (21.7%) cases were tested for high-risk HPV. Tested patients were slightly younger (median age 64 vs 66, $p < 0.001$) and less likely to have comorbidities (307, 22.9%, vs 1155, 25.6%, $p = 0.045$). No other clinicopathologic differences were identified. The majority of the tested cohort were male (818, 64.2%) and white (978, 76.8%). Approximately half were attributed to the nasal cavity (616, 48.4%) and paranasal sinuses (657, 51.6%). The majority were advanced stage (stage III-IV, 658, 63.4%). HPV-positive tumors comprised 28.1% (366) of the tested population. Among 34 hospitals that tested ≥60% of non-oropharyngeal squamous cell carcinomas for HPV, a similar proportion HPV-positive SNSCC was observed (27.9%, 19/68). Surgery, (305, 25.1%); followed by surgery and adjuvant radiotherapy (303, 24.9%) were the most common treatments. A minority (246, 20.3%) underwent surgery and chemoradiotherapy. In multivariable regression, younger age (<60, OR = 1.81, 95% CI = 1.39-2.36, $p < 0.001$) and nasal cavity location (compared to paranasal sinuses, OR = 2.00, 95% CI = 1.49-2.70, $p < 0.001$) were associated with higher rates of HPV-positive tumors. Five-year overall survival was 55.6% (95% CI = 50.9%-60.7%). In multivariable regression, HPV-positive tumors were associated with significantly improved overall survival (HR = 0.70, 95% CI = 0.50-0.98, $p = 0.04$); while older age, male sex, paranasal sinus location, advanced stage, and lymphovascular invasion were associated with worse outcomes.

Conclusion: Currently only a minority of SNSCCs are tested for HPV. These data suggest that a sizable minority of SNSCC may be HPV related; and that HPV-positive tumors are associated with improved survival. Routine HPV testing, as currently recommended for oropharyngeal tumors, might be warranted in SNSCC as well. The impact of HPV association on survival of SNSCC needs further investigation.

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Hafnium oxide nanoparticles (NBTXR3) activated by radiotherapy for the treatment of frail and/or elderly patients with locally advanced HNSCC: a phase I/II study

C. Le Tourneau,[1] V. Calugaru,[1] E. Borcoman,[1] V. Moreno,[2] E. Calvo,[3] X. Liem,[4] S. Salas,[5] B. Doger,[3] T. Jouffroy,[1] X. Mirabel,[4] J. Rodriguez,[1] A. Chilles,[1] K. Bernois,[6] M. De Rink,[6] E. Baskin-Bey,[6] N. Fakhry,[7] S. Wong Hee Kam,[8] and C. Hoffmann[1]; *[1]Institut Curie, Paris, France, [2]Hospital Fundación Jimenez Diaz, Madrid, Spain, [3]START Madrid, Madrid, Spain, [4]Centre Oscar Lambret, Lille, France, [5]Assistance Publique Hôpitaux de Marseille, Timone Hospital, Marseille, France, [6]Nanobiotix, Paris, France, [7]Hôpital Timone, Marseille, France, [8]Hôpital Timone, APHM, Marseille, France*

Purpose/Objective(s): Elderly and/or frail patients (pts) with head and neck squamous cell carcinoma (HSNCC) remain a challenging to manage and neglected population regarding clinical trials and data generation to support treatment choices. Despite representing 20% of the HNSCC population no consensus exists on what is the optimal treatment for these pts with locally advanced (LA) disease, vulnerable to treatment-induced toxicities with the current standard of care. New approaches are needed to improve clinical outcomes without adding toxicity. NBTXR3 hafnium oxide nanoparticles injected intratumorally may represent such an option. Otherwise inert; this first-in-class radioenhancer, augments the radiotherapy (RT) dose within tumor cells when activated by RT, increasing tumor cell death compared to RT alone. The results presented here demonstrate the feasibility and safety of NBTXR3 activated by RT in elderly/frail patients, a population with few therapeutic options.

Materials/Methods: Elderly/frail pts received a single intratumoral injection of NBTXR3 and intensity modulated radiation therapy (IMRT; 70 Gy/35 fractions/7 weeks). The study was a 3 + 3 dose escalation to test the NBTXR3 dose equivalent to 5, 10, 15, and 22% of baseline theoretical tumor volume, followed by a dose expansion. Primary endpoints include Recommended Phase 2 Dose (RP2D) determination and early dose limiting toxicities (DLT). NBTXR3 presence in surrounding healthy tissues and anti-tumor activity (RECIST 1.1) were also evaluated.

Results: Enrollment was completed at all dose levels: 5% (3 pts), 10% (3 pts), 15% (5 pts), and 22% (8 pts). No early DLT or SAE related to NBTXR3 or injection were observed. One G1 AE (asthenia; 22%) related

to NBTXR3 and four AEs (G2 oral pain, G1 tumor hemorrhage, asthenia, and injection site hemorrhage) related to injection were observed. RT-related toxicity was as expected with IMRT. The RP2D was determined to be 22%. CT-scan assessment demonstrated localization of NBTXR3 intratumorally without presence in surrounding healthy tissues. At a median follow-up of 231 days, 9/13 (2 unconfirmed) evaluable pts receiving doses ≥10%, achieved a complete response of the treated tumors. The final dose escalation safety and efficacy results will be presented herein.

Conclusion: NBTXR3 was well tolerated at all tested doses and demonstrated preliminary anti-tumor activity. A dose expansion phase at the RP2D is ongoing. These results highlight the potential of NBTXR3 as a novel treatment option for elderly/frail pts with LA HNSCC and address an unmet medical need.

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Definitive Radiotherapy for Elderly Patients with Locally Advanced Squamous Cell Head and Neck Cancer (LAHNSCC): A Single-Institution Experience

T. Smile,[1] C.A. Reddy,[1] B. Matia,[2] C.W. Fleming,[1] C. Domb,[3] J.L. Geiger,[4] N.P. Joshi,[1] N.M. Woody,[1] B.B. Burkey,[5] J. Ku,[5] B. Prendes,[5] E. Lamarre,[5] J. Scharpf,[5] S. Koyfman,[1] D. Chute,[2] and D.J. Adelstein[4]; *[1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Department of Radiation Oncology, Cleveland, OH, [4]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [5]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): The elderly comprise an increasing percentage of patients with locally-advanced head and neck squamous cell carcinoma (LAHNSCC). In these patients, definitive treatment is often compromised due to concerns about medical comorbidities, performance status and the anticipated tolerance of treatment toxicities. We reviewed our experience with definitive management in our elderly (age ≥70) patients with LAHNSCC.

Materials/Methods: From our IRB-approved registry, all patients age ≥ 70 years with AJCC 7th (and earlier) edition stage III-IV, M0 LAHNSCC who were treated with definitive radiotherapy (RT) with or without systemic therapy between 1993 and 2019 were identified. A similar cohort of patients ages 60-69 was also identified for comparison. Chemotherapy added to RT was indicated for T3-4 or N2-3 per AJCC 7th edition or if extracapsular extension (ECE) was found on surgical pathology. Univariate (UVA) analyses were performed to assess association with pretreatment Charlson comorbidity index, Karnofsky Performance Status (KPS), chemotherapy delivered, and RT dose. Cumulative incidence of recurrence was defined using Fine and Gray regression with death as a competing event. Overall (OS) and progression-free survival (PFS) were analyzed using the Kaplan-Meier method.

Results: There were 126 elderly patients identified with a median age of 73.4 years, and median follow up of 36.3 months. There were 224 patients age 60-69 years identified, with a median age of 64 years and a median follow up of 47.4 months. The mean RT dose in 2 Gy-equivalent fractions was 69.3 Gy for the elderly and 69.5 Gy for patients age 60-69. Tumor primary site was hypopharynx, larynx and oropharynx in 10%, 33%, and 57% of the elderly patients, and 1%, 9% and 90% in those age 60-69. HPV status was positive in 69 (55 %) elderly patients and in 190(85%) patients ages 60-69. Systemic therapy was indicated in 113 (90%) patients from the elderly cohort and in 199 (89%) patients age 60-69 years. 87 (69%) of the elderly were given systemic therapy; 66 of these (76%) were given platinum-based chemotherapy and 21 (24%) received Cetuximab. 195 (87%) of the 60-69 year olds were given systemic therapy; 171 of these (88%) received platinum-based chemotherapy and 24 (12%) received Cetuximab. The 2-year cumulative incidences of recurrence for patients ages 60-69, 70-79 and ≥80 were 13.9%, 24.9% and 30.3%, respectively (p=0.0133). Median PFS and OS for the elderly cohort were 58.3 and 67.5 months, respectively. Charlson comorbidity index score 2-3 vs. 0-1 (HR 2.08, 95% CI 1.04-4.18; p=0.038) was predictive for recurrence in the elderly patients.

Conclusion: Compared to younger patients, elderly patients received less aggressive treatment and experienced higher recurrence rates. Overall, favorable results were still likely after definitive RT in elderly patients. Age alone should not preclude curative-intent management.

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Radical Reduction of Radiation Therapy Dose Prescription for Elective Treatment Areas in Human Papillomavirus (HPV) - Associated Oropharyngeal Carcinoma (OPC)

C.J. Tsai,[1] S. McBride,[1] N. Riaz,[2] J.J. Kang,[2] Y. Yu,[2] L. Chen,[2] D. Gelblum,[2] R.J. Wong,[3] J.O. Boyle,[3] L. Dunn,[4] E. Sherman,[5] D.G. Pfister,[6] and N. Lee[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, [4]Memorial Sloan Kettering Cancer Center, Department of Medical Oncology, New York, NY, [5]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [6]Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, NY*

Purpose/Objective(s): In March 2017, we implemented a new radiation guideline to allow substantial dose reduction to elective treatment regions in patients with HPV-associated OPC receiving definitive chemoradiation. We then prospectively followed the patients for treatment outcomes.

Materials/Methods: We applied routine de-escalated radiation dose to most elective regions to 30 Gy in HPV-associated OPC patients treated with concomitant chemotherapy, mostly high-dose cisplatin (excluding cetuximab), while continued treating grossly visible disease to 70 Gy. Patients were treated to 30 Gy for the elective treatment regions (15 fractions of 2 Gy), followed by cone-down of 40 Gy to a total of 70 Gy to all sites of gross disease. Some patients also received an intermediate dose of 50 Gy in a small field immediately adjacent to the 70 Gy region.

Results: From March 2017 to December 2018, a total of 199 consecutive HPV-positive OPC patients received concurrent chemoradiation with 30Gy elective nodal irradiation. The median age was 60 years and 47% of them were never smokers. Seventy percent of the patients had T1-T2 primary disease, 25% T3-T4, and 5% unknown primary. Sixteen percent of the patients had bilateral nodal disease. Eighty percent of them received high-dose cisplatin. During a median follow up of 13 months, there was no regional recurrence within the 30Gy elective nodal region. No patient had local recurrence at the primary disease site and 2 patients (1%) developed regional nodal recurrence within the high-dose 70 Gy fields at 9 month and 16 months post therapy. Both patients received salvage neck dissection and had no evidence of disease at last follow up. Five patients (2.5%) had distant metastases but remained alive, and 6 patients (3%) died from causes unrelated to their cancer. When restricting to a subset of the cohort treated through March 2018 with a longer median follow up of 18 months, there remained the same 2 (2%) regional failure in the high-dose fields and no failure within 30 Gy elective regions.

Conclusion: This early report indicates uncompromised disease control by adapting radical reduction of radiotherapy dose to 30 Gy for the elective treatment areas in HPV-associated OPC patients receiving definitive chemoradiation. Longer follow up is needed to affirm comparable outcomes compared to standard radiotherapy dosing regimen.

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Patterns of Care and Outcomes in Verrucous Carcinoma of the Larynx Treated in the Modern Era

S. Abel,[1] R.E. Wegner,[1] E. Interval,[2] and A. Colonias[1]; [1]*Department of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA,* [2]*Allegheny Health Network, Pittsburgh, PA*

Purpose/Objective(s): Verrucous carcinoma is an uncommon, relatively indolent form of laryngeal squamous cell carcinoma. Historically, surgery has been the favored approach, due to concerns of potential anaplastic transformation and secondary metastasis theoretically associated with radiotherapy. To examine national trends in the treatment of verrucous carcinoma of the larynx, we utilized the National Cancer Database (NCDB).

Materials/Methods: We queried the NCDB from 2004-2015 for patients with laryngeal verrucous carcinoma and recorded treatment modality employed (surgery vs. radiation). Multivariable logistic regression was used to identify predictors of radiation use. Cox regression was used to calculate hazard ratios for survival. A propensity score was calculated and a matched Kaplan Meier analysis compared surgical treatment to definitive radiation.

Results: We identified 732 patients with laryngeal verrucous carcinoma. The majority were cTis-T2 (87%) N0 (96%). Surgery was used in 47% of patients while 17% received radiation. We identified 286 and 110 Tis-T2N0 patients treated surgically and with definitive radiation, respectively. Predictors of radiation were treatment at a community center, no insurance, and higher T stage. Cox regression identified increased age, higher comorbidity score, and governmental insurance as predictive of worse survival. Propensity matching revealed worse survival with definitive radiation, median survival of 98 months compared to 143 months ($p=0.02$). When including only T1-2 lesions, the trend towards increased survival with surgery [98 months vs. 135 months ($p=0.08$)] persisted.

Conclusion: Surgery remains the primary treatment modality for patients with verrucous carcinoma of the larynx, with a trend towards a modest survival benefit in invasive lesions.

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Reirradiation with SBRT, IMRT and Proton Therapy for Recurrent Oropharynx Squamous Cell Carcinoma: Efficacy and Toxicity Outcomes

J. Phan,[1] A. Bagley,[2] G. Adam,[2] S.J. Frank,[3] G.B. Gunn,[2] D.I. Rosenthal,[4] J. Reddy,[2] C.D. Fuller,[3] W.H. Morrison,[1] S.J. Shah,[5] A.C. Moreno,[1] R. Ferrarotto,[3] E.M. Sturgis,[6] and N.D. Gross[7]; [1]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX,* [2]*MD Anderson, Houston, TX,* [3]*University of Texas MD Anderson Cancer Center, Houston, TX,* [4]*The University of Texas MD Anderson Cancer Center Institution *, Houston, TX,* [5]*Dept. of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Sugar Land, TX,* [6]*MD Anderson Cancer Center, Houston, TX,* [7]*Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): The purpose of this study was to analyze locoregional control and survival in patients with recurrent oropharyngeal cancerfollowing reirradiation with intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and proton beam therapy (PBT).

Materials/Methods: We performed a retrospective review of oropharyngeal cancer patients who developed oropharyngeal recurrences and were reirradiated at our institution from 1999 to 2017. Locoregional control (LRC), progression-free survival (PFS), distant-metastasis free survival (DMFS), and overall survival (OS) were calculated from the completion of reirradiation by the Kaplan-Meier method. Statistical analysis was performed with JMP Pro 14.

Results: We analyzed 41 patients with median age of 63 years (range 27−81 years) who received reirradiation for oropharyngeal cancer. The median radiation dose of the initial therapy was 70 Gy (45−75 Gy). Recurrence types were recurrent primary tumors (85%) and second primary tumors (15%). The initial disease site was base of tongue in 19 patients (46%), tonsil in 18 patients (44%), soft palate in 3 patients (7%), and pharyngeal wall in 1 patient (2%). 25 patients (61%) were reirradiated with IMRT, 6 with SBRT (15%), and 10 with PBT (24%). The median reirradiation doses were 66 Gy for IMRT and PBT (34−70 Gy) and 45 Gy (45−45 Gy) for SBRT. The median reirradiation target volumes were 67 cm^3 (20−271 cm^3) for IMRT, 47 cm^3 (18−191 cm^3) for PBT, and 17 cm^3 (8−42 cm^3) for SBRT. Chemotherapy was given to 30 patients (73%). Concurrent chemotherapy was platinum-based in 20 patients (48%), cetuximab in 8 patients (20%), and docetaxel in 1 patient (2%). There were 8 local failures in the reirradiated bed (36%), 3 nodal failures in the neck (14%), 2 failures in non-targeted mucosa $>$ 2 cm from the high-dose volume (9%), and 9 distant failures (41%). With a median follow-up of 22 months (0−168 months), the 1-year local control rate was 88%, regional control rate was 88%, and overall LRC rate was 77%. The 1-year PFS was 50%, DMFS 51%, and OS 55%. Median PFS and OS were 13 and 23 months, respectively. Feeding tubes were placed before reirradiation in 14 patients (34%) and during or after reirradiation in 14 patients (34%). Grade 3+ late toxicity occurred in 15 patients (37%) (48% of IMRT, 16% of SBRT, and 20% of PBT).a

Conclusion: Reirradiation of oropharyngeal cancer with highly conformal techniques provides improved disease control in selected patients, but locoregional failures and late toxicity remain significant challenges. The decision to recommend reirradiation must be individualized for each patient, balancing the benefit of locoregional control with potential toxicities of retreatment.

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Does Accelerated Fractionation Improve Radiation Results in Patients with Cancer of Nasopharynx? Results of 10-years Follow-up

A. Wygoda,[1] J.J. Mrochem-Kwarciak,[2] T. Rutkowski,[1] A. Mazurek,[3] M. Kentnowski,[1] D. Księżniak-Baran,[1] A. Brewczyński,[1] A. Bieleń,[1] B. Pilecki,[1] K. Dębiec,[1] D. Leś,[1] and K.A. Skladowski[1]; *[1]I Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [2]The Analytics and Clinical Biochemistry Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [3]Center for Translational Research and Molecular Biology of Cancer, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland*

Purpose/Objective(s): The treatment of choice in patients with cancer of nasopharynx (NPC) is conventionally fractionated radiotherapy (CFRT) combined with chemotherapy (CHT), especially given in simultaneous matter. Results of many trials conducted in patients (pts) with head and neck cancer show that accelerated radiotherapy (AFRT) improves survival parameters. The objective of this presentation is to report survival outcomes and treatment toxicity in patients with NPC treated with AFRT compared with CFRT as part of phase II clinical trial.

Materials/Methods: 78 pts (50 men and 28 women) with moderately advanced and advanced NPC treated with AFRT (39 pts) and CFRT (39 pts) were evaluated. Median age was similar in both arms (AFRT-51, CFRT-49). AFRT was realized with everyday irradiation (including weekends) to the total dose 68,0Gy-72,0Gy (median radiation treatment time was 40 days). In CFRT arm total radiation dose was 70,0Gy given in median time equal to 50 days. In 40 pts (20 pts in each arm) CHT based on cisplatin was combined simultaneously with RT. Induction and adjuvant CHT with cisplatin and 5-fluorouracil was given in 37 and 15 pts respectively in both arms depending on tumor advance and differentiation. In all pts acute mucosal radiation reactions were evaluated once a week and late reactions were assessed every 6 months during follow-up.

Results: 10-years survival parameters (AFRT vs CFRT) showed similar results in both arms - for local control, nodal control, disease free survival and overall survival were: 85% vs 88% (p=0,81), 83% vs 77% (p=0,64), 66% vs 68% (p=0,97) and 68% vs 65% (p=0,55) respectively. All 78 patients realized radiation treatment schedule although in 5 patients (2 treated with AFRT and 3 treated with CFRT) radiotherapy had to be temporarily stopped because of intensity of acute mucositis (duration of treatment gap was 8-23 days). Serious late toxicities were not observed during follow-up.

Conclusion: Our observations show that AFRT in patients with NPC give no benefit compared with CFRT. Treatment tolerance for both schedules was similar and acceptable.

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In Patients with Lateralized Oral Cavity and Oropharynx Squamous Cell Carcinoma with N2b Disease, Is It Safe to Omit Radiotherapy to the contralateral clinical N0 Neck?

J.D. Gruhl,[1] A.M. Torgeson,[2] K. McComas,[3] M. Monroe,[2] and Y.J. Hitchcock[4]; *[1]Huntsman Cancer Institute, Salt Lake City, UT, [2]Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT, [3]University of Utah College of Medicine, Salt Lake City, UT, [4]University of Utah Huntsman Cancer Institute, Salt Lake City, UT*

Purpose/Objective(s): In patients with lateralized squamous cell carcinomas (SCCs) of the head and neck (H&N) with positive ipsilateral node(s), guidelines are unclear regarding whether radiotherapy (RT) should also be given to the contralateral, node-negative neck.

Materials/Methods: Patients with SCC of the H&N (oral cavity or oropharynx) with lateralized primary tumors and ≥1 positive ipsilateral nodes (N1, N2a, N2b), treated at the Huntsman Cancer Institute from 2006 – 2017, were analyzed. Treatment was with radiotherapy (RT) or chemoradiotherapy (CRT) to the primary and ipsilateral or bilateral neck. The primary endpoint was failure rate in the contralateral neck.

Results: A total of 71 patients were included for analysis. Most patients had tumors originating in the tonsil (63), followed by the buccal mucosa (7) and gingiva (1). 51 patients had N2b disease (AJCC 7th ed.); 20 had N1 or N2a disease. 30 (42%) patients received RT to the primary site and ipsilateral neck; 41 (58%) patients received RT to the primary site and bilateral neck. 10 (14%) patients experienced a cancer recurrence: 3 distant-only, 1 distant and primary, 1 ipsilateral neck, 2 primary and bilateral neck, and 3 contralateral/midline neck only. Of the 3 contralateral/midline failures, all 3 had N2b disease and were treated with CRT to the primary and ipsilateral neck alone. Of the 3 contralateral/midline neck failures, 2 were advanced buccal mucosa primaries with ≥4 positive ipsilateral nodes involving multiple neck levels, with ENE positivity; the 2 cases were staged as pT1N2bM0, and pT2N2bM0, respectively. The third contralateral failure was an HPV-negative, cT2N2b tonsil primary, with 2 positive ipsilateral level II nodes. In the 51 patients with initial N2b disease, 37 received primary and bilateral RT or CRT, versus 14 who received RT or CRT to the primary and ipsilateral neck alone. In the 20 patients with initial N1 or N2a disease, 16 received RT or CRT to the primary and ipsilateral neck alone, versus 4 who received RT or CRT to the primary and bilateral neck; there were no contralateral neck failures regardless of whether the contralateral neck was treated. Overall, the contralateral neck failure rate was 10% if treated to the primary and ipsilateral neck alone in patients with T3-4 and/or ≥4 positive ipsilateral nodes, compared to 0% if treated to the primary and bilateral neck.

Conclusion: Our data demonstrated that it was safe to treat lateralized SCC of the H&N with ≥1 positive ipsilateral nodes (N1, N2a, N2b) with ipsilateral RT or CRT. The risk of contralateral/midline nodal failure increased with advanced T stage and/or a high number of involved LNs (≥ 4) involving multiple nodal levels, ENE (+), and possibly P16 (-) in oropharyngeal cancer. Patients with lateralized H&N primaries with a single positive ipsilateral node (N1 or N2a) can likely be safely treated to the primary and ipsilateral neck alone.

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An Update on Trends and Disparities in Utilization of Total Laryngectomy: a Population-Based Analysis

D. Jacobs,[1] H.S.M. Park,[2] M.R. Young,[2] C. Breen,[1] R. Rahmati,[3] S. Mehra,[3] and B.L. Judson[3]; *[1]Yale School of Medicine, New Haven, CT, [2]Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT, [3]Department of Surgery, Section of Otolaryngology, Yale School of Medicine, New Haven, CT*

Purpose/Objective(s): Total laryngectomy (TL) is a definitive surgical approach for larynx cancer, but may not be performed as often in the upfront setting after publication of the VA Larynx Trial in 1991. The aim of the study is to evaluate trends in the upfront utilization of TL as well as patient and oncologic factors associated with TL utilization. We hypothesized that laryngectomy rates would continue to decline with the most recent population data and that racial disparities would narrow.

Materials/Methods: The Surveillance, Epidemiology, and End Results Program (SEER) consisting of 13 registries from 1992 through 2015 was queried to analyze the trends in TL receipt. Total laryngectomy was grouped with pharyngolaryngectomy. 2-year averages were used and rate ratios were calculated. Binary logistic regression was used to adjust for temporal, patient, tumor, and clinical features to calculate odds ratios (OR) for receiving TL. 95% confidence intervals (CI) are reported.

Results: 30,851 patients with known laryngeal cancer treatment were included, among whom 4,292 received upfront TL (13.9%). Upfront TL was used in 22.1% (CI: 20.2, 24.2) of cases in 1992-1993, which decreased to 10.5% (CI: 9.1, 11.9) of cases in 2014-2015. The trend was similar in glottic cancer with a decrease from 13.6% (CI: 11.7, 15.8) to 7.4% (CI: 6.0, 9.2) and supraglottic cancer with a decrease from 28.7% (CI: 24.9, 33.1) to 10.8 % (CI: 8.5, 13.5). Rates of TL have plateaued since 2004 and are higher for patients with higher-stage disease. Given recent evidence of racial disparities in laryngectomy rates, we evaluated how total laryngectomy rates differed by race. Since 1992, black patients have consistently been more likely to receive upfront TL than white patients with an average rate ratio of 2.16 (CI: 2.00, 2.33), which remained similar in 2014-2015 at 2.07 (CI: 1.47, 2.86). On binary logistic regression, black patients remained more likely to receive upfront TL than white patients for glottic cancer (OR 1.66; CI: 1.18, 2,32) but not supraglottic cancer (OR 1.28; CI: 0.92, 1.78). For both glottic and supraglottic cancers, variables associated with upfront TL included age (p-values <0.001 and 0.007, respectively) and tumor stage (p-values both <0.001). Tumor grade showed a significant association with upfront TL only in glottic cancer (p-value 0.012) but not for supraglottic cancer (p-value 0.62). Sex was not associated with use of TL in either glottic (p-value 0.55) or supraglottic cancer (p-value 0.66).

Conclusion: Upfront total laryngectomy has declined in use since at least 1992. Nationally, racial disparities may continue to exist in the use of TL in glottic cancer but not supraglottic cancer even after adjusting for temporal, patient, tumor, and clinical factors.

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Survival and Quality of Life Analysis in a Randomized Deintensification Trial for Locally Advanced HPV Positive Oropharynx Cancer Patients

M. Posner,[1] D.K. Misiukiewicz,[2] M. Hwang,[3] V. Gupta,[4] B. Miles,[5] R.L. Bakst,[4] E. Genden,[5] I. Selkridge,[3] J.T. Surgeon,[3] H. Rainey,[3] N. Camille,[3] E. Roy,[3] D. Zhang,[3] Y. Fei,[3] R. Jia,[3] E. Moshier,[3] P. Som,[3] and M. Bonomi[6]; *[1]Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY, [2]Icahn School of Medicine at mount Sinai, New York, NJ, [3]Icahn School of Medicine at Mount Sinai, New York, NY, [4]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [5]Department of Otolaryngology — Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, [6]Ohio State University, Columbus, OH*

Purpose/Objective(s): Human Papillomavirus-related oropharyngeal carcinoma (HPVOPC) is highly responsive to therapy and has significantly better long term survival compared to environmentally-related oropharynx cancer. Patients with HPVOPC are often over treated with standard dose chemoradiotherapy (sdCRT) and endure unnecessary long term consequences and reduced quality of life (QoL). We hypothesized that reduced dose chemoradiotherapy (rdCRT) after IC would be equally effective to sdCRT and QoL in patients with rdCRT vs sdCRT would be better.

Materials/Methods: Patients with untreated, p16+, locally advanced HPVOPC received IC with 3 cycles of docetaxel, cisplatin, and 5-fluorouracil (TPF) and then patients with PCR positive High Risk (HR) HPV were randomized (1:2) to sdCRT or rdCRT with weekly carboplatin. Patients were followed for Progression Free Survival (PFS) and Overall Survival (OS). The MD Anderson Dysphagia Inventory and Symptom Inventory (MDADI, MDASI), Xerostomia Questionnaire (XQ), European Organization for Research and Treatment of Cancer Questionnaire (EORTC) with head and neck module (EORTC HN) were administered for QOL assessment.

Results: 20 patients were randomized to rdCRT (12 subjects) or sdCRT (8 subjects); 16 were HPV16+ and 4 (20%) were other HR variants; 70% had high risk features (T4, N2c, or N3). At 68 months median follow up (range 53-81), PFS and OS are 87.5% and 83.3% for sdCRT and rdCRT, respectively (log-rank test p=0.85). There are 3 failures, all local and all within 4 months of treatment completion. There have been no further events. Two (50%) patients with HR HPV variants relapsed vs 1 (13%) with HPV16. There was no difference in baseline QoL between groups. QOL remained stable through induction TPF among all patients. At 3-6 month post CRT follow up, patients receiving rdCRT had significantly less decrement in QoL in EORTC global health score and functional scale (1.85 vs -31.67, P=0.0363; 3.51 vs -25.8, P=0.003), MDADI (-10.44 vs -38, P=0.0307), XQ (2.78 v 5.8, P=0.047), EORTC HN (0.45 vs 23.37, P=0.029), and MDASI symptom interference (-0.22 vs 4.07, P=0.014) then sdCRT patients and significant reductions compared to post TPF. Differences in QoL disappeared by 12 month follow up.

Conclusion: rdCRT after TPF in locally advanced HPVOPC is feasible and resulted in equivalent survival and significantly less acute decrement in QoL then sdCRT. Non-HPV-16 variants may have a worse prognosis. Longer follow-up is needed to assess long term morbidity. Although this is a small study the QOL and survival data support the use of Induction therapy with rdCRT in locally advanced high risk HPVOPC and reflect results seen in Phase 2 trials. Larger randomized trials in this high risk HPVOPC are indicated.

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Lymph node yield and survival in node-negative oral cavity cancer

J. Zenga,[1] V. Divi,[2] M. Stadler,[1] B. Massey,[1] B. Campbell,[1] M.E. Shukla,[1] M. Awan,[1] C.J. Schultz,[1] A. Shreenivas,[1] S. Wong,[1] R.S. Jackson,[3] and P. Pipkorn[3]; *[1]Medical College of Wisconsin, Milwaukee, WI, [2]Department of Otolaryngology—Head and Neck Surgery, Stanford University, Stanford, CA, [3]Washington University School of Medicine, Department of Otolaryngology, St. Louis, MO*

Purpose/Objective(s): To determine the effects of nodal yield on survival in early stage oral cavity squamous cell carcinoma (OCSCC) in the context of primary tumor depth of invasion (DOI).

Materials/Methods: Patients with early-stage clinically node-negative OCSCC who underwent upfront surgery at the primary site were identified using the National Cancer Database between 2004 and 2015.

Results: There were 3,384 patients with <4mm DOI and 1,387 patients with ≥4mm DOI identified. Management of the neck included observation (40%), END with <18 nodes harvested ± postoperative radiation (ND<18, 16%), and END with ≥18 nodes harvest ± postoperative radiation (ND≥18, 44%). When adjusted for relevant covariates, ND≥18 demonstrated statistically significant improvements in overall survival for both DOI <4mm and ≥4mm (DOI<4mm: HR 0.67, 95%CI 0.54-0.85; DOI≥4mm: HR 0.47, 95%CI 0.34-0.64). However, ND<18 showed no significant difference from observation of the neck regardless of DOI (DOI<4mm: HR 0.82, 95%CI 0.63-1.07; DOI≥4mm: HR 0.72, 95%CI 0.51-1.03). Of patients undergoing END, the most significant factors associated with obtaining a nodal yield of 18 or more were age less than 40 years (HR 2.58, 95%CI 1.84-3.63) and treatment at an academic facility (HR 2.47, 95%CI 2.06-2.96).

Conclusion: END with 18 or more nodes is associated with improved survival outcomes in patients with early stage OCSCC regardless of DOI. END with less than 18 nodes, however, does not appear significantly different than observation of the neck alone. Achieving a lymph node yield of 18 or more is multifactorial and includes both patient and provider factors.

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Time to Treatment Initiation is Associated with Clinical-to-Pathologic Upstaging in Primary Total Laryngectomy

M.Y. Lee,[1] M. Belfiglio,[1] C.W. Fleming,[2] B. Matia,[3] S. Koyfman,[2] N.P. Joshi,[2] B.B. Burkey,[4] E. Lamarre,[4] B. Prendes,[4] R.R. Lorenz,[4] N.M. Woody,[2] D.J. Adelstein,[5] J.L. Geiger,[5] D. Chute,[3] and J. Ku[4]; *[1]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH, [5]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Increased time to treatment initiation (TTI; time from diagnosis to surgery) in head and neck cancer has been associated with worse oncologic and functional outcomes. One proposed mechanism is clinical-to-pathologic upstaging as a result of tumor progression. We hypothesize that increased TTI is associated with clinical-to-pathologic upstaging in patients receiving primary total laryngectomy (TL).

Materials/Methods: We performed an IRB approved retrospective analysis of patients who underwent primary TL for larynx cancer between 1/1/01-8/31/18 at a single tertiary care center. Descriptive statistics were used for demographic data. Factors associated with up/down staging and survival were analyzed using binary or multinomial logistic regression and Cox proportional hazards models, respectively. Optimal cutoffs were analyzed by receiver operating characteristic (ROC).

Results: In the 134 patients included, median follow up was 24 months (range 2.5-162.5), mean age was 63 (SD 10), and 105 (78%) were male. Pathologic disease stages were T4 (n=94, 70%), T3 (n=37, 27.6%), and T2 (n=3, 2.2%); and N0 (n=55, 41%), N1 (n=12, 9%), N2, (n=58, 43.3%), N3 (n=9, 6.6%). Patients received adjuvant CRT (n=32, 24%), XRT (n=67, 50%), chemotherapy only (n=1, 1%), or none (n=34, 25%). Overall (OS) and disease-free survival (DFS) were 85.4% and 74.9% at 1 year and 56.3% and 47.5% at 5 years. 20 (15%) patients were T-upstaged (Tup) (18 cT3 to pT4; 1 cT2 to pT3; 1 cT2 to pT4) and 29 (22%) patients were N-upstaged (Nup) (12 cN1 to pN2, 6 cN0 to pN2, 5 cN0 to pN1, 5 cN2 to pN3, 2 cN0 to pN3). 12 (9%) patients were T-downstaged (Tdown) (10 cT4 to pT3, 1 cT4 to pT2, 1 cT3 to pT2) and 13 (10%) patients were N-downstaged (Ndown) (9 cN2 to pN0, 2 cN1 to pN0, 1 cN2 to pN1, 1 cN3 to pN2). Patients Tup were more likely Nup ($p=0.04$) and vice versa ($p=0.04$). Median TTI was 28 days (IQR 19-45). On univariable analysis, increased TTI was associated with OR of 1.02/day for Tup ($p=0.02$), but was not associated with Nup (OR=1, $p=0.59$). No other factors were associated with T/Nup and TTI was not associated with T/Ndown. On multivariable analysis, TTI remained a significant predictor of Tup (OR=1.02, $p=0.02$). Multivariable analysis showed that Tdown was associated with better DFS (HR=0.29, $p=0.05$) while Tup trended towards worse DFS (HR=2.46, P=0.08). TTI was not associated with worse OS/DFS. ROC analysis identified >43 days as a cutoff for predicting Tup. On uni and multivariable analysis, TTI >43 days was associated with Tup ($p<0.01$)

Conclusion: In our study T (15%) and N (22%) upstaging were common. Median TTI was 1 month. Increased TTI was associated with risk of Tup (OR=1.02) and Tup trended towards worse DFS (HR=2.46). Since TTI is a modifiable risk factor, treatment delays should be minimized with a goal of ≤43 days.

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Patterns of care and outcomes of early-stage sarcomatoid squamous cell carcinomas of the larynx

Z.D. Horne, S. Abel, R.E. Wegner, and A. Colonias; *Department of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA*

Purpose/Objective(s): Sarcomatoid squamous cell carcinoma of the larynx is a rare entity comprising <1% of diagnoses. Case reports/series report a more aggressive disease course and call for more aggressive therapy, though data in this realm are lacking.

Materials/Methods: We queried the National Cancer Database for patients with cT1-2N0M0 squamous cell and sarcomatoid carcinomas of the glottis larynx. Utilization of treatment modalities and baseline characteristics were compared with Chi-squared and independent t-test. A propensity-matched model was built for comparison of survival, analyzed in a Cox multivariable model.

Results: A total of 38, 028 patients were identified. Patients with sarcomatoid-SCC comprised 1.3% (485) of patients. There were no differences in percentage of patients presenting with cT1 vs cT2 disease by histology ($p=0.105$). The utilization of surgical management, however, was significantly higher for patients with sarcomatoid-SCC. 83.3% of patients with SCC received treatment with definitive radiation whereas only 68.2% of patients with sarcomatoid-SCC were treated with radiation ($p<0.001$), as they were significantly more likely to undergo surgery with partial/total laryngectomy being utilized in 7.9%/6.8% of patients with sarcomatoid-SCC vs 4.7%/2.7% of SCC patients, respectively ($p<0.001$). Median overall survival was not statistically different between histologies (92.8 vs 94.8 months, SCC vs sarcomatoid-SCC, respectively, $p=0.816$). In the propensity-adjusted multivariable Cox model, sarcomatoid-SCC histology did not have an impact on overall survival (HR 0.947 [95%CI 0.812-1.103], $p=0.483$).

Conclusion: Sarcomatoid squamous cell carcinoma is a rare variant of laryngeal cancer with small reports of more aggressive behavior, reflected in more aggressive patterns of care nationally without evidence of a survival advantage.

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Examining the roles of surgery and chemoradiation in hypopharynx cancer: a study of the National Cancer Database

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

Purpose/Objective(s): There are few data specifically addressing hypopharynx cancer and thus treatment decisions for it are often extrapolated from laryngeal cancer experiences. We conducted a large population-based analysis of treatment patterns and survival in hypopharynx cancer with the National Cancer Database (NCDB), which to our knowledge has not been done for a non-medicare cohort.

Materials/Methods: The NCDB includes 8410 patients diagnosed with hypopharyngeal squamous cell carcinoma without distant metastases from 2004-2016. The association between treatment modality and overall survival was analyzed using Kaplan-Meier survival curves. Multivariable Cox regression was used to determine hazard ratios for each treatment while adjusting for age, grade, year of diagnosis, and facility type (community vs cancer center), stratified by clinical stage.

Results: Of the 8410 patients, 18% were treated with surgery, 68% with chemoradiation (CRT) and 14% with radiation (RT) alone. Patients ≤ 60 years old accounted for 41% of the cohort. The majority (80%) were male. At diagnosis, 6% of patients had AJCC clinical stage I, 12% had stage II, 23% had stage III, 49% had stage IVA and 10% had stage IVB. Overall survival at 5 years was 45% for AJCC clinical stage I, 40% for II, 37% for III, 33% for IVA and 21% for IVB. For each stage, the percent of patients

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	1 (n=483)		2 (1009)		3 (1889)		4A (4085)		4B (793)	
	%	HR	%	HR	%	HR	%	HR	%	HR
Surgery	35	1.15	26	1.19	17	1.18	15	1.20* (.0008)	10	1.35* (.049)
CRT (ref)	25		45		71		76		82	
RT	40	0.65* (.0136)	29	1.03	12	1.39* (.0007)	9	1.45* (<.0001)	8	1.40* (.031)

* statistically significant

receiving a given treatment is listed below. Adjusted hazard ratios for death by treatment modality are also tabulated, with chemoradiation as the reference. When significant, p values are listed in parentheses. When stratifying by T category alone, there was not a significant difference in adjusted hazard ratio for death between surgery and chemoradiation for clinical T3 and T4 disease (p values were 0.13 and 0.97, respectively).

Conclusion: Unlike larynx cancer, this NCDB study shows worse survival for surgery versus chemoradiation in clinical stage IVA and IVB disease. Many patients with stage I-II hypophyarngeal cancer receive CRT, however in the stage I cohort, CRT was associated with worse outcomes than RT alone.

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Establishment of a Novel De-escalation Protocol for HPV Associated Oropharyngeal Squamous Cell Carcinoma: One Institution's Experience

C. Meyer[1] and R. Lindau III[2]; *[1]Naval Medical Center Portsmouth, Portsmouth, VA, [2]Nebraska Methodist Health System, Nebraska, NE*

Purpose/Objective(s): HPV associated oropharyngeal squamous cell carcinoma (OPSCC) has improved disease free survival compared to non-HPV OPSCC which has led many to attempt to de-escalate the radiation and chemotherapy regimens. The 8th edition American Joint Commission on Cancer staging for HPV OPSCC adjusted these cancers to better align with target survivability curves, thus reducing the stage for many HPV OPSCC. However, it is unclear what impact this adjusted staging will have on the effectiveness of de-escalation protocols. Our institution established a novel de-escalation protocol to evaluate the validity of this proposal: that reduced radiation and chemotherapy treatments can provide equivalent disease free and overall survival, even when applied to the new AJCC staging. To our knowledge, this is the first such protocol based on the revised AJCC staging. Establishing such a novel treatment protocol that incorporates multiple departments and specialties can be met with significant logistical and institutional difficulties, limiting the effectiveness of the implementation. This study evaluated the effectiveness of the implementation of the de-escalation treatment protocol at a single high volume institution.

Materials/Methods: Retrospective analysis of prospectively collected data was performed on all patients eligible for inclusion in the de-escalation protocol from July 2018 to September 2019. Protocol treatment patterns were then compared to treatment patterns for the 14 months prior to protocol implementation to assess the impact of the protocol on patient care.

Results: Of 72 patients presented at the Multidisciplinary Head & Neck Tumor Board, 51 met protocol eligibility, 33 (65%) were enrolled. The most common reason for non-enrollment was travel/treatment at non-protocol institution, representing 72%. The majority of those enrolled were stage 1 (78%); 14% were stage II, 8% stage III and no stage IV. Of those enrolled, 97% received primary protocol treatment, with only 1 protocol deviation due to patient preference. Most common treatment modality was chemoradiation (48%), followed by surgery alone (30%). Only 2 patients, 6%, received triple modality therapy.

Conclusion: Early data shows that the long term, multi-specialty care required for cancer care be protocolized and successfully implemented through close cooperation and a multidisciplinary approach. The greatest limitations were in overcoming institutional inertia, accommodating patient logistical constraints and supply/care access limitations. Initial results also shows significant change in treatment patterns following protocol implementation, resulting in significantly reduced radiation dosing for treatment of oropharyngeal squamous cell carcinoma.

Author Disclosure: **C. Meyer**: Owner; Alicia's Place. **R. Lindau**: None.

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A Pilot Study of Intra-Treatment MRI/PET to Define Favorable and Unfavorable Radiographic Signatures of Patients with p16-Positive Oropharynx Cancer

M.E. Witek,[1] P.M. Harari,[2] A. Burr,[2] T. Chandereng,[3] M. Yu,[4] R.J. Kimple,[1] and G. Avey[3]; *[1]Department of Human Oncology, University of Wisconsin, Madison, WI, [2]Department of Human Oncology, University of Wisconsin Hospital and Clinics, Madison, WI, [3]Univeristy of Wisconsin, Madison, WI, [4]University of Wisconsin, Madison, WI*

Purpose/Objective(s): Prognostic approaches of identifying patients with intermediate-risk p16-postive oropharynx squamous cell carcinomas (IR p16+OPSCC) that exhibit favorable clinical outcomes remain to be defined. We assessed the efficacy of evaluating early intra-treatment responses to definitive radiotherapy with combined MRI/PET technology to identify patients with IR p16+OPSCC that exhibited a similar radiographic response as patients with low-risk p16+OPSCC (LR p16+OPSCC).

Materials/Methods: We performed a single arm pilot study at a single academic hospital enrolling patients with AJCC 7th edition clinical stage III-IVB p16+OPSCC. Patients were defined as either LR (T1-T3N0-N2b and £ 10 pack-years cigarette smoking (py)) or IR (cT4, ^{3} cN2c, or $>$ 10 py) and received comprehensive head and neck radiotherapy to a dose of 70 Gy in 33 fractions with concurrent systemic therapy. Prior to treatment and between fractions 10 and 12, patients underwent combined MRI/PET scans. Radiographic metrics included for analysis included volume, SULmax, SULmedian, SULpeak, and diffusion of the primary tumor and largest node. Changes between radiographic metrics were compared using the standard *t*-test. Imputation of missing values (e.g. complete response of the primary tumor) was performed using the Monte Carlo method. Patients were clustered using K-means with the Euclidean distance function. Silhouette widths provided information on the similarity between the objects within each cluster. The number of clusters (k = 2) was based on silhouette width.

Results: From August 23, 2018 to July 25, 2019, eleven (5 LR and 6 IR) patients were enrolled and completed the study. SULmax and SULpeak of the largest node showed the greatest change between patients with LR and IR p16+OPSCC ($p < 0.05$). Two distinct groups were identified using K-means cluster analysis. Three patients with IR p16+OPSCC (patient 1: cT4aN2c, 25 py; patient 2: cT2N2b, 36 py; patient 3: cT4aN2c, 45 py) exhibited similar radiographic changes compared to LR p16+OPSCC while three IR p16+OPSCC (patient 1: cT4aN2c, 0 py; patient 2: cT4aN2b, 16 py; patient 3: cT2N2b, 25 py) were significantly different from the rest.

Conclusion: We prospectively demonstrate the potential in this on-going trial to discriminate patients with p16-positive oropharynx squamous cell carcinoma and intermediate risk factors based on classic tumor and patient characteristic into two distinct cohorts using radiographic signatures generated using pre- and intra-treatment MRI/PET data sets. Further study is needed to confirm these findings which may enable real-time therapy de-intensification approaches for patients with intermediate-risk p16-positive oropharynx squamous cell carcinoma.

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Primary Surgery for Early-Stage Oropharyngeal Carcinoma: A Superior Treatment or a Matter of Selection Bias?

P. Papanikolaou,[1] M. Fakhreddine,[2] and T.D. Wagner[2]; *[1]Long School of Medicine, UT Health San Antonio, San Antonio, TX, [2]Department of Radiation Oncology, Mays Cancer Center, UT Health San Antonio, San Antonio, TX*

Purpose/Objective(s): Recent years have seen an increasing trend in the use of surgery as the primary treatment modality for early-stage (T1-2, N0-1) oropharyngeal squamous cell carcinoma (OPSSC) as new surgical techniques such as Transoral Robotic Surgery (TORS) have become available. The National Comprehensive Cancer Network (NCCN) guidelines for early-stage OPSSC recommend definitive radiation therapy (RT), surgery with or without RT/systemic therapy depending on adverse features, or chemoradiation in the case of T1-2, N1. The objective of our study is to investigate changes in treatment trends and outcomes for OPSSC over time.

Materials/Methods: We identified 3,958 patients over age 18 with T1-2, N0-1 OPSSC diagnosed between 2004 and 2013 in NCI's Surveillance, Epidemiology, and End-Result (SEER) Database. We grouped these patients based on primary therapy, with one group consisting of patients receiving surgery with or without adjuvant RT, and the other group with patients receiving primary radiation therapy. Patients receiving non-oncologic surgeries (excisional biopsies) were not counted as primary surgery candidates, while patients receiving radical surgeries and those with unknown treatment status were excluded from the study altogether. The percentage of patients receiving primary surgery was plotted by year and analyzed with a linear regression slope test to assess significance. The same was done for 36 month survival for all patients by year of diagnosis. We then compared the survival of the two groups using Kaplan-Meier curves and Wilcoxon tests.

Results: In the first year of data recorded (2004), primary surgery accounted for 42.62% of treatment, while in the last year (2013), it accounted for 55.17%. Linear regression slope test showed a positive slope with a significant p-value (.0008). The 2004 sample showed a 36 month survival of 82.58%, while the 2011 sample (2012-2013 were excluded due to insufficient follow up data) showed a 36 month survival of 82.71%, with linear regression slope test showing an insignificant p-value of .2769. Univariate survival analysis showed a significant difference between groups with a significant p-value (<.0001). The primary surgery group showed 5 and 10 year survival rates of 79.89% and 65.6% respectively, while the primary RT group showed 5 and 10 year survival rates of 65.19% and 45.89% respectively.

Conclusion: This study demonstrates that the use of primary surgery has increased significantly over time. Compared to patients undergoing surgery, patients undergoing primary RT have significantly worse survival outcomes. However, overall survival has not improved, suggesting that the patients undergoing primary RT likely have worse outcomes due to selection bias, as healthier patients are typically the ones selected for surgery.

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The Prognostic Value of HPV in Sinonasal Squamous Cell Carcinoma

E.S. Markovic,[1] K.E. Marqueen,[2] J.T. Liu,[3] K. Sindhu,[3] M. Posner,[4] W.H. Westra,[5] B. Miles,[4] E. Genden,[4] and R.L. Bakst[2]; *[1]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2]Icahn School of Medicine at Mount Sinai, New York, NY, [3]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [4]Department of Otolaryngology – Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, [5]Department of Anatomic and Clinical Pathology, Icahn School of Medicine at Mount Sinai, New York, NY*

Purpose/Objective(s): HPV has long been implicated in the pathology of oropharyngeal head and neck cancers but the role of HPV in sinonasal carcinoma has not been well established. This study compares patient characteristics, treatments, and outcomes between patients with HPV-positive and HPV-negative sinonasal carcinoma.

Materials/Methods: Patients with sinonasal cancer between 2011 and 2018 at one institution were identified using ICD 9 and ICD 10 diagnosis codes. 34 patients with squamous cell carcinoma and minimum 3-month follow up were identified and stratified by HPV status and subtype. 19 (55%) were HPV-positive (subtypes 11, 16, 18, 33, 35, 45, 56, and 69) and 15 were HPV-negative. Endpoints including recurrence, metastases and death were calculated using Kaplan Meier survival curves and compared using log-rank tests, using SPSS. For endpoints without statistical power, descriptive analysis was performed.

Results: The median age (range) in the present study was 59.5 years (45 - 87 years). The median (range) follow-up time was 30.7 months (3.5 – 122.5). There were no significant differences between groups for gender, race, age, smoking status, clinical stage, pathologic stage, or follow up time. No patients had metastatic disease at presentation. There was a trend toward significant difference in HPV status and nasal cavity vs sinonasal site (p=0.06) with HPV+ more prevalent in nasal cavity cancers. Survival and local failure did not differ by HPV status. Among patients with HPV+ tumors, nasal cavity tumors had a non-significant lower recurrence rate than sinus tumors. When stratifying by treatment type, the lowest rate of recurrence occurred in patients receiving surgery and chemoradiation. Of those treated with radiation, there was only 1 infield failure using proton therapy.

Conclusion: While previous studies have been equivocal on the prognostic role of HPV+ status in sinonasal cancers, this study demonstrates that HPV+ status does not seem to provide an advantage and perhaps is even associated with worse outcomes. More than 50% of our cases were HPV+. However, the sample size is not large enough to demonstrate a statistical difference. This may be explained by differences between the behaviors of nasal cavity and sinus tumors or by differences in treatment modalities.

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Impact of p16-overexpression on overall and progression free survival outcomes in oral cavity squamous cell carcinomas: A semi-national, population based study

K. Schneider,[1] J. Schmidt Jensen,[1] C. Grønhøj,[2] K.K. Jakobsen,[1] I. Wessel,[3] A. Christensen,[1] L. Specht,[4] and C.V. Buchwald[5]; *[1]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark, Copenhagen, Denmark, [2]Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]Department of Otorhinolaryngology, Head & Neck Surgery and Audiology at Copenhagen University Hospital, Rigshospitalet, Denmark, Copenhagen, Denmark, [4]Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [5]Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): p16-overexpression is found in head and neck cancer and has been identified as a principal cause and favorable prognostic factor of oropharyngeal squamous cell carcinomas. The impact of p16-overexpression in the pathogenesis and prognosis of oral cavity squamous cell carcinomas (OSCC) is still undetermined, and therefore we want to examine the prognostic implication of p16 in OSCC.

Materials/Methods: We included all patients diagnosed with OSCC in Eastern Denmark in the period 2008-2014. Survival was evaluated as overall survival (OS) and progression free survival (PFS) by Kaplan-Meier survival curves, including a log-rank test, and multivariate Cox-regression analyses.

Results: We included 575 patients from which 13% (n=69) of the cases had p16-positive tumors. The 5-year OS were 55% and 62% for the p16-negative and p16-postive patients, respectively, and the 5-year PFS were 48% and 50%, respectively. In a multivariate survival analysis, p16-positivity showed no significant influence on OS (HR: 1.06 [0.67-1.70], p=0.79) and PFS (HR: 1.11 [0.76-1.63], p=0.58).

Conclusion: In this population-based cohort of non-selected OSCC patients, there was no difference in survival outcomes when stratified on p16-overexpression status.

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A risk-based trial design of multidisciplinary treatment intensification for head-and-neck cancer

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

Purpose/Objective(s): The aim of the current study was to design a clinical study with different treatment options for different risk groups of head-and-neck cancer (HNC) patients, including dose-painting radiotherapy with inhomogeneous dose prescriptions, as well as primary surgery as an option for selected high-risk patients. We hypothesized that our design, when simulated in a cohort of previously treated patients, would assign reasonable numbers of patients in the different arms, to show feasibility in terms of statistical power and patient characteristics.

Materials/Methods: A cohort of 573 patients treated for HNC was stratified by low (< 14.3%)- intermediate(14.3% - 43.0%)- and high risk (> 43.0%), using a cause-specific cox model for loco-regional failure (LRF) from a previously published model[1]. Trial inclusion was simulated with the following inclusion criteria: Arm 1. Standard radiotherapy: low-risk patients, including all 16+ oropharynx patients. Arm 2. Randomization between standard and dose-painting radiotherapy: intermediate-risk patients, plus high-risk patients with oral cavity or p16- oropharynx cancer and Arm 3. Primary surgery+RT: high-risk patients with hypopharynx or larynx cancer.

Results: With the suggested trial design, 203 (35%), 297 (52%) and 73 (13%) where assigned to arm 1, 2 and 3, respectively (patient/tumor characteristics, see Table 1). Power/sample size calculations suggest that 40+40 patients are needed in Arm 2 (randomized phase I-II study with difference in number of central relapses as endpoint). Arm 3 (primary surgery) would with a Simonś two-stage design need 43 patients (loco-regional control rate: 50%, alternative hypothesis: 70%) in a single arm to assess recommendation for further trials.

Conclusion: The trial design showed feasibility in terms of statistical power/sample size in the different arms. Our group plan to proceed with the suggested trial design.

1. Håkansson K, Rasmussen JH, Rasmussen GB, et al. A failure-type specific risk prediction tool for selection of head-and-neck cancer patients for experimental treatments. *Oral Oncol*. 2017;74C:77-82.

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Abstract 233; Table 1 Patient/tumor characteristics for all patients and stratified by study arm when trial inclusion was simulated using the suggested design.

Variable	Levels	Total (n=573)	Arm 1: Standard therapy (n=203)	Arm 2: Dose-painting RT randomization (n=297)	Arm 3: Surgery + RT (n=73)
Tumor subsite	Oropharynx, p16+	183	183	0	0
	Oropharynx, p16-	108	0	108	0
	Oral cavity	51	0	51	0
	Hypopharynx	95	0	41	54
	Larynx	136	20	97	19
T classification	T1/T2/T3/T4	71/229/184/89	37/100/52/14	31/116/99/51	3/13/33/24
N classification	N0/N1-N2b/N2c-N3 (incl. N2)	80/240/253	28/96/79	52/132/113	0/12/61
Performance status	0/1/2/3/missing	351/162/37/10/13	161/31/6/0/5	154/105/24/7/7	36/26/7/3/1

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The Evolution of Intermediate Risk Oropharyngeal Cancer in a Veteran Population: a 15 Year Study

D. Wilde, P. Castro, A. Haugen, J. Shi, S. Lai, E. Chiao, D. Hernandez, A. Sikora, and V.C. Sandulache; *Baylor College of Medicine, Houston, TX*

Purpose/Objective(s): Oropharyngeal squamous cell carcinoma (OPSCC) incidence is increasing at an epidemic rate, fueled by human papillomavirus (HPV) infections. Whereas HPV-associated OPSCC (HPV+OPSCC) often occurs in non-smokers in the general population, smoking prevalence is much higher in the Veteran population resulting in a large intermediate-risk (HPV+ tumors in patients with significant smoking history) OPSCC cohort whose outcomes remain poorly described to date. Our goal was to evaluate oncologic and functional outcomes for OPSCC in a Veteran population and ascertain shifts in survival and relative disease burden within this intermediate-risk cohort. We hypothesized that intermediate-risk OPSCC represents a majority of new OPSCC diagnoses among Veterans.

Materials/Methods: We conducted a retrospective analysis of 301 OPSCC patients treated at a single Veterans Affairs tertiary referral institution in a large metropolitan setting between 2000 and 2015. Patients were predominantly male (98%) with a mean age of 62; African Americans constituted 23% of the study population.

Results: Two hundred fifty two patients (84%) initiated curative-intent treatment of which 225 underwent radiation-based treatment (90%); 5% of patients did not complete the prescribed radiation course and nearly 30% required dose modification or de-escalation of chemotherapy. The ratio of p16+ (HPV surrogate) to p16- disease rose from 1.06 (2000-2005) to 2.05 (2006-2010) to 3.7 (2011-2015) during the study period, although smoking history remained unchanged across the patient cohort with respect to prevalence and mean pack-years of exposure. p16 positivity was associated with improved overall survival (OS; p<0.001), locoregional control (LRC; p<0.001) and distant metastasis (DM; p=0.04) rates. LRC increased over the study time frame from 55% to 75% (p=0.023) and OS increased from 45% to 74% (p=0.002). On multivariate analysis OS was impacted by p16 status, T-classification, and the addition of chemotherapy to radiation; LRC was impacted only by p16 status. Among 116 patients which demonstrated recurrence/progression, 82% of events occurred locoregionally. Although 128 patients underwent gastrostomy placement and 43 underwent tracheostomy placement, among 153 survivors, only 31 patients remained

partially or completely gastrostomy dependent and 3 remained tracheostomy dependent.

Conclusion: We are experiencing an epidemic of intermediate risk HPV+OPSCC among Veterans which remains poorly understood and is not adequately addressed by current clinical trials. Dedicated efforts are required to develop precision oncology approaches for this patient population designed to maximize oncologic control while preserving adequate functional outcomes.

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Patterns of Cervical Lymph Node Metastasis and Relatively Risk Factors in Locally Advanced Supraglottic Squamous Cell Carcinoma

Y. Xu,[1] Y. Zhang,[1] and J. Yi[2]; *[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [2]Department of Radiation Oncology, National Cancer Center / Cancer Institute & Hospital, Chinese Academic of Medical Sciences, Peking Union Medical College, Beijing, China*

Purpose/Objective(s): To investigate the prevalence and distribution of cervical lymph node metastasis (LNM) in locally advanced supraglottic squamous cell carcinoma (LASCC).

Materials/Methods: We reviewed patients defined as LASCC from 2000.1-2017.12 in our hospital. Primary tumor was operated using partial or total laryngectomy and all patients underwent bilateral neck dissection (level II–IV). Univariate and multivariate logistic regression were used to find risk factors associated with prevalence of neck node metastasis.

Results: A total of 206 patients was enrolled. The frequency of LNM to levels II, III, IV were 44.2%, 37.4%, 8.7%, respectively. In all, 110 cases were with lateral tumors. Ipsilateral metastasis of lateral lesions was detected in levels II, III, IV with a frequency of LNM 44.5%, 34.5%, 10%, respectively, while contralateral metastasis of 19.1%, 10%, 2.7%, respectively. Only positive ipsilateral lymph nodes contributed to contralateral metastasis. Involvement of ipsilateral level II or III was associated with metastasis of level IV. 130 cases were with clinically negative neck lymph node. Prevalence of occult neck metastasis was 35.4%. 31 cases (23.8%) were metastatic to level II, 29 cases (22.3%) to level III, 3 cases (2.3%) to level IV, respectively. The rate of occult metastasis to ipsilateral neck levels II, III, IV were 21%, 11.1%,1.6%, respectively, while contralateral neck levels were 6.3%, 4.8%,0%, respectively. Histopathological differentiation was related to occult metastasis ($p=0.003$).

Conclusion: Neck levels II, III are most frequently invaded for LASCC. There is a high prevalence of contralateral metastasis in tumors with positive ipsilateral lymph nodes. Involvement of ipsilateral level II or III is an independent prognostic factor of LNM in level IV. Histopathological differentiation is related to occult metastasis.

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Trends in Intensity Modulated Radiation Therapy for Early Stage Glottic Larynx Cancer and Impact on Outcome

J. Bergin,[1] S. Abel,[2] A. Colonias,[2] and R.E. Wegner[2]; *[1]Allegheny Health Network, Department of Radiation Oncology, Pittsburgh, PA, [2]Department of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA*

Purpose/Objective(s): Definitive radiation remains a treatment option for early stage glottic larynx cancer. Intensity modulated radiation therapy (IMRT) has been the standard treatment for more advanced head and neck cancers, while 3D conformal radiotherapy (3D CRT) has remained standard for early glottic cancers. We used the National Cancer Database (NCDB) to identify predictors of IMRT use and effect on outcome in these patients.

Materials/Methods: We queried the NCDB from 2004-2015 for squamous cell carcinoma of the glottic larynx staged T_{is}-T2N0 treated with radiation alone. Logistic regression was used to identify predictors of IMRT. Cox regression was used to identify factors predictive of overall survival. Propensity matching was conducted to account for indication bias.

Results: We identified 15,627 patients, of which 11% received IMRT. IMRT use rose from 2% in 2004 to 16% in 2015. Predictors of IMRT were increased comorbidity, T2 stage, urban location, chemotherapy, treatment at an academic center, and later year. Predictors of improved survival were female gender, higher income, lower stage, no chemotherapy, academic facility, and more remote year. There was no difference in survival between 3D CRT and IMRT across all stages. When limited to T2, there was worse survival with IMRT, median of 92 months compared to 76 months, $p=0.0129$.

Conclusion: The rate of IMRT use for early stage glottic larynx cancer has risen over time. There was no difference in outcome across the cohort. The difference seen in the T2 subset is likely explained by other undocumented factors which could not be controlled.

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Changing the Paradigm in HPV-Negative Oropharyngeal Cancer: Deintensification Based on Low Risk of Locoregional Relapse

J.J. Kang,[1] O. Cartano,[1] D. Fan,[1,2] M. Fan,[1,3] H. Wang,[1,4] S. Kitpanit,[1,5] A. Lee,[1] D. Gelblum,[1] E. Sherman,[6] L. Dunn,[7] M. Cohen,[8] J.O. Boyle,[8] R.J. Wong,[8] C.J. Tsai,[1] S. McBride,[1] K. Zakeri,[1] L. Chen,[1] Y. Yu,[1] N. Riaz,[1] and N. Lee[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Oncology, Xiangya Hospital, Central South University, Changsha, China, [3]Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China, [4]Department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China, [5]Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [6]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [7]Memorial Sloan Kettering Cancer Center, Department of Medical Oncology, New York, NY, [8]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): To identify HPV−negative oropharyngeal cancer (OPC) patients who may be candidates for treatment deintensification by low risk of locoregional relapse.

Materials/Methods: Stage III or IV OPC treated with definitive chemoradiation from 2001 to 2018, with chemotherapy at the discretion of medical oncology. Patients were excluded if either HPV ISH or P16 IHC was positive, or if both HPV and P16 status were unknown. In total, 99 consecutive patients were identified. The Kaplan-Meier method was used to estimate time-to-event outcomes on univariate analysis (UVA) and the Cox proportional hazards model was used to determine the effects of covariates (T stage, N stage, age, smoking history, chemotherapy) on multivariate analysis (MVA).

Results: Median follow-up was 4.0 years [0.3-15.2]. Results are listed in Table 1.

Local control (LC) was influenced by T stage (4yr: 91% T1-T2 vs. 62% T3-T4, $P<0.001$) and chemotherapy UVA. Regional control (RC) was influenced by T stage (4yr: 90% T1-T2 vs. 62% T3-T4, $P<0.001$) and smoking history on UVA. Distant metastasis (DM) was influenced by T stage (4yr: 86% T1-T2 vs. 55% T3-T4, $P<0.001$) and smoking history on

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OUTCOME	UVA	MVA
4 yr LC	T1-T2, 92% vs. T3-T4, 63% (P<0.001)	HR 5.0[1.8-13.9], P=0.002
	cisplatin, 86% vs. other chemo, 68% (P=0.028)	HR 2.2[0.9-5.1], P=0.084
4 yr RC	T1-T2, 90% vs. T3-T4, 62% (P<0.001)	HR 4.0[1.4-11.3], P=0.009
	Ever-smoker, 72% vs. Never-smoker, 90% (P=0.028)	P=NS
4 yr DM	T1-T2, 86% vs. T3-T4, 55% (P<0.001)	HR 4.0[1.6-9.9], P=0.003
	Ever-smoker, 68% vs. Never-smoker, 82% (P=0.056)	P=NS
T1-2N0-2 subgroup only	4yr LC: cisplatin, 95% vs. other, 86% (P=0.15)	
	4yr RC: cisplatin, 92% vs. other, 88% (P=0.57)	
	4yr DM: cisplatin, 85% vs. other, 86% (P=0.94)	

UVA. Cancer specific survival (CSS) was influenced by T stage (4yr: 86% T1-T2 vs. 62% T3-T4, P<0.001), N stage, and age on UVA. On MVA, T stage was the only independent predictor of LC (HR 5.0 [1.8-13.9], P=0.002), RC (HR 4.0 [1.4-11.3], P=0.009), DM (HR 4.0 [1.6-9.9], P=0.003), and CSS (HR 5.3 [2.1-13.0], P<0.001). Subgroup analysis of T1-T2 N0-2 patients showed trends for improved outcomes with concurrent cisplatin over other chemotherapy (4yr LC 95% vs. 86%, P=0.15; 4yr RC 92% vs. 88%, P=0.57; 4yr DM 85% vs. 86%, P=0.94).

Conclusion: Outcomes in HPV-negative OPC are driven by T stage, regardless of N stage. Patients treated with non-cisplatin chemotherapy or with prior smoking history may have inferior LC and CSS, though not significant on MVA. T1-2N0-2 HPV-negative OPC patients treated with cisplatin have comparable outcomes to HPV-positive OPC patients who were de-escalated on randomized trials. This patient population may benefit from prospective clinical trials examining de-intensification of therapy.

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Concurrent Irradiation of ^{18}F-FDG Avid Contralateral Tonsils in HPV-Positive Oropharyngeal Squamous Cell Carcinoma Treated with Definitive Chemoradiation

M. Froehlich,[1] P. Morgan,[1] E. Hilliard,[1] W. Reiter,[1] J. Kaczmar,[2] D. Neskey,[1] and A.K. Sharma[1]; *[1]Medical University of South Carolina, Charleston, SC, [2]Hollings Cancer Center, Charleston, SC*

Purpose/Objective(s): Management of contralateral tonsils with abnormal ^{18}F-FDG PET/CT avidity in p16-positive oropharyngeal SCC is unclear. Definitive diagnosis requires diagnostic tonsillectomy of the FDG-avid tonsil. We aimed to evaluate the SUV uptake and radiation dose received by the contralateral tonsil in patients treated with definitive chemoradiation when the contralateral neck is electively treated.

Materials/Methods: This was a single institution, retrospective study of patients treated for oropharyngeal SCC. Eligible patients had primary p16-positive SCC of the palatine tonsil treated with definitive chemoradiation. Eligible patients required a dedicated head and neck ^{18}F-FDG PET/CT scan and a radiation treatment plan. Demographic data, clinical data including AJCC7 and AJCC8 staging, maximum standardized uptake values (SUV_{max}) of the contralateral tonsil, and radiation doses to the contralateral tonsil were collected. The contralateral tonsil was classified as suspicious if its metabolic activity was significantly greater than the physiologic activity of the surrounding oropharyngeal mucosa. Radiation dosages to the contralateral tonsil were calculated using Eclipse, Pinnacle, or VelocityAI.

Results: Twenty-three patients were identified, with a median age of 68.0 years. All patients were Caucasian and 91.3% were male. With clinical staging by the AJCC eighth edition, 17.4% of patients presented as Stage I, 52.2% as Stage II, and 30.4% as Stage III. The majority of patients presented with N2 disease (60.9%), with 17.4% presenting with N0, as well as N1 disease. Only 4.3% patients presented with N3 disease. The mean SUV_{max} of the contralateral tonsil was 5.20 (range: 2.8-8.7 SUV). The mean SUV_{max} of the 13 contralateral tonsils suspicious for abnormal activity was 6.49. This was significantly greater ($p<0.001$) than the SUV_{max} of 3.43 for the 9 tonsils deemed not suspicious. Twenty-one patients received bilateral neck radiation, the average mean radiation dose to the contralateral tonsil was 6037.2 cGy (range: 5083.7-7310.6 cGy). Reasons for contralateral neck radiation were contralateral neck disease, multi-level ipsilateral neck disease or primary involvement extending to base of tongue or soft palate. The rate of recurrence of the 19 patients who become disease-free was 0.0%, with a median disease-free survival of 33.8 months (range: 3.2-93.1 months).

Conclusion: In patients with p16-positive SCC of the palatine tonsil treated definitively by concurrent chemotherapy with bilateral neck radiation, the contralateral tonsil received overlapping therapeutic doses of radiation. Thus, elective radiation to the contralateral palatine tonsil with concerning PET avidity may not be warranted.

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Clinical Outcomes and Toxicities in Oropharyngeal Cancer (OPC) Patients Treated with Proton Therapy: A Single Institutional Experience

S. Kitpanit,[1,2] A. Lee,[1] D. Fan,[1,3] M. Fan,[1,4] H. Wang,[1,5] N. Mohamed,[1] D. Spielsinger,[1] D. Gelblum,[1] E. Sherman,[6] L. Dunn,[7] J.O. Boyle,[8] R.J. Wong,[8] M. Cohen,[8] J.J. Kang,[1] C.J. Tsai,[1] S. McBride,[1] K. Zakeri,[1] L. Chen,[1] Y. Yu,[1] N. Riaz,[1] and N. Lee[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [3]Department of Oncology, Xiangya Hospital, Central South University, Changsha, China, [4]Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China, [5]Department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China, [6]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [7]Memorial Sloan Kettering Cancer Center, Department of Medical Oncology, New York, NY, [8]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): To assess clinical outcomes, acute and late toxicities in newly diagnosed OPC treated with upfront proton therapy (PT) with curative intent.

Materials/Methods: Between 2014-2019, newly diagnosed OPC patients treated with PT at our center were retrospectively reviewed. Patients with <6 months follow-up time were excluded. Overall survival (OS), local control (LC), regional control (RC) and distant metastasis free survival (DMFS) were defined as time between date of PT completion to date of target events and calculated using Kaplan-Meier method. Acute and late toxicities were graded using CTCAE version 4.03.

Results: 27 patients were included for the analysis. The median age was 60 years (range 43-80.4). All patients had baseline Karnofsky performance

status of 90-100 and 74.1% were male. The most common primary sites were tonsil (63%) followed by base of tongue (29.6%) with predominantly T2 (48.1%) and N2b (37%). 96.3% were squamous cell carcinoma. HPV or p16 were positive in 92.6%. 66.7% of patients received definitive PT while 33.3% received post-operative PT. Median PT dose for definite and post-operative settings were 70 CGE in 35 fraction and 66 CGE in 33 fractions. PT was delivered in uniform scanning beam 22.2% and pencil beam scanning using intensity modulated PT 77.8%. 66.7% of patients received concurrent systemic therapy with PT in which 63% received cisplatin. The median follow-up time was 19 months (range 9.9-54.6). 1-year OS, LC, RC and DMFS were 100%, 100%, 100%, 96.3%. 1 patient had biopsy proven lung metastasis at 9 months after PT completion. Most common acute grade 1-2 toxicities were skin (92.6%), mucositis (85.1%) and odynophagia (81.5%). Grade 3 toxicities were rare including mucositis, dysphagia and skin (each N = 1). One patient developed significant dysphagia requiring PEG tube insertion at 3.4 weeks after PT initiation, however, the tube was removed shortly after PT completion due to patient's recovery. No grade 4-5 acute toxicity was observed. Late toxicities were mostly limited to grade 1. No odynophagia persisted at later follow-up. 22.2% of patients had no late xerostomia while the rest had grade 1. Two patients developed grade 2 osteoradionecrosis (ORN) of the jaw at 6 months and 2.4 years after PT completion, respectively. Both patients were treated with long-term antibiotics. Grade 3 late toxicities were hearing impairment requiring hearing aid (N = 1) and chronic weight loss (N = 2). 1 patient developed dysphagia required esophageal dilatation and grade 2 fibrosis. No grade 4-5 late toxicities were observed.

Conclusion: Proton therapy in newly diagnosed OPC patients resulted in excellent disease control and survival with limited toxicities. Larger population is warranted to verify this observation.

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Oncologic and Functional Outcomes Following Primary Total Laryngectomy

M.Y. Lee,[1] M. Belfiglio,[1] C.W. Fleming,[2] B. Matia,[3] S. Koyfman,[2] N.P. Joshi,[2] B.B. Burkey,[4] E. Lamarre,[4] B. Prendes,[4] J. Scharpf,[4] R.R. Lorenz,[4] N.M. Woody,[2] D.J. Adelstein,[5] J.L. Geiger,[5] D. Chute,[3] and J. Ku[4]; *[1]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH, [5]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Primary total laryngectomy (TL) is an option for patients with laryngeal cancer who are poor candidates for organ preservation. The purpose of this study was to evaluate complications, functional outcomes, and survival after primary TL for patients with laryngeal cancer.

Materials/Methods: We performed an IRB approved retrospective analysis of all patients who underwent primary TL for laryngeal cancer between 1/1/01-8/31/18 at a single tertiary care institution. Descriptive statistics were used to describe demographic data. Kaplan Meier analysis/Cox proportional hazards models were used to analyze survival/predictive factors.

Results: Of the 134 patients included, 105 (78%) were male and average age was 63 (SD 10). Median follow up was 24 months (2.5-162.5). Pathologic disease stages were T4 (n = 94, 70%), T3 (n = 37, 27.6%), T2 (n = 3, 2.2%); and N0 (n = 55, 41%), N1 (n = 12, 9%), N2, (n = 58, 43.3%), N3 (n = 9, 6.6%). Patients received adjuvant CRT (n = 32, 24%), XRT (n = 67, 50%), chemotherapy alone (n = 1, 1%), or none (n = 34, 25%). Overall (OS) and disease-free survival (DFS) were 85.4% and 74.9% at 1 year and 56.3% and 47.5% at 5 years. Recurrence happened locally in 12 (9%), regionally in 10 (7.5%), and distantly in 26 (19.4%) patients. On univariable analysis, factors associated with worse DFS were lack of smoking history, pre-op swallowing dysfunction, illicit drug use, positive lymph nodes, extracapsular extension, pT, pN, cN, and M stage, positive margins, perineural invasion, discharge to skilled nursing facility (SNF), 30-day readmission, and post-op feeding tube dependence ($p<0.05$). On multivariable analysis, past or current smoking (HR = 0.13, $p<0.01$) and pre-op grade 3 voice dysfunction (HR = 0.36, $p=0.04$) were associated with better DFS. Factors associated with worse DFS were pre-op dysphagia needing tube feeding (HR = 3.6, $p=0.04$) or ICU admission (HR = 22.7, $p=0.02$), discharge to SNF (HR = 2.13, $p=0.02$), pT4 (HR = 3.29, $p<0.01$), cN3(HR = 39.3, $p<0.01$), and long term feeding tube dependence (HR = 7.68, $p<0.01$). Through last follow up, common complications were 90-day unplanned ED visit/hospitalization (n = 82, 61%), TEP complications (n = 52, 39%), psychiatric toxicity (n = 26, 19.4%), stricture requiring dilation (n = 22, 16.4%), and fistula (n = 21, 15.7%). 111 (83%) patients received primary TEP, while 14 (10%) patients received secondary TEP. Within 90 days of surgery, 99 (73.9%) patients were consistently using their alternative speech modalities and 112 (83.5%) patients had normal or soft oral diet, while 16 (12%) were feeding tube dependent.

Conclusion: Primary total laryngectomy offers acceptable survival for patients with advanced disease, with 5-year DFS of 47.5%. While there is substantial risk of complications, the majority of patients are able to generate TEP speech and rely on an oral diet.

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Normal Tissue Sparing via Adaptive Radiation Therapy for Head and Neck Cancers: Analysis with Biologically Effective Dose Distributions

B.K.Y. Lee,[1] J. Zhang,[2,3] J.J. Cho-Lim,[2] W. Inouye,[2] and S.P.H. Lee[2,4]; *[1]Loma Linda University Department of Radiation Medicine, Loma Linda, CA, [2]VA Long Beach Healthcare System, Long Beach, CA, [3]Southern California Permanente Medical Group, Los Angeles, CA, [4]University of California, Los Angeles, Los Angeles, CA*

Purpose/Objective(s): Retrospective analysis of adaptive radiation therapy (ART) for head and neck (H&N) cancers in a homogenous Veterans Affairs patient population by incorporating biologically effective dose (BED) distributions.

Materials/Methods: With suspicion for rapid anatomic changes, 39 patients receiving IMRT for H&N cancers via simultaneous integrated boost (SIB) technique with 3 planning target volume (PTV) levels underwent a repeat CT-simulation at some time during their treatment courses. Of these, 27 were judged to show significant anatomic difference from their original CT images, thus re-planning was done for each according to the updated anatomy. Subsequent treatment was completed for the remaining fractions based on the new dosimetry. The therapeutic gains in terms of dose coverages for PTVs as well as normal tissues (both serial and parallel structures such as spinal cord and parotids, respectively) were analyzed from corresponding dose-volume histograms (DVH) by comparing the re-planned dosimetric results (i.e. with ART) to those of the original treatment plan but applied unadjusted upon the new CT anatomy (i.e. without ART). Furthermore, analysis using BED distributions was performed to mitigate the fact that a combined effect as inferred otherwise from simple summation of physical dosages before and after re-planning can be misleading biologically (especially for late-reacting normal tissues) due to its failure to account for the different fractional doses at the structure of interest (i.e. the "double-trouble" effect). Using the parotid to exemplify a parallel-structured normal tissue (with a/b assumed to be 3 Gy), the

combined BEDs received by 50% of the organ volume ($BED_{50\%}$) for both high-risk (HR, i.e. ipsilateral to the primary tumor site) and low-risk (LR, i.e. contralateral) parotid glands were determined.

Results: The median time point when a repeat CT-simulation was performed was at 57% of the originally planned course. In comparison with original CT images, the average HR-parotid volume changed from 33.2 cc to 26.6 cc, and the average LR-parotid volume changed from 34.3 cc to 27.5 cc ($p<0.05$ for both). In terms of the total physical dose received after re-planning, the HR-parotid $D_{50\%}$ changed from 13.7 Gy without to 11.4 Gy with ART ($p=0.011$), while the LR-parotid $D_{50\%}$ changed from 11.3 Gy without to 9.9 Gy with ART ($p=0.014$). After BED determinations to enable summation of biological effects before and after re-planning, the combined HR-parotid $BED_{50\%}$ changed from 35.3 Gy_3 without to 31.4 Gy_3 with ART ($p=0.013$), while the LR-parotid $BED_{50\%}$ changed from 28.4 Gy_3 without to 26.1 Gy_3 with ART ($p=0.011$).

Conclusion: After displaying significant anatomic changes during H&N cancer radiotherapy, patients who complete the remaining treatment portion via ART may benefit from more parotid sparing as predicted from BED analysis quantitatively.

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Surveillance Imaging for Patients with Head and Neck Cancer Treated with Definitive Radiotherapy: A Partially Observed Markov Decision Process Model

S.P. Ng,[1] T. Ajayi,[1,2] A.J. Schaefer,[2] C. Pollard III,[3] H. Bahig,[4] A.S. Garden,[5] D.I. Rosenthal,[6] G.B. Gunn,[7] J. Phan,[8] W.H. Morrison,[8] J.M. Johnson,[9] A.S. Mohamed,[8] E.M. Sturgis,[7] and C.D. Fuller[5]; *[1]MD Anderson, Houston, TX, [2]Rice University, Houston, TX, [3]Dept. of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [4]Centre Hospitalier de l'Universite de Montreal (CHUM), Montreal, QC, Canada, [5]University of Texas MD Anderson Cancer Center, Houston, TX, [6]The University of Texas MD Anderson Cancer Center Institution *, Houston, TX, [7]MD Anderson Cancer Center, Houston, TX, [8]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [9]The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): The goal of this model is to guide surveillance imaging policies after definitive radiotherapy.

Materials/Methods: A partially observed Markov decision process model was formulated to determine the optimal times to scan patients. Transition probabilities were computed using a dataset of 1508 patients with HNC who received definitive radiotherapy between years 2000 - 2010. Kernel density estimation was used to smooth the sample distributions. The reward function was derived using cost estimates from the literature. Additional model parameters were either estimated using data in the literature or clinical expertise.

Results: When considering all forms of relapse, our models showed that the optimal time between scans is longer than the time intervals used in the institutional guidelines. The optimal policy dictates that there should be less time between surveillance scans immediately following treatment compared to years after treatment. Comparable results also held when only locoregional relapses were considered as relapse events in the model. Simulation results for the inclusive relapse cases showed that 15% of patients experienced relapse over a simulated 36-month surveillance program.

Conclusion: This model suggests that less frequent surveillance scan policies can maintain adequate information on relapse status for patients with HNC treated with radiotherapy. This model could potentially translate to a more cost-effective surveillance program for this group of patients.

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Hyperfractionated Radiotherapy Alone or in Sequential Combination Chemotherapy in Patients with Advanced Nasopharynx Cancer with Contraindications to Concurrent Radio-Chemotherapy - Long Term Results

A. Wygoda,[1] T. Rutkowski,[1] J.J. Mrochem-Kwarciak,[2] M. Kentnowski,[1] D. Księżniak-Baran,[1] A. Bieleń,[1] D. Leś,[1] A. Brewczyński,[1] B. Pilecki,[1] K. Dębiec,[1] and K.A. Skladowski[1]; *[1]I Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland, [2]The Analytics and Clinical Biochemistry Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland*

Purpose/Objective(s): The standard treatment of patients (pts) with advanced nasopharyngeal cancer (NPC) is conventional fractionated radiotherapy (CFRT) combined with concurrent platinum based chemotherapy (CHT). Induction CHT followed by CFRT or CFRT followed by adjuvant CHT may be effective in selected NPC pts, especially with low differentiated and/or bulky tumors. Our experiences with comorbidity touched HNC pts have recognised concurrent radio-chemotherapy as a too toxic for them and suggested that radiotherapy (RT) alone or RT combined with sequential CHT should be considered. In order to avoid the loss of chemoradiation enhancement of tumor responsiveness hyperfractionated RT (HpfxRT) is dedicated for such a pts allowing radiation dose escalation in the same time as for CFRT. The objective of this presentation is to report survival outcomes and treatment toxicity in pts with advanced NPC treated with HpfxRT alone or combined with induction or/and adjuvant CHT.

Materials/Methods: The data of 30 pts (19 men and 11 women) with locally advanced NPC in median age 45,5 years (range: 17-75) were retrospectively analysed. There were 3 pts with II, 9 with III and 18 with IVA of tumor stage. RT was performed with dose per fraction 1,1-1,2 Gy given twice a day to the median total dose 76,6 Gy (range: 71,4-79 Gy). Overall irradiation time was in range of 45-58 days (median 50). In 16 pts CHT based on cisplatin alone or in combination with 5-fluorouracil (PF scheme) was introduced at least in one part of treatment (in 3 and 11 pts as induction and adjuvant line, respectively; in 2 pts both schedules were administered).

Results: 5- and 10-years survival parameters were 75% and 62% for local control, 73% and 64% for nodal control, 49% and 35% for disease free survival (DFS) respectively. Overall survival (OS) was equal (66%) for 5- and 10-years observation period. In CHT group 5- and 10-years DFS was significantly better in comparision with RT alone − 68% vs 28% and 51% vs 19% respectively ($p=0,014$). OS was also longer in pts who had CHT combined with RT (78% vs 50%, $p=0,096$), this same for 5- and 10-years observation. Confluent mucositis was developeded in all pts but RT had to be interrupted only in one case (RT alone group). No grade 3-4 late radiotherapy-induced toxicities were observed.

Conclusion: HpfxRT combined with sequential CHT is effective treatment and should be considered in selected pts with advanced NPC with contraindication to simultaneous radio-chemotherapy. HpfxRT alone is less effective but may be also curative. Treatment tolerance of HpfxRT is satisfactory.

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Local Control and Survival Rates in Patients with T2N0M0 Carcinoma of the Glottis treated with Primary Radiotherapy

M.S. Iqbal,[1] J. O'Hara,[2] C.G. Kelly,[1] W. Dobrowsky,[1] C. Dobeson,[3] G. Shaikh,[1] and J. Kovarik[1]; [1]*Northern Centre for Cancer Care, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom,* [2]*Otolaryngology, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom,* [3]*Northern Centre for Cancer Care, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, Newcastle, United Kingdom*

Purpose/Objective(s): To investigate the local control (LC) and overall survival (OS) rates of patients with T2N0M0 carcinoma of the glottis (TNM 7th edition) treated exclusively with radiotherapy.
Materials/Methods: Between 2010 − 2016, 77 patients with biopsy proven T2N0M0 carcinoma of the glottis treated with primary radiotherapy at our centre were included in the study. Data was collected retrospectively. Survival rates were estimated using Kaplan-Meier curve.
Results: There were 69 males and 8 females. Mean age was 67.3 years (range: 45 − 91, SD 10.6). 91% patients had WHO performance status 0 or 1. There was supraglottic extension in 21 patients (27%), subglottic extension in 19 (25%), both supraglottic and subglottic extension in 6 (8%) and bulky tumour limited to vocal cord causing impaired mobility in 31 patients (40%). Forty eight per cent patients were treated with 3D conformal radiotherapy and 52% had IMRT. The dose fractionation was as below; 55Gy in 20 fractions in 19 patients (25%) and 63-65Gy in 30 fractions in 58 patients (75%). In 43 patients (56%) the neck lymph nodes were treated with a prophylactic dose of 54Gy in 30 fractions and in remaining 34 patients (46%) only the primary tumour was treated. With a median follow up of 3.4 years, local control rate was 79.2%. Nine patients (12%) required salvage laryngectomies. Five patients (6.5%) developed distant metastases. 31patients have died; 20 with non-laryngeal cancer causes and 11 died of disease. 5-year estimated LC was 77%, disease specific survival (DSS) was 82% and 5-year OS was 58%. Radiotherapy modality (3D vs IMRT) wasn't prognostic factor ($p=0.36$). Implying neck irradiation was associated with worse LC ($p=0.027$) but there was potential selection bias as more aggressive tumours were treated with neck irradiation as it would be unlikely that neck irradiation in itself would cause worse oncological outcome. Eighteen patients (23%) developed grade III dysphagia (17 patients i.e. 22% required nasogastric tube feeding). No grade ≥IV acute toxicity. Four patients (5%) developed late grade III/IV toxicities (2 developed oesophageal stenosis requiring dilation and 2 developed cartilage necrosis).
Conclusion: Radiotherapy including hypofractionated radiotherapy regimen provides an excellent treatment outcome with acceptable toxicity in early glottis cancer. Addition of prophylactic irradiation of the neck lymph nodes had no impact on regional control.
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Cetuximab Versus Other Non-Cisplatin Agents in the Treatment of Patients with Head and Neck Cancer Receiving Concurrent Chemoradiotherapy

R. Morse,[1] R.G. Ganju,[2] M.J. Tennapel,[3] P. Neupane,[4] K. Kakarala,[3] L. Shnayder,[3] A. Bur,[3] and C.E. Lominska[1]; [1]*Department of Radiation Oncology, University of Kansas School of Medicine, Kansas City, KS,* [2]*University of Kansas, Kansas City, KS,* [3]*University of Kansas Medical Center, Kansas City, KS,* [4]*The University of Kansas School of Medicine, Kansas City, KS*

Purpose/Objective(s): Standard of care for radiosensitization in head and neck squamous cell carcinoma (HNSCC) is concurrent cisplatin chemoradiotherapy. These regimens are toxic and alternative agents may be required for patients who cannot tolerate cisplatin. Cetuximab plus radiotherapy has been shown by a randomized trial to be better than radiation alone. Other regimens supported by phase 2 studies are often used. Little is known about the comparative efficacy of these alternative regimens. We compared our experience with cetuximab versus other non-cisplatin agents for radiosensitization.
Materials/Methods: Consecutive patients with non-nasopharyngeal HNSCC at a single institution between 2011 and 2016 treated with radiation concurrent with non-cisplatin chemotherapy were reviewed. Concurrent chemoradiotherapy was delivered with or without induction therapy. Cohorts were divided by those receiving cetuximab (CTX) versus non-cetuximab systemic therapy (NCC). Standard dosing was 70 Gray (Gy) in the definitive setting and 60 Gy in the post-operative setting. Antineoplastics received were cetuximab (50 patients); carboplatin/paclitaxel (14 patients); carboplatin (7 patients); paclitaxel (3 patients); docetaxel (3 patients); carboplatin/etoposide (1 patient); and cetuximab/docetaxel (1 patient). The Kaplan-Meier method was performed to calculate 3-year overall survival (OS) and 3-year progression free survival (PFS) and outcomes were evaluated by chi-squared tests.
Results: Seventy-nine patients met inclusion criteria with a median follow-up of 36.9 months (range, 1.5- 81.2 months). An oropharyngeal site was more common in CTX patients ($p=0.005$), otherwise patients were well balanced (stage, p16 status, use of induction chemotherapy). Most patients were Caucasian (90%) and younger than 65 years old (58.2%). Sixty-three patients were current or former smokers. Primary surgical resection was received by 22.7% of patients. The most common subsite was oropharynx (60.8%), followed by larynx/hypopharynx (21.5%). Of the oropharyngeal population, 68.8% were p16 positive. Sixteen patients received induction chemotherapy. ECOG performance status was comparable: 2 or greater (26% versus 27.6%, $p=0.399$). The NCC group missed significantly more radiation days due to toxicity, were more likely to have radiation delays greater than 1 week, and experience chemotherapy dose-limiting toxicity ($p=0.019$, $p=0.032$, $p=0.001$, respectively). When comparing CTX versus NCC, 3-year OS (76% versus 55.2%, respectively, $p= 0.021$) and 3-year PFS (70% versus 48.3%, respectively, $p= 0.042$) were statistically significant.
Conclusion: Although non-randomized, our results suggest poor outcomes in non-cisplatin cytotoxic chemotherapy compared to cetuximab. Further prospective study is needed to clarify these differences in patients unable to receive cisplatin.
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Long-term comorbidity following treatment of Oropharyngeal Squamous Cell Carcinoma with known HPV and p16 status: a population-based, case-control study of 475 patients

M. Zamani,[1] K.K. Jakobsen,[2] J.T. Friborg,[3] C. Grønhøj,[1] and C.V. Buchwald[4]; [1]*Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [2]*Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark, Copenhagen, Denmark,* [3]*Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [4]*Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): Patients with Human Papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) show better prognosis compared to HPV-negative (HPV−) OPSCC, likely explained by a lower burden of comorbidities in HPV+ OPSCC cases. The objective of this study was to compare characteristics and comorbidities of long-term survivors of HPV+ and HPV− OPSCC in a population-based setting.
Materials/Methods: We included all OPSCC-cases diagnosed in Eastern Denmark in 2000-2014 who survived at least five years following

treatment. Comorbidities were obtained from the Danish National Patient Registry (DNPR) and quantified using the Charlson Comorbidity Index (CCI). A 1:10 ratio age-gender matched control population was used to compare CCI. Overall survival (OS) was stratified by HPV-status and analysed with Kaplan-Meier curves and logistic regression.

Results: In total, 475 patients (31% of the original cohort) were included (median follow-up 8.2 years, range 5.1-16.3 years). Overall, 71% of patients (n=338) had HPV+ cancers. As CCI-score, the HPV+ group had fewer comorbidities at the time of diagnosis (p=0.04), and even fewer comorbidities at last follow-up (p<0.01). 10-year OS of HPV+ OPSCC was 84%, 81%, and 66% for CCI-scores 0-1, 2-3 and 4+, respectively (p=0.04). 10-year OS of HPV- OPSCC was 57%, with no significant difference between CCI groups (p=0.55). Logistic regression revealed that overall survival of HPV+ cases was linked to younger age, fewer pack years, localized tonsillar tumors, lower TNM-stage, and lower CCI-score. The same findings were evident for HPV- cases, but these were not statistically significant.

Conclusion: For long-term survivors of OPSCC in East-Denmark, patients with HPV− OPSCC accumulated more comorbidities during their follow-up duration in comparison to patients with HPV+ OPSCC. The two groups also differed significantly in many clinical aspects, and HPV+ cases had a greater overall survival.

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Surgical Resection is Justifiable for Oral T4b Squamous Cell Cancers with Masticator Space Invasion

H.M. Baddour,[1] M. Ochsner,[1] M.R. Patel,[1] J. Switchenko,[2] J.J. Beitler,[3] K.R. Magliocca,[4] C.A. Solares,[5] C. Steuer,[6] K.L. Baugnon,[7] and M.W. El-Deiry[8]; *[1]Department of Otolaryngology, Emory University School of Medicine, Atlanta, GA, [2]Department of Biostatistics & Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, [3]Emory University School of Medicine, Atlanta, GA, [4]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, [5]Department of Otolaryngology Emory University, Atlanta, GA, [6]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [7]Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, [8]Otolaryngology, Winship Cancer Institute of Emory University, Atlanta, GA*

Purpose/Objective(s): To examine survival endpoints in patients with pathologically proven masticator space invasion (T4b) OCSCCA treated with definitive surgery.

Materials/Methods: In this retrospective cohort study conducted at a tertiary care center, records of 25 consecutive patients with T4b OCSCCA treated with primary surgery from May 2012 to December 2016 were examined. Only patients with ≥ 2 years follow-up from date of surgery were included. Multiple demographic and clinical variables were included. All cases were defined as T4b based on masticator space involvement as assessed by pathologic analyses. No cases with pterygoid plate involvement, skull base involvement or internal carotid artery encasement were performed. All T4b OCSCCA patients underwent primary surgery with or without adjuvant therapy. Survival endpoints from the date of surgery including overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS) and distant recurrence-free survival (DRFS) were estimated using the Kaplan-Meier method, and were compared using log-rank tests. Median, 6-month, 12-month, and 24-month survival rates were reported. Demographic and clinical variables were analyzed using a univariable Cox proportional hazards model to determine prognostic significance.

Results: Median follow-up time was 39 months from date of surgery. Among all 25 patients (13 [52.0%] female; mean age, 64.7 years; range, 36-91 years), 9 (36%) had > 10 pack-year smoking history, 18 (72.0%) had a perioperative medical complication and 12 (48.0%) had a surgical complication Using specimen-driven margin analyses, the mean margin clearance was 1.79 mm with twenty-three patients (95.8%) having at least one final surgical margin ≤ 5 mm. Seven patients did not receive adjuvant therapy, 2 received XRT and 16 patients (66.7%) received adjuvant chemoradiation. OS, DSS and RFS at 24 months were 44.0%, 63.2% and 52.6%, respectively. On univariate analyses, adjuvant chemoradiation versus no adjuvant therapy was associated with improved OS (hazard ratio [HR], 0.16; 95% CI, 0.05-0.48) and LRFS (HR, 0.15; 95% CI, 0.02-0.88). Advanced age as a continuous variable was associated with worse OS (HR, 1.11; 95% CI, 1.04-1.19), DSS (HR, 1.12; 95% CI, 1.01-1.23) and RFS (HR, 1.14; 95% CI, 1.03-1.27). Prolonged length of hospital stay was associated with decreased OS (HR, 1.05; 95% CI, 1.01-1.11).

Conclusion: For pT4b OCSCCA involving the masticator space, primary surgical resection followed by adjuvant chemoradiation demonstrates 24 month DSS of > 50% and OS of 44%. Despite suboptimal margins, modern surgical techniques have improved our ability to resect and potentially cure patients with tumors with masticator space involvement

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The impact of the MR-Linac field length on head and neck cancers patient selection

B. Ng-Cheng-Hin,[1] D. Mcquaid,[2] C.M. Nutting,[3] S. Bhide,[4] K.H. Wong,[5] K. Harrington,[6] and K. Newbold[4]; *[1]The Institute of Cancer Research and Royal Marsden NHS Trust, London, United Kingdom, [2]The Royal Marsden Hospital NHS Foundation Trust/ The Institute of Cancer Research, London, United Kingdom, [3]The Institute of Cancer Research, Sutton, United Kingdom, [4]The Royal Marsden NHS Foundation Trust, London, United Kingdom, [5]The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom, [6]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Purpose/Objective(s): The design of the 1.5 T Elekta Unity MR-Linac limits the craniocaudal (CC) radiation field length at the isocentre to 22 cm. A 1 cm margin in all directions is recommended for plan adaptation to the daily anatomy and to correct for set-up errors due to a static couch. This reduces the radiation field further to 20 cm in the CC direction. A restricted CC field length may influence the selection and absolute number of head and neck cancer (HNC) patients who can be treated on the MR-Linac using a single isocentre technique. The study aims to investigate the impact of a restricted CC field length on HNC patient selection at our institution.

Materials/Methods: 100 locally advanced HNC patients who underwent radical primary or adjuvant (chemo)radiotherapy at our institution were retrospectively analysed. CC field length was calculated by measuring the absolute distance between the most cranial and caudal aspect of the planning target volumes (PTV) on VMAT plans. The proportion of radiotherapy plans with a CC field length of < 20 cm was determined. Baseline characteristics such as gender, TNM stage, height and tumour primary sites were collected. Using Graphpad Prism software (Version 8.2.0; San Diego, CA), the data were analysed using descriptive analysis and linear regression. The significance threshold was set at p £ 0.05.

Results: The majority of patients within this study were male (72%), oropharyngeal cancers (51%) and T-stage ³ 2 (75%). Overall, 96% HNC patients demonstrated a CC field length < 20cm, with the majority (67%) ranging between 15 to 19.9 cm. Nasopharyngeal (n = 3), oropharyngeal (n = 67) and unknown primary (n = 9) HNC demonstrated the longest median CC field lengths at 21 cm, 18 cm and 17 cm, respectively. 4 patients with a CC field length ³ 20 cm had nasopharyngeal (n =2), oropharyngeal and paranasal cancers. These patients were male and taller with a mean height of 181 cm (SD 3.1 cm) compared to an overall mean patient height of 161.4 cm (SD 3.5 cm). In a subgroup analysis of oropharyngeal cancers, females (n = 11) demonstrated a shorter mean CC field length of 16 cm (SD 2.11 cm) and mean height of 165 cm (SD 7.9 cm), compared to males (n = 40) who

measured 177 cm (SD 5.5cm) with a CC field length of 18 cm (SD 1.03 cm). There was a significant, but weak correlation ($r^2 = 0.23$, $p = 0.0019$) for males between patient height and CC field length, suggesting that as the patient's height increased, the CC length also increased. This relationship was not significant for females ($p = 0.0677$).

Conclusion: The data suggests that the majority of head and neck cancers at our institution have a treatment target treatable on the MR-Linac. However, the absolute CC field size may vary according to primary sites and patient factors such as gender. Nasopharyngeal cancer with cranial extension may not be suitable for treatment on MR-Linac using a single isocentre.

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A Systematic Method to Increase Enrollment in Head and Neck Cancer Clinical Trials

M. Stewart, J. Johnson, V. Bar-Ad, R. Goldman, D. Cognetti, J.M. Curry, and A. Luginbuhl; *Thomas Jefferson University Hospital, Philadelphia, PA*

Purpose/Objective(s): Head and neck cancer patients are frequently referred to a surgical oncology practice as first point of entry into academic institutions. The purpose of this work is to determine potential barriers to clinical trial enrollment to both the patient and the clinical team in the setting of a busy head and neck surgery clinic. We hypothesize that specific factors within the cancer center's or clinician's control can be systematically identified and specific implementations can be deployed to reduce the burden of trial enrollment for a patient, leading to increased enrollment yield.

Materials/Methods: Prospective observational study. Variables surrounding new head and neck cancer patient visits within an academic tertiary surgical oncology office are collected for all surgeons. Collection tool focuses on whether a clinical trial was discussed, offered, or if patient enrolled as well as patient response to a trial and reasons for enrolling or not enrolling. Length of visit and wait time as well as if patients had access to clinical trial coordinators during the visit are recorded.

Results: We present the timepoint in a patient encounter when clinical trial opportunities are introduced and the likelihood of enrollment. Correlations of time management within a clinical visit including delays and time for patients to see coordinator and medical oncologist with likelihood of patient enrollment. Follow up data on reasons patients say 'yes' to clinical trial at the first visit, but then withdraw that interest will also be presented.

Conclusion: Head and neck surgical oncology offices with patients who are introduced to clinical trials can improve enrollment. We present a concept for a simple but systematic method that helps clinicians and cancer centers identify areas of improvement in the process of enrollment of eligible patients in clinical trials. Following accrual period, variables will be analyzed to develop a specific implementation for clinical trial enrollment. Head and neck cancer clinical trial enrollment will then be compared pre- and post-implementation.

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Clinicopathological Characteristics of Nonsmoker Nondrinker Oral Cavity Cancer

M. Sandelski, C. Liu, and A. Mantravadi; *Indiana University School of Medicine, Indianapolis, IN*

Purpose/Objective(s): To evaluate clinical and pathological characteristics of oral cavity cancer in the nonsmoker nondrinker (NSND) population.

Materials/Methods: A retrospective chart review was completed on patients presenting to a single institution for primary surgical treatment for oral cavity cancer between July 2013 and July 2018. 105 patients were included and the following information was recorded: demographics, smoking and drinking history, location of primary cancers, and clinical and pathological staging and characteristics.

Results: There were 29 patients who denied any obvious smoking or drinking history. A larger percentage of women (65.5% vs 19.7%, $p < 0.0001$) and younger patients (52.3 vs 62.8, $p < 0.05$) comprised the NSND group compared to patients with a smoking and drinker history. NSND patients presented more often with T1/T2 tumors (69% vs 38.2%, $p < 0.01$) than smoker drinkers. Both groups had roughly 40% of patients with nodal disease. Histological grade, perineural invasion, and lymphovascular evasion were all less common in NSND patients, however only perineural invasion was significant (24.1% vs 47.4%, $p < 0.05$). There were similar rates of recurrence and survival in both smoker drinker and NSND groups.

Conclusion: NSND oral cavity cancer form a distinct subgroup that has similar characteristics to smoker drinker oral cavity cancer. These patients have similar clinical and pathologic characteristics and should be treated with the standard of care. NSND patients do not require more aggressive treatment.

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Successful Tri-Modality Treatment of Atypical Carcinoma Ex-Pleomorphic Adenoma with More Than 50 Nodal Metastases

F.L. Ampil,[1] N. Dela Cruz,[1] T.A. Richards,[1] C.A.O. Nathan,[2] and B. Chang[1]; [1]*Louisiana State University Health Sciences Center, Shreveport, LA,* [2]*Louisiana State University Health, Shreveport, LA*

Purpose/Objective(s): In the described categories of carcinoma ex pleomorphic adenoma (CEPA) invasiveness, the widely invasive class is more commonly encountered and is an extremely aggressive tumor. Although level 1 evidence-based management algorithm for CEPA does not exist (due to the neoplasm's rarity), definitive surgery is the accepted mainstay of treatment, and postoperative radiotherapy is usually advocated when recognized risk factors for locoregional recurrence are present. Currently, it is not known whether there is a role for adjuvant chemotherapy in CEPA, especially when very many nodal metastases are found. The purpose of this study was to present the clinical characteristics and course of two patients with atypical CEPAs and supernumerary nodal metastases (SNM) that were managed by the tri-modality treatment scheme.

Materials/Methods: Three hundred seventy people were diagnosed with head and neck cancer at our institution between January 2016 and December 2017. From this population, two patients formed the subjects of this short report because both individuals underwent definitive surgery and contemporary postoperative chemoradiotherapy for CEPA with SNM (metastatic disease present in more than 50 cervical lymph nodes).

Results: The men were in the sixth and seventh decade of life and had stage IVa T2N2bM0 disease. CEPA was of the widely invasive category, and the malignancy originated in the parotid lymph nodes or submaxillary gland; additional risk factors such as tumor-positive surgical margins, lymphovascular and perineural invasion as well as high-grade neoplasm were histologically observed. PET-CT surveillance imaging (performed at more than two months post-treatment) did not show tumor in both studied subjects. Durations of disease-free follow-up after multimodality therapy were 24 months and 34 months.

Conclusion: The correct determination of the risks and selection of multimodality therapy in the two presented cases of CEPA-SNM led to an acceptable, intermediate-term outcome. These promising results may eventually assist in the establishment of postoperative chemoradiotherapy as standard of care for this particular neoplastic disease entity.

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Prognostic significance of Human Papillomavirus and Epstein-Bar Virus in Nasopharyngeal Carcinoma

N. Verma,[1] S. Patel,[1] V.W. Osborn,[2] S. McBride,[1] N. Riaz,[3] A. Lee,[3] N. Katabi,[1] E. Sherman,[4] N. Lee,[1] and C.J. Tsai[1]; *[1]Memorial Sloan Kettering Cancer Center, New York, NY, [2]SUNY Downstate Medical Center, Forest Hills, NY, [3]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [4]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): To investigate the patient, tumor and treatment characteristics and prognostic significance of Epstein-Barr virus (EBV) and human papillomavirus (HPV) associated nasopharyngeal cancer (NPC).

Materials/Methods: We identified 352 consecutive patients with NPC diagnosed between 1998 and 2017 and treated at our institution. Of these 6 patients with a diagnosis of recurrent NPC, 2 patients with a diagnosis of squamous cell carcinoma of unknown primary and 1 patient with incomplete data were excluded. Among the remaining 343 patients, 169 tested positive for EBV by in situ hybridization for EBV encoded RNA. 21 were HPV positive by p16 immunohistochemistry or by HPV PCR-MassArray, and 12 were negative for both EBV and HPV by these methods. We also included 36 patients without EBV pathological results in our EBV positive category because they had characteristics typical of EBV-associated NPC including Asian ethnicity and NPCs with non-keratinizing or poorly differentiated histology. 105 patients were characterized as having unknown viral background, 68 were white, 15 were black, 9 were Hispanic, and 13 were of other or unknown ethnicity. Chi-square was used to assess for any association between viral status and patient-, tumor-, or treatment-related characteristics. Kaplan-Meier methods were used to estimate overall survival (OS) and cox proportional regression was used to determine the hazard ratio (HR) for prognostic factors.

Results: Among the 238 patients of known viral status, 205 (86%) were classified as EBV positive, 21 (9%) were HPV positive and 12 (5.0%) were viral negative. The racial distribution was 38.2% Caucasian, 50.4% Asian and 11.4% of other ethnicities. Compared to HPV and viral negative patients, patients with EBV-associated NPCs were more likely to be of Asian ethnicity and have a negative smoking history. HPV-associated NPCs were more likely to present at a higher T-category. At a median follow-up time of 59.9 months (range: 0.1 - 222.4 months) EBV, HPV, viral negative and unknown viral NPCs showed no significant difference in OS ($p=0.198$), progression free survival (PFS, $p=0.770$) or time to distant metastasis (DM, $p=0.849$). EBV, HPV and unknown viral NPCs showed no significant difference in time to local failure (LF, $p= 0.403$) or time to regional failure (RF, $p=0.383$). Only older age (HR: 3.121, 95%CI: 1.604 − 6.073, $p = 0.001$) and higher overall stage (HR: 3.762, 95%CI: 1.783 − 7.940, $p = 0.001$) were associated with worse OS. Higher KPS functional scale (HR: 0.339, 95%CI: 0.176 - 0.652, $p = 0.001$) was associated with improved survival.

Conclusion: In our population, smoking and advanced T classification were enriched among HPV-positive NPCs. We did not find any difference in LF, RF, OS, PFS or DM between EBV, HPV and viral negative NPCs.

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Risk Factors for Human Papillomavirus-Positive Nonoropharyngeal Squamous Cell Carcinoma

M.J. Windon,[1] G. D'Souza,[2] T. Waterboer,[3] L. Rooper,[1] W.H. Westra,[4] T. Troy,[1] D.M. Pardoll,[5] M. Tan,[6] S. Yavvari,[1] A.P. Kiess,[7] B. Miles,[8] W. Mydlarz,[1] P. Ha,[9] N. Bender,[10] D. Eisele,[5] and C. Fakhry[5]; *[1]Johns Hopkins, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, United States, [3]German Cancer Research Center, Heidelberg, Germany, [4]Department of Anatomic and Clinical Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]Department of Otolaryngology Johns Hopkins University School of Medicine, Baltimore, MD, [7]Johns Hopkins University, Baltimore, MD, [8]Department of Otolaryngology − Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, [9]University of California San Francisco, San Francisco, CA, [10]German Cancer Research Center, Heidelberg, ME, Germany*

Purpose/Objective(s): It is well established that human papillomavirus (HPV)-positive oropharyngeal cancer (HPV-OPC) is distinct from HPV-unassociated head and neck squamous cell cancer (HNSCC). However, it is unknown whether risk factors for and characteristics of HPV-positive *non*-oropharyngeal (HPV-nonOPC) cancer and HPV-OPC are similar. This analysis aimed to describe these entities with the hypothesis that they are distinct.

Materials/Methods: Incident cases of HPV-positive head and neck squamous cell cancer and matched non-cancer controls were enrolled in a multi-institutional, prospective study examining risk factors, biomarkers, tumor morphology and survival. HPV tumor status was determined by RNA in situ hybridization testing for E6/E7 oncoproteins from high-risk HPV types. Regression models were used to evaluate characteristics of HPV-nonOPC cases compared with matched non-cancer controls, and compared with HPV-OPC. Kaplan-Meier and Cox regression methods were used to evaluate overall (OS) and recurrence-free (RFS) survival of HPV-nonOPC versus HPV-OPC.

Results: The study population included 20 HPV-nonOPC, 80 non-cancer controls, and 185 HPV-OPC. HPV-nonOPC were significantly more likely to have a history of smoking than controls (OR 3.49, 95%CI 1.11-10.9) and HPV-OPC (OR 3.28, 95%CI 1.10-10.2). Compared with HPV-OPC, HPV-nonOPC were less likely to have had over 3 lifetime oral sexual partners (OR 0.29, 95%CI 0.06-0.9), and were more likely to have prevalent anemia (OR 5.37, 95%CI 1.46-19.7) and multimorbidity (OR 3.30, 95%CI 1.04-10.5). HPV-nonOPC were less likely to have antibodies to HPV16 E6 oncoprotein (90% vs. 28%, OR 0.05, 95%CI 0.02-0.2) and were less likely to exhibit non-keratinizing pathology (75% vs. 91%, $p=0.03$) compared to HPV-OPC. Finally, HPV-nonOPC had significantly worse 4-year OS (77% vs. 96%, $p=0.001$) and RFS (69% vs. 94%, $p<0.001$) than HPV-OPC.

Conclusion: Patients with HPV-positive nonoropharyngeal cancers have behavioral risk factors, comorbidities, biomarkers, and survival that is distinct from HPV-OPC, and resembles HPV-negative head and neck cancer (HNSCC). These findings are important for understanding the population at risk for HPV-positive HNSCC and generating hypotheses regarding biological differences by anatomic location. Our results support consideration of HPV tumor status as a distinguishing clinical and prognostic feature primarily among head and neck cancers in the oropharynx.

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Clinicopathologic characteristics associated with oral cavity squamous cell carcinoma in nonsmokers

A.M. Tufano, N. Kohn, N. Seetharamu, L. Pereira, D. Kamdar, E. Gabalski, M. Ghaly, B. Parashar, J. Fantasia, D. Frank, and P. Goncalves; *Northwell Health, New Hyde Park, NY*

Purpose/Objective(s): Tobacco use is the most significant risk factor associated with oral cavity squamous cell carcinoma (OCSCC). However, there is a subset of OCSCC that occurs in non-smokers (NS) for unclear reasons. We retrospectively described a population of NS with OCSCC to report overall survival (OS) and factors associated with tumor recurrence after initial surgery.

Materials/Methods: We queried our institution's tumor registry for all NS (defined as no past or present use of any tobacco products) who have been diagnosed with primary OCSCC from 2009-2019). Analysis was performed of 153 patients (pts). Pt demographics, tumor characteristics and treatment approaches were abstracted from electronic medical charts. OS was estimated with the Kaplan-Meier product limit method and compared with the log-rank test. For time to recurrence, the cumulative incidence function was calculated and then compared (method of Gray), with death treated as a competing risk.

Results: Median age was 58 and 68 yrs for males and females respectively, (15-93). 125 pts (81.7%) were older than 50 yrs. 98 pts (64.1%) were female and 94 (61.4%) were white. A small subset of 42 pts (27.5%) reported alcohol use, and only 3 pts (2%) had clinically significant alcohol use. The most common primary site was the anterior tongue (65.4%, N=100), and buccal mucosa (9.2%, N=14). Premalignant lesions were noted in the biopsy or clinical examination of 36 pts (23.8%), with most common being dysplasia, (25%) and leukoplakia, (22.2%). 137 pts (89.5%) had surgery as the initial treatment. 32 pts (21.2%) received adjuvant chemotherapy and 68 pts (45.6%) received adjuvant radiotherapy. OS for the entire cohort was 80.5% at 3 yrs and 73.4% at 5 yrs. OS differed significantly by stage ($p<0.004$). For local disease (stages I-II), 3 and 5 yr survival were 93.0% and 81.3% respectively, and for locally advanced disease (LAD; stages III-IVB), OS was 65.6% and 61.2%. The cumulative incidence of recurrence was 38.4% at 3 years and 42.1% at 5 years. For tumors with perineural invasion (PNI) at diagnosis (N=36), the cumulative incidence of recurrence at both 3 and 5 yrs was 55.3% and for those without PNI (N=54), the cumulative incidence of recurrence at 3 yrs was 38.3% and 47.1% at 5 yrs ($p<0.033$). Extracapsular extension (ECE) was seen in 16.7% pts (N=15), but sample size was too small to assess for association with recurrence.

Conclusion: In our retrospective series, we found that OS for NS pts with OCSCC is similar to what is reported in the literature for all pts with OCSCC, and is worse for those with LAD at diagnosis. Presence of PNI at surgical biopsy is associated with recurrence. NS pts with OCSCC are predominantly female, white and do not use alcohol, which is a departure from the traditional descriptors for smokers with OCSCC, highlighting the need for a better understanding of the factors associated with cancer development in this population.

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Gender disparities among race in the incidence and overall survival of head and neck squamous cell carcinoma

A.N. Naik,[1] A. Mazul,[2] K.Y. Zhan,[1] and S.V. Puram[2]; *[1]The Ohio State University Department of Otolaryngology - Head & Neck Surgery, Columbus, OH, [2]Washington University, St. Louis, MO*

Purpose/Objective(s): Historically, the incidence of head and neck squamous cell carcinoma (SCC) has been higher among males compared to females. Recent studies also suggest that there is no significant difference in survival based on gender. However, there are limited analyses and studies assessing gender disparities within specific races. The purpose of this study was to comprehensively examine and characterize the effect of gender on overall survival among head and neck SCC patients with race serving as a significant co-variate.

Materials/Methods: We constructed a retrospective cohort from the National Cancer Database for primary SCC of oral cavity, larynx, and hypopharynx sub-sites from 2010 to 2015 treated with curative intent. Kaplan-Meier all-cause survival plots were constructed and log-rank p-values were calculated. Hazard ratios (HR) for gender were estimated by Cox proportional hazards regression.

Results: 254,234 cases of head and neck SCC were identified and 23.6% were female. Female patients were significantly older (average 63.1 years vs. 61.0 years in males) at time of diagnosis, less likely to have private insurance than males (36.9% vs 44.5%), and more likely to be treated at a tertiary academic center (51.5% vs 42.0%). Females were more likely to have oral cavity SCC (34.0% vs. 16.3%). Oral cavity cancer was more common in Hispanic (59.9%) and White females (53.1%) than Black females (31.1%). In general, females had better overall survival compared to males. The difference in five-year overall survival between males and females was greater for Black patients with SCC (47.1% vs 52.8%, respectively), followed by Hispanic patients (57.9% vs 61.0%) and White patients (56.2% vs 57.5%). For oral cavity SCC, there continued to be a gender disparity among Black and Hispanic patients based on the restricted mean survival time in which females lived 0.23 years longer than males (p-value 0.006 and 0.039, respectively). In the multivariate analysis, females across all races had better overall survival compared to males (White females, aHR 0.92, 95% CI: 0.88-0.93; Black females, aHR 0.92, 95% CI: 0.87-0.98; Hispanic females, aHR 0.71, 95% CI: 0.63-0.80). Black males had significantly worse survival than compared with White males (aHR 1.12, 95% CI: 1.08-1.16).

Conclusion: In general, females had better overall survival compared to males, which is consistent with previous analyses. However, our study highlights a gender disparity based on race in overall survival that was greater among Black and Hispanic patients. These observations could be influenced by a variety of social factors including personal behaviors and differences in healthcare access and/or treatment adherence that need to be further elucidated. Moreover, additional studies are warranted as these findings may also reflect biologic, hormonal, and potential tumor-specific differences associated with gender and race.

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Head and Neck Surgery Global Outreach Amongst AHNS Members: Ethics, Planning, and Impact

M. Stewart,[1] C. Kahue,[2] J.M. Curry,[1] M. Zafereo,[3] D. Weed,[4] C. Zender,[5] and A. Luginbuhl[1]; *[1]Thomas Jefferson University Hospital, Philadelphia, PA, [2]University of Kansas Medical Center, Kansas City, KS, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]University of Miami Health System, Miami, FL, [5]University Hospitals Cleveland Medical Center, Cleveland, OH*

Purpose/Objective(s): The Lancet Commission on Global Surgery has clearly defined objectives and goals for the global surgical community to help address burdens of disease in low-income and middle-income countries. Head and neck surgical oncology and reconstruction are uniquely suited for such efforts. At present, these efforts are not well recognized within our specialty despite significant ongoing efforts. We sought to capture the current state of global outreach throughout our society of surgeons.

Materials/Methods: The AHNS membership was assessed to determine which physicians were engaged in international humanitarian head and neck surgical outreach trips. The resultant group was divided into two

groups: those who perform free flap reconstruction and those who do not. The surveys created where constructed to focus on four major aspects: 1) trip planning, execution and post trip follow-up, 2) operative management, 3) training, and 4) ethical considerations. The surveys were sponsored by American Head and Neck Surgery (AHNS) Global Outreach Service.

Results: Forty surgeons were identified as engaged in head and neck and/or free flap reconstruction in developing nations. Twenty-three groups were contacted that reported trips involving ablative without free flap reconstruction (16/23, 70% response rate to survey) and 16 identified as incorporating free flap surgery into their outreach work (14/16, 80% response rate to survey). Surgeons reported an average of seven trips to over 70 destinations across the globe. Identification of surgical candidates, financial considerations, on-site patient care, complications, long-term postsurgical care, and educational goals are reported in detail across both ablative and reconstructive survey takers. We report on the collective results of 125 free flaps performed in these settings with eight reported failures and a flap success rate of 94%. Although the two groups differed on their opinions of the ethics of free flap transfer, they held similar beliefs in over-all ethical considerations. The limitations of patient care where strongly highlighted by both teams due to resource limitation to treat cancer patients adequately. Training remained an important component of these trips with a greater emphasis on training local surgeons in the free flap cohort.

Conclusion: The efforts to answer the call for alleviating the global burden of surgical disease is strong within our specialty. There is a shared focus on humanitarian effort and teaching generations of residents, fellows, and host surgeons advanced techniques. Ethics of high resource surgeries such as free flap reconstruction remains controversial, but is met with strong advocacy by those who perform them and the results to substantiate this advocacy.

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Incidence and characteristics of HPV-associated oropharyngeal cancer: An 18-year Danish population-based study with 2,169 patients

M. Zamani,[1] C. Grønhøj,[1] D. Hellelstrup,[1] A. Carlander,[1] T. Agander,[2] K. Kiss,[2] C. Olsen,[3] L. Baandrup,[3] F.C. Nielsen,[4] E. Andersen,[5] J.T. Friborg,[6] and C.V. Buchwald[1]; *[1]Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Pathology, Rigshospitalet, Copenhagen, Denmark, [3]Department of Pathology, Roskilde Hospital, Roskilde, Denmark, [4]Department of Genomic Medicine, Rigshospitalet, Copenhagen, Denmark, [5]Department of Oncology, Herlev Hospital, Copenhagen, Copenhagen, Denmark, [6]Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): The incidence of oropharyngeal cancer is on the rise, particularly in the Western World. Much of this increase is due to human papillomavirus (HPV) infection. Currently, HPV vaccination covers the most common viral genotypes, that affect the oropharynx, but these vaccines were initially only available to women. The objectives of this study were to investigate the incidence and HPV genotypes in tumours of all patients diagnosed with oropharyngeal squamous cell carcinoma (OPSCC) during an 18-year period in Eastern Denmark.

Materials/Methods: This was a population-based, consecutive, semi-national registry study. All patients diagnosed with OPSCC from 2000-2017 in Eastern Denmark were evaluated at head and neck oncological departments at public university hospitals. Analyses included tumour characteristics (HPV-positive [HPV+] vs. HPV-negative [HPV−]), age-adjusted incidence rates (AAIR), average annual percentage change (AAPC) of OPSCC, patient demographics and proportion of HPV+ OPSCC. Additionally, viruses present in HPV+ OPSCCs from 2011-2017 were genotyped.

Results: In total, 55% of 2,169 patients had HPV+ OPSCC. HPV+ cases were more commonly male (76%) than HPV- cases (67%). HPV16, HPV33, and HPV35 or other types were found in 86%, 7%, 4% and 3% of HPV+ cases from 2011-2017, respectively. The AAIR per 100,000 of all OPSCCs was 1.8 in 2000, which increased to 5.1 in 2017 (HPV+: three-fold increase, HPV−: two-fold increase). The AAPC from 2000 to 2017 increased by 7% (HPV+ increased by 10% and HPV− by 4%). The mean age at diagnosis for all patients increased during the 18-year study period (HPV+: 58 to 61 years, $p<0.001$; HPV−: 60 to 65 years, $p<0.001$).

Conclusion: A five-fold increase in OPSCC incidence was observed, of which the largest increase was due to HPV+ OPSCC, and the median age at diagnosis increased significantly. Over 93% of HPV genotypes in HPV+ OPSCC are included in current HPV vaccines, except for HPV35 (4%). HPV vaccination of both sexes is advised, and inclusion of HPV35 in the currently available HPV vaccines would be ideal.

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Depth of Invasion and Overall Survival in Oral Cavity Cancer Subsites

A.D. Schuman,[1] M.M. Chen,[2] M.E. Spector,[2] A. Rosko,[2] and S.B. Chinn[2]; *[1]University of Michigan Medical School, Ann Arbor, MI, [2]Department of Otolaryngology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): The relationship between depth of invasion (DOI) and overall survival (OS) is well known for early stage tongue cancer, and DOI has been incorporated into American Joint Committee on Cancer (AJCC) 8thedition T staging. Our goal was to characterize the relationship between DOI and overall survival for oral cavity cancer subsites, particularly non-oral tongue sites.

Materials/Methods: We analyzed the National Cancer Database (NCDB) for all patients with oral cavity squamous cell carcinoma (OCSCC) diagnosed from 2010-2016. Patients initially treated surgically with a recorded DOI and tumor size were included. DOI was categorized into <5mm, 5-10mm, and >10mm. T classification was based on AJCC 8thedition guidelines, including tumor size, DOI, and bone invasion. We used Kaplan-Meier estimation and Cox proportional hazards models for survival analysis by oral cavity subsite.

Results: Data from 23,463 patients with OCSCC were included. There were 2,748 (11.7%) gum, 1,639 (7.0%) buccal, 3,739 (15.9%) floor of

Abstract 259; Table 1 Five Year Overall Survival by OCSCC Subsite

	Oral tongue	Floor of mouth	Gum/Palate	Buccal/ retromolar trigone	Overall
Five Year OS (%, 95% CI)					
<5mm	64.7 (63.4-65.9)	56.0 (53.5-58.3)	57.4 (54.9-60.0)	49.5 (46.6-52.3)	60.1 (59.1-61.0)
5-10mm	57.7 (54.5-60.8)	49.8 (43.3-56.0)	49.6 (42.8-56.1)	48.0 (40.4-55.2)	53.8 (51.3-56.2)
>10mm	44.7 (41.4-47.9)	41.7 (36.3-47.1)	37.8 (31.7-43.9)	43.3 (36.3-50.0)	43.2 (41.0-45.6)
p-value	<0.001	0.055	<0.001	0.594	<0.001

mouth, 553 palate (2.4%), 341 mucosal lip (1.5%), 1,083 retromolar trigone (4.6%), and 686 other mouth (2.8%), with the remainder oral tongue (12,697, 54.1%). Patients were treated with surgery alone (12,832, 54.7%) or surgery followed by radiation/chemoradiation (45.3%). DOI was significantly associated with 5-year OS when all OCSCC was pooled and for patients with oral tongue and gum/palate cancer, but not for floor of mouth or buccal/retromolar trigone (Table 1). Similar results were seen with subgroups defined by T classifications. Cox models controlling for age, race, sex, grade, nodal status, metastasis, radiation status, tumor size, and bone invasion showed a hazard ratio (HR) of 1.37 comparing DOI >10mm to <5mm (95% confidence interval [CI] 1.27-1.49). Similar relationships (DOI >10mm vs <5mm) were present on subgroup analysis of OCSCC subsites: oral tongue (HR 1.48, 95% CI 1.33-1.65), floor of mouth (HR 1.36, 95% CI 1.12-1.64), and gum/palate (HR 1.40, 95% CI 1.12-1.75). This was not present for buccal/retromolar trigone (HR 1.14, 95% CI 0.91-1.44).

Conclusion: Depth of invasion is significantly associated with 5-year OS for oral tongue cancer, gum and palate, and floor of mouth; however, no such association was present for buccal or retromolar trigone malignancies. These findings are important in considering the stage, prognosis, and counseling of patients with different depths of invasion.

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Body-Mass Index (BMI) and early stage as predictors of papillomavirus infection in H&N cancers

N. Mladkova,[1] A. Olausson,[2] M.E. Gamez,[1] J.C. Grecula,[1] E.D. Miller,[1] S.R. Jhawar,[2] P. Bhateja,[3] M. Old,[4] A. Agrawal,[5] E. Ozer,[5] R. Carrau,[5] S. Kang,[5] N. Seim,[2] J.W. Rocco,[6] M. Bonomi,[2] and D.M. Blakaj[1]; *[1]Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, OH, [2]Ohio State University, Columbus, OH, [3]The Ohio State University, Columbus, OH, [4]The Ohio State University Wexner Medical Center, Columbus, OH, [5]The Ohio State University Department of Otolaryngology - Head & Neck Surgery, Columbus, OH, [6]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): The presence of HPV/p16 is associated with better prognosis in head and neck (H&N) tumors, yet less is known regarding individual patient factors that may affect the likelihood of HPV presence in their tumors. Previous data evaluated the correlation between BMI and HPV in H&N cancer has been inconsistent. Obesity has been linked to better prognosis in H&N cancer, but the associated with HPV upon presentation has not been explored. The purpose of this study was to determine factors that increase the likelihood of HPV infection upon presentation among H&N cancer patients.

Materials/Methods: We analyzed retrospectively data obtained from patients who were treated at the Ohio State Radiation Oncology Department for H&N cancer between 2013- 2018. HPV positivity was defined as P16 presence on pathology. Factors analyzed included age, BMI, smoking status and stage at presentation. AJCC8 was used for staging. Self-reported data were used to determine smoking status. BMI was obtained within 45 days of diagnosis. Statistical analysis was conducted in R using logistic regression.

Results: A total of 489 with HPV status information were included in the analysis. 379 (77.5%) of tumors were positive for HPV/p16. 371 (75%) of tumors represented oropharyngeal cancer. The average BMI was 29.3 (25.4 for HPV negative, 30.4 for HPV/p16 positive). The likelihood of HPV presence increased with increasing BMI ($p=0.00149$); conversely, it decreased with increasing AJCC8 stage at presentation. HPV presence was not impacted by age at diagnosis, smoking status or prior smoking history in the cohort. Subset analysis of oropharyngeal tumors showed strong negative prediction of HPV presence among current smokers ($p=0.020976$). In this cohort, a more advanced stage (III vs. I) at presentation significantly increased the likelihood of current smoking ($p=0.000838$), and was associated with lower BMI ($p=0.002201$).

Conclusion: To our knowledge this is the first study to associate HPV infection with BMI and early stage. This suggests that patients who present with non-HPV etiologies conversely present with lower BMI and more advanced stage. Subset analysis of oropharyngeal cancer patients confirmed an inverse relationship between smoking and HPV presence, and confirmed increased likelihood of advanced stage among current smokers and those with lower BMI. Our data suggest that BMI may represents a surrogate prognostic marker for H&N cancer patients receiving radiation treatment.

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Real World Immuno-oncology Treatment Patterns and Outcomes in US Patients with Metastatic Head and Neck Cancer

K. Bell,[1] A. Bruno,[1] D. Stafkey,[2] S. Murty,[2] and M. Ballas[1]; *[1]GlaxoSmithKline, Collegeville, PA, [2]Xcenda, Palm Harbor, FL*

Purpose/Objective(s): Pembrolizumab, approved 5 Aug 2016, and Nivolumab, approved 10 Nov 2016, are indicated in the treatment of recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. Limited information on real-world (RW) clinical practice exists in metastatic head and neck (mHN) cancer immuno-oncology (IO) treatment. The objectives of this retrospective study were to evaluate treatment patterns and RW outcomes of patients with mHN cancer treated in the US community setting.

Materials/Methods: Electronic health records and charts were reviewed from the International Oncology Network database for patients with a diagnosis of mHN, any histology, initiating an IO agent between Sept 2015 & Sept 2017.

Results: Of the 93 patients who met initial study criteria, 65 met chart review criteria; 34 initiating nivolumab and 31 initiating pembrolizumab, no other PD(L)-1s were used. Average age was 62.3 years, 23.1% female, and 70.8% initiated IO treatment in 2015 or 2016. Seven patients with a documented Eastern Cooperative Oncology Group (ECOG) performance status had a score of 2 or greater at the time of IO initiation. Of those initiating an IO, 36.9% were line 1 metastatic (1L), 40% were line 2 metastatic (2L), and 15.4% were line 3 metastatic(3L). Median real world progression free survival (rwPFS) in months was 2.40 (1.12, 3.95), 1.38 (0.89, 2.27), and 1.81 (0.72, 4.61) for 1L, 2L, and 3L, respectively. Real world overall survival (rwOS) in months was 6.15 (4.05, NR), 4.01 (2.01, 18.85), and 7.11 (1.64, 7.83) for 1L, 2L, and 3L, respectively.

Conclusion: IO therapy was utilized in patients with HN cancer prior to US regulatory authorization in recurrent/metastatic HNSCC with disease progression on or after platinum-containing chemotherapy, including considerable use in 1L setting prior to data release from randomized clinical trials. Results suggest that rwPFS outcomes for this population, irrespective of histology, fall within the range of median PFS values observed in IO clinical trials, while mOS were lower. Patients were the same age compared to clinical trial participants, but likely had poorer performance. Future research should explore treatment patterns and RW outcomes following the 10 June 2019 1L IO regulatory authorization. This study (HO-18-18739) was funded by GlaxoSmithKline.

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90-day mortality after radical radiotherapy for head and neck cancer: a population-based comparison between rural and urban patients

R.A. Olson,[1,2] R.C.J. Schlijper,[2] S. Bos,[2] S.N. Hamilton,[3] E. Tran,[4] E. Berthelet,[3] and J. Wu[3]; *[1]University of British Columbia, Vancouver, BC, Canada, [2]BC Cancer, Prince George, BC, Canada, [3]British Columbia Cancer Agency, Vancouver, BC, Canada, [4]BC Cancer, Vancouver, BC, Canada*

Purpose/Objective(s): We previously demonstrated a 3.6% 90-day mortality in patients treated with radical radiotherapy for head and neck cancer. This study assesses whether this rate differs between patients living in rural and urban areas, as we hypothesized decreased access to supportive care services (e.g. speech-language-pathologists, dietitians) in rural areas could result in higher rates of treatment-related death (e.g. dehydration, aspiration pneumonia).

Materials/Methods: All head and neck cancer patients treated between 1998-2014, with radiotherapy with or without chemotherapy/ surgery in British Columbia were included. Two classification systems (Statistics Canada [SC] and Modified Statistics Canada [mSC]) were used to divide patients into rural and urban centres, because of the controversy in which is most appropriate. In SC, rural areas are defined as a population <1,000 and a density of <400 people/km2 or 1,000-30,000 people with a density ≥400/km2 and urban areas as population of ≥30,000 or more and density ≥400/km2. mSc classifies a population <30,000 as rural and ≥30,000 as urban. Multivariable logistic regression analyses were performed to assess associations between 90-day mortality and rurality and other patient or treatment characteristics.

Results: 5,554 patients were included in this study. Median age was 63 years, 76% was male and 77% of patients was treated with ≥60 Gy. According to the SC and mSC definitions, 53% and 68% of patients, respectively, lived in urban centres. Neither definitions were associated with 90-day mortality in univariate or multivariable analyses (SC: OR 0.95, 95%CI 0.68-1.31, p=0.74; mSC: OR 1.23 95%CI 0.86–1.77, p=0.26). In both models, factors associated with a lower 90-day mortality were age <60 years, stage I/II, radiation dose of ≥70 Gy and initial surgery (P<0.05). Factors associated with higher early mortality were oral-cavity primary tumor, stage IVb, radiation doses between 0-39 Gy, 40-49 Gy and 50-59 Gy. A separate analysis with patients receiving ≥60 Gy (n=4318) did not show a significant difference in mortality for both rurality definitions. Lower odds for 90-day mortality were found for Stage I disease and age 50-60 for both definitions. Higher odds were found for Stage IVb and IVc disease, oral cavity primary and age ≥80.

Conclusion: After controlling for potentially confounding factors, we did not find an association between 90-day mortality and rurality in patients that were treated with radiotherapy for head and neck cancer in British Columbia.

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Incidence of head and neck cancer in adolescents and young adults: a Danish nationwide study from 1978-2014

K.K. Jakobsen; *Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark, Copenhagen, Denmark*

Purpose/Objective(s): Information on trends in incidence rates for head and neck cancers (HNCs) in adolescents and young adults remain sparse and few descriptive epidemiological studies have been published. This nationwide study aims to report incidence rates of HNC in adolescents and young adults in the Danish population from 1978-2014.

Materials/Methods: Patient between the age of 15-24 years, registered in the Danish Cancer Registry with a HNC, diagnosed in the period 1st of January 1978 and 31st of December 2014, were included. Based on the WHO-standard population and Danish age-specific population counts age-adjusted incidence rates (AAIR), and average annual percentage change (AAPC) were calculated and evaluated in relation to gender, anatomical location, and histology.

Results: In total, 424 patients (62.7% female) were diagnosed with a HNC. The median age at diagnosis was 21 years. Females had a significantly higher AAIR compared to men with an AAIR in females of 3.7 (95% CI2.0; 6.2) per 100,000 person years in 2014 compared to males with an incidence of 1.9 (95% CI 0.5; 3.8) per 100,000 person years in 2014. The AAIR was higher amongst patients aged 20-24 years compared to the age group of 15-19 year olds. When stratified according to location a significant increase in incidence was observed for thyroid cancer between the time periods 1978-2000 and 2000-2014. (p<0.0001). The AAPC for the total cohort was 3.1 (95% CI 2.2; 4.1).

Conclusion: This nationwide study describes a significant increase in incidence of HNC in adolescents and young adults from 1978-2014 along with a significantly higher incidence in females.

Author Disclosure: **K.K. Jakobsen**: None.

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Changing Demographics of Laryngeal Cancer: Are Patients Getting Younger?

D. Jacobs,[1] H.S.M. Park,[2] R. Rahmati,[3] S. Mehra,[3] and B.L. Judson[3]; *[1]Yale School of Medicine, New Haven, CT, [2]Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT, [3]Department of Surgery, Section of Otolaryngology, Yale School of Medicine, New Haven, CT*

Purpose/Objective(s): Clinically, we have noticed an apparent increase in the number of young patients being treated for laryngeal cancer. The purpose of the study is to investigate whether there has been a rise in the incidence rate of laryngeal cancer in young patients.

Materials/Methods: The Surveillance, Epidemiology, and End-Results Program (SEER) consisting of 9 registries was queried from 1975 through 2016. An age-period-cohort (APC) analysis using the National Cancer Institute (NCI) APC Web Tool was performed to understand the effects of age, calendar period, and birth cohort on laryngeal cancer incidence. 6-year intervals were chosen with patients aged 19 through 84 years at diagnosis. 95% confidence intervals (CI) were calculated.

Results: Query of the SEER database revealed 40,708 cases of laryngeal cancer. The incidence rate of laryngeal cancer has been decreasing steadily from 1975-2016 at an average annual percentage change (AAPC) of -2.02% per year (CI: -2.26, -1.77). Analysis of AAPC based on age cohort (local drift) revealed a U-shaped deviation. Patients at the extremes of age showed slower rates of decline than patients in middle age cohorts. AAPCs for age cohorts containing 19-24 year-olds and 79-84 year-olds were 0.20% (CI: -1.75, 2.19) and -0.35% (CI: -0.62, -0.09), respectively, while the largest magnitude of AAPC was in the 37-42 year-old age cohort at -3.25% (CI: -3.69, -2.81). The 19-24 year-old cohort was the only cohort with a positive AAPC. Analysis of effect of birth cohort revealed a non-linear relationship. Compared to the 1944 birth cohort, the incidence rate ratio of laryngeal cancer was approximately constant between birth cohorts 1896 and 1926 with ratios of 1.78 (CI: 1.55, 2.03) and 1.68 (CI: 1.61, 1.75), respectively. The incidence rate ratio thereafter decreased steadily to 0.37 (CI: 0.29, 0.47) in the 1974 birth cohort. Since 1974, the incidence rate ratio has remained the same or increased to 0.85 (CI: 0.33, 2.22) in the 1992 birth cohort.

Conclusion: Given the slower decline in laryngeal cancer incidence in the very young and very old compared to middle-aged persons, the relative proportion of patients seen in the clinic may be moving toward the extremes of age. However, given the relative rarity of laryngeal cancer in young patients, an increasing incidence of laryngeal cancer in the very young and in recent birth cohorts cannot be excluded.

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Short-term Mortality Risks Among Oropharynx Cancer Patients by Human Papillomavirus Status

Z.H. Fullerton,[1] S.S. Butler,[2] B.A. Mahal,[3] V. Muralidhar,[4] J.D. Schoenfeld,[5] R.B. Tishler,[5] and D.N. Margalit[5]; *[1]Dana Farber Cancer Institute, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Harvard Radiation Oncology Program, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA, [4]Harvard Radiation Oncology Program, Boston, MA, [5]Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA*

Purpose/Objective(s): There is substantial variation in head and neck cancer (HNC) mortality and competing mortality amongst HNC patients. This study characterizes the causes and risks of short-term mortality amongst oropharynx cancer (OPC) patients and how these risks differ by human papillomavirus-status (HPV).

Materials/Methods: A custom SEER dataset with HPV-status was used to identify 4,930 OPC patients diagnosed with non-metastatic (M0) cancer from 2013-2014, including 3,560 (72.2%) HPV-positive and 1370 HPV-negative cases. Causes of death and cumulative incidence estimates for HNC-specific mortality, competing mortality, second-cancer mortality and non-cancer mortality were analyzed by HPV-status. Risk factors for mortality events were determined using multivariable competing risk regression models.

Results: Compared to HPV-negative OPC patients, HPV-positive OPC patients have a lower risk of 2-year cumulative incidence of all-cause mortality (10.4% vs. 33.3%, $p<0.0001$) and a low risk of both HNC-specific mortality (4.8% vs. 16.2%, $p<0.0001$), and competing-cause mortality (5.6% vs. 16.8%, $p<0.0001$). In HPV-negative OPC patients, second-cancer mortality (2.4% vs. 10.8%, <0.0001) was the most common cause of non-HNC mortality; the rate of non-cancer mortality was higher compared to HPV-positive cases (3.2% vs. 6.1%, $P\leq0.0001$). The median follow-up was 11 months (range 1-23 months) in this cohort with known HPV-status.

Conclusion: HPV-positive and HPV-negative OPC patients have significantly different rates of both HNC mortality and competing mortality. HPV-negative patients are at substantial risk of competing mortality, even within 2 years of cancer diagnosis and treatment. These differences can inform power calculations for clinical trials and patient management in the acute and survivorship settings.

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Patient Outcomes and Chemotherapy Use for HPV positive Oropharyngeal Cancer in the United States, 2010-2016

K.S. Aujla,[1] D.P. Singh,[1] and H. Zhang[2]; *[1]Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY, [2]Wilmot Cancer Institute, University of Rochester, Rochester, NY*

Purpose/Objective(s): To examine overall survival for HPV positive (+) oropharynx cancer (OPX) patients, and to assess trends in chemotherapy use for HPV+ locally advanced (stage III-IV) OPX.

Materials/Methods: The custom Surveillance, Epidemiology, and End Result (SEER) Head and Neck with HPV Status Database (2010-2016) includes data on the HPV status of patients (18,586) with OPX. The known status of HPV increased significantly between 2010 (27%) to 2016 (72%), and therefore the use of the data set to estimate HPV incidence was strongly discouraged. The proposal of this study, to evaluate survival and chemotherapy use, was approved by the SEER custom data group. Patients with primary sites other than the OPX (2,673), histology other than squamous cell carcinoma (180), and unknown stage (762) were excluded.

Results: Among 14,971 eligible patients, 10,822 (72.3%) were HPV + and 4,149 (27.7%) were HPV -. HPV+ patients were more likely to be <60 year old (48% vs. 41%), White (91% vs. 83%), and Male (87% vs. 76%). The 2y overall survival (OS) for HPV+ vs. HPV-, stage I-II (962 vs. 686), stage III-IV (9,565 vs. 3,226), and stage M1 (295 vs. 237) patients was: 92.3% vs. 74.2% ($p<0.001$), 87.9% vs. 64.5% ($p<0.001$), and 45.3% vs.22.0% ($p<0.001$) respectively. Younger age (<60y) was associated with improved O.S. (HR = 0.67, $p<0.001$), while patients with level 1 lymph node involvement had worse O.S. (HR = 1.27, $p<0.001$). Chemotherapy use for HPV+, stage III-IV OPX improved 2y O.S. (89.4% vs. 82.9%) ($p<0.001$). The rate of chemotherapy use for HPV+, stage III-IV OPX for 2010-2016 was 76.4% overall, but decreased steadily from 2010 (85%) to 2016 (71%).

Conclusion: HPV status had a significant impact on predicting O.S., including for M1 patients. Chemotherapy appears to provide a survival benefit for HPV+, locally advanced patients. However the rate of chemotherapy use for HPV+, stage III-IV patients has been de-escalating in the United States from 2010-2016. Further investigation is indicated to explore the trend in survival outcome despite decreasing chemotherapy usage for this population.

Author Disclosure: **K.S. Aujla**: None. **D.P. Singh**: None. **H. Zhang**: None.

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Association between head and neck cancer and sexually transmitted diseases: a nationwide, case-control study

C. Grønhøj,[1] K.K. Jakobsen,[2] and C.V. Buchwald[3]; *[1]Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark, Copenhagen, Denmark, [3]Department of Otorhinolaryngology, Head &*

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HPV+/Stage III-IV	2010	2011	2012	2013	2014	2015	2016	Overall
Chemotherapy	430/504 (85%)	625/755 (83%)	878/1073 (82%)	1135/1441 (78%)	1267/1691 (75%)	1418/1910 (74%)	1550/2191 (71%)	7304/9565 (76%)

Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Purpose/Objective(s): An association between sexually transmitted diseases (STDs) and occurrence of head and neck cancer (HNC) has been proposed. This study determined the association between selected STDs (syphilis, gonorrhoea, and HIV) and HNC from 1978-2014 in Denmark.
Materials/Methods: Patients diagnosed with HNC in Denmark between 1978 and 2014 were included. Using individual identifier numbers, these were cross-linked to a nationwide hospital and clinic registry to examine occurrence of the STDs before cancer diagnosis. Patients were age- and sex-matched in a 1:10 ratio with general population controls. Univariate and multivariate analyses were performed using the Cox regression model to assess the correlation between STD and HNC.
Results: A total of 39,405 HNC patients and 393,238 controls were included. Patients with cancer of the upper aerodigestive tract had a significantly higher prevalence of a STD prior to the HNC compared to the reference population. Most HNC patients with a prior STD (64.1%) developed the HNC within five years after the STD diagnosis.
Conclusion: This study provides a complete description and analysis of the prevalence of STD in HNC patients and in a matched reference population. Although the studied STDs are rare, we showed that patients with cancer of the upper aerodigestive tract more commonly had a previous diagnosis of STD. The study indicates a causal link between the exposures leading to STD and HNC, however more studies to determine causality are needed.
Author Disclosure: **C. Grønhøj**: None. **K.K. Jakobsen**: None. **C.V. Buchwald**: None.

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Oropharyngeal Carcinoma related to human papillomavirus (HPV). A Latin American Experience.

A.H. Falco,[1] M. Angel,[2] A. Ostinelli,[3] G. Cefarelli,[3] M. Leiva,[3] M.T. Pombo,[3] M. Chacon,[3] and R. Chacon[3]; *[1]Instituto Alexander Fleming, Buenos Aires 1426, Argentina, [2]Alexander Fleming Institute, Buenos Aires 1426, Argentina, [3]Instituto Alexander Fleming, Buenos Aires, Argentina*

Purpose/Objective(s): Describe epidemiological characteristics of patients (pts) with Human Papiloma Virus (HPV) + Oropharyngeal Squamous Cell Carcinoma (OSCC), evaluating efficacy and toxicity, in an oncological institution in Latin America (Argentina).
Materials/Methods: Retrospective, descriptive analysis of pts with OSCC HPV +. Revision of medical records from 07/2013 to 02/2019. HPV Status: staining of p16 +/- in situ hybridization (CISH). Statistical analysis with Statistix 8.0.
Results: Of 302 pts with Head and Neck Squamous Cell Carcinoma (SCHNC), 65 (21.5%) were OSCC and of these, 46 HPV + (70.7%). 31 men (67%), median (md) age 56 years (y). 12 pts (26%) $\leq$ 10 pack /y and 16 pts (35%) non-smoking history. Marijuana abuse: 8%. 56% poorly differentiated or basaloid histology. 30 (14%) p16 (+) were CISH (+). 26 pts (57%) were Stage III. T1 / 2: 47% and N2-3: 41%. Primary treatment: Radiotherapy (RT) plus Chemotherapy (Ch) 97.5%, RT dose md 7000 cGy, Cisplatin greater/equal 200 mg/sqm: 88%. 11 % received RT plus Cetuximab as a primary treatment. Efficacy: RT-Ch response: 81% complete responses. 2y Disease free survival: 88.1%. 2y Overall Survival: 97.1%. GIII-IV toxicity: 63%.
Conclusion: With the bias of being a mono-institutional retrospective analysis, the HPV + OSCC population evaluated in this study shows epidemiological, clinical, pathological and prognostic characteristics similar to those reported in the literature.
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Survival and characteristics of 772 patients with oropharyngeal cancer and specific human papillomavirus genotypes: A Danish population-based study from 2011-2017

A. Carlander,[1] M. Zamani,[2] C.G. Larsen,[3] D. Hellelstrup,[4] T. Agander,[5] K. Kiss,[6] C. Olsen,[7] L. Baandrup,[7] F.C. Nielsen,[8] E. Andersen,[9] J.T. Friborg,[10] and C.V. Buchwald[11]; *[1]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Oe, Denmark, København N, Denmark, [2]Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]1Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Oe, Denmark, København N, Denmark, [4]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Oe, Denmark, Copenhagen, Denmark, [5]Copnehagen Univsersity Hospital, Copenhagen, Denmark, [6]Department of Pathology, Rigshospitalet, Copenhagen, Denmark, [7]Department of Pathology, Roskilde Hospital, Roskilde, Denmark, [8]Copenhagen University Hospital, Copenhagen, Denmark, [9]Department of Oncology, Herlev Hospital, Copenhagen, Copenhagen, Denmark, [10]Department of Oncology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Oe, Denmark, Copenhagen, Denmark, [11]Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): Human papillomavirus (HPV) is a well-known risk factor for oropharyngeal cancers (OPSCCs). We have previously demonstrated an increased incidence of HPV-related OPSCCs in Eastern Denmark from 2000-2017, mainly caused by infection with HPV16. But other subtypes have been found as well, most prevalently HPV33 and 35. The purpose of this study is to investigate how infection caused by specific HPV genotypes in HPV-related OPSCC correlates to prognosis, including recurrence free survival (RFS), overall survival (OS) and second primary cancers in Eastern Denmark from 2011-2017.
Materials/Methods: All patients (n=772) with OPSCC positive for HPV DNA and p16 from 2011-2017 in Eastern Denmark were included. Patients were all evaluated and treated at head and neck oncological centers in public university hospitals covering Eastern Denmark, a geographical zone comprising 46% of the national population. All tumours were genotyped by sequencing. As previously reported were 85,6 % (661/772) HPV16+, 7,4 % (57/772) HPV33+, 3,6 % (28/772) HPV35+, 1 % (8/772) HPV18+ and 2,4 % were positive for other subtypes (HPV11, 26, 31, 45, 56, 58, 59 and 67). Coinfections were found in 10 cases. Analyses included OS, RFS, secondary primary tumours and patient demographics that could influence survival and recurrence including alcohol consumption, smoking and performance status. Kaplan-Meier curves were used to analyze OS and RFS, and multivariate analyses were used to analyze significant predictors of OS and RFS.
Results: In progress.
Conclusion: This study will reveal whether extra attention to specific subtypes of HPV in relation to HPV + OPSCC is needed, in case these subtypes are related to more aggressive cancer disease. This might indicate a need for more intensive treatment and closer follow up in specific cases. Also, a great difference in survival between various subtypes could call for routine genotyping in the clinic as well as providing a basis for the choice of a prophylactic HPV-vaccine with greater coverage for the various HPV-subtypes.
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Deep learning detects actionable molecular and clinical features directly from head/neck squamous cell carcinoma histopathology slides

J. Dolezal,[1] J.N. Kather,[2] S. Kochanny,[1] J. Schulte,[1] A. Patel,[3] B. Munyampirwa,[1] S. Morin,[4] A. Srisuwananukorn,[5] N. Cipriani,[1] D. Basu,[6] and A. Pearson[1]; *[1]University of Chicago, Chicago, IL, [2]Universitätsklinikum RWTH Aachen, Aachen, Germany, [3]Ichan School of Medicine at Mt. Sinai, New Yord, NY, [4]Duke University, Durham, NC, [5]University of Illinois - Chicago, Chicago, IL, [6]University of Pennsylvania, Philadelphia, PA*

Purpose/Objective(s): The purpose of this abstract is to describe the application of deep learning to digital histopathology slide data for detection of clinically relevant features. Deep learning is a form of artificial intelligence which can process graphical data and "learn" to extract hidden features. Here we test the ability of deep learning to detect human papilloma virus, location of origin, and other features.

Materials/Methods: A deep convolutional neural network optimized to pathology imaging was used to extract features from digital head/neck squamous cell carcinoma (HNSCC) tumor tiles downloaded from the cancer genome atlas (TCGA). We downloaded digital slides, genomic annotations, and clinical data from 512 HNSCC TCGA cases. A pathologist manually annotated the tumor regions of interest on each slide. Individual image tiles were first extracted from regions of interest at 302 µm x 302 µm. Pixel data from extracted image tiles were then normalized and then trained via a Tensorflow/Keras implementation of the Xception model, with weights initialized using ImageNet pretraining. In order to reduce bias against sparse categories, training batches were filled with tiles in a manner that was balanced according to the output category. Training performance was evaluated on a validation dataset chosen at the time of training using 3-fold cross-validation, averaged across the folds.

Results: Provided only digital pathology slides, our deep learning approach can identify a number of HNSCC features with high accuracy. The receiver operator curve (ROC) area under the curve (AUC) for detecting HPV was 0.89. Within HPV positive HNSCC tumors, the ROC AUC for detecting an oropharynx (vs. other location) primary was 0.89. Interferon gamma signature was detected with a ROC AUC up to 0.66.

Conclusion: A functional deep learning pipeline can generate class predictions rapidly, and can be applied very inexpensively from remote locations, requiring only a digital slide. This emerging field of artificial intelligence may speed diagnosis and reduce cost in head/neck cancer. Further validation is warranted.

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The Prognostic Value of Pretreatment FDG PET/CT in Patients with Oropharyngeal Squamous Cell Carcinoma

J. Schmidt Jensen,[1] J.T. Christensen,[1] K.E. Hakansson,[2] M. Zamani,[1] I. Vogelius,[2] J. Löfgren,[3] B.M. Fischer,[3] J.T. Friborg,[2] C.V. Buchwald,[1] and J.H. Rasmussen[1]; *[1]Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, University of Copenhagen, Denmark, Copenhagen, Denmark*

Purpose/Objective(s): Traditional staging is developed with overall survival as sole endpoint. However, with more treatment options becoming available for patients with head and neck squamous cell carcinoma the risk of not only overall survival, but also the risk of local, regional and/or distant recurrence is relevant and important to aid in clinical decision making. Individualized treatment requires to address key questions: Whom to treat? Where to treat? As such, individualized treatment requires individualized prognostication beyond p16 status and UICC stage. The purpose of this study was to investigate if FDG uptake in primary tumor and lymph node metastases in patients with oropharyngeal squamous cell carcinoma (OPSCC) has a prognostic value beyond UICC8 staging and to develop a competing risk model with four clinically relevant endpoints.

Materials/Methods: Patients with OPSCC treated with primary radiotherapy at Rigshospitalet, University of Copenhagen in the period 2010−2017 were included. All patients had pretreatment FDG PET/CT scan performed. Four cause-specific Cox regression models were built for the hazard ratios (HR) of recurrence in T-, N-, M-site, and death with no evidence of disease (NED), respectively. The following variables were included: T-stage, N-stage, p16 status, metabolic tumor volume and FDG uptake in both primary tumor and lymph nodes. A competing risks analysis was performed and absolute risk estimates were estimated using the Aalen−Johansen method.

Results: Overall, 441 patients were included. Thirty-four patients had T-site recurrence, 31 had N-site recurrence, 32 had M-site recurrence and 52 patients had death NED as event. Nodal FDG uptake had a significant impact on N- and M-site recurrence, with HRs of 2.13 (95%CI: 1.20-3.77) and 2.18 (95%CI: 1.16-4.10). The individual prognostication of absolute risk of the four events for any given patient can be assessed in the online tool (https://rasmussen.shinyapps.io/OPSCCmodelFDG_PET/).

Conclusion: High nodal FDG uptake increases the risk of N- and M-site recurrence in patients with OPSCC in a competing risk scenario and these patients might be relevant candidates to include in trials testing systemic treatments in combinations with conventional treatments. The reported results are available in an easy applicable online tool and can help identify relevant candidates for future trials testing treatment approaches.

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Age-Related Tumor Immune Microenvironment Differences in Patients with Squamous Cell Carcinoma of the Oral Tongue

K. Chatzopoulos,[1] A.R. Collins,[2] X. Chen,[3] M.L. Hinni,[4] C.A. Ramsower,[3] M.A. Zarka,[3] J.J. Garcia,[5] and S.H. Patel[6]; *[1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic Alix School of Medicine, Rochester, MN, [3]Mayo Clinic, Scottsdale, AZ, [4]Department of Otorhinolaryngology, Mayo Clinic, Phoenix, AZ, [5]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, [6]Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ*

Purpose/Objective(s): Squamous cell carcinoma (SCC) is the most common malignancy of the oral tongue, usually affecting older patents, but occasionally also patients younger than 40 years old, mostly women. No genomic differences have been reported in the different age groups, but little is known about the tumor immune microenvironment. We performed an exploratory analysis for potential age-related differences in the tumor inflammation signature (TIS), which can be predictive for potential responders to PD-1 / PD-L1 checkpoint inhibitors in a variety of cancer patients.

Materials/Methods: RNA from tumor and normal tissue was extracted from archival formalin fixed paraffin embedded tissues from 16 patients with oral tongue SCC on this IRB approved study. Gene expression assessment was performed with the PanCancer IO 360 Panel (NanoString

Technologies, Inc., Seattle, WA) on separate tumor and normal tissue controls, and TIS was calculated with the research use only (RUO) algorithm, based on the expression of 18 immune response related genes expressed at the tumor microenvironment on the tumor samples. Clinicopathologic data were collected from chart review. Statistical analysis included Shapiro-Wilk test for normality, t-test for mean differences of normal variables, Wilcoxon signed rank test for non-parametric paired variables, Spearman's rho for non-parametric correlations and log rank test for impact on survival.

Results: Our cohort includes 16 patients, of which 5/16 (31%) are older with a median age of 76 years, 4/5 (80%) female and 1/5 (20%) male. The remaining 11/16 (69%) are younger than 40 years old with a median age of 28 years, 7/11 (64%) female and 4/11 (36%) male. Tumors have an overall higher TIS than their normal tissue counterparts (Wilcoxon signed Rank Test $p=0.002$). Older patients show a correlation trend towards higher tumor TIS (Spearman's rho 0.487, $p=0.056$), which is significantly higher (t-test $p=0.042$) than that of younger patients. At the end of the follow up period (mean 44 months, range 6-140) 3/16 (19%) of the patients died of their disease. Tumor TIS is inversely correlated with survival time (Spearman's rho -0.677, $p=0.004$) and older patients have more favorable, although not statistically significant, overall survival than younger patients (log rank $p=0.344$).

Conclusion: Although oral tongue SCCs produce a robust increase in immune-related gene expression, younger patients display lesser active tumor immune microenvironment than older patients, as defined by the TIS. Despite the lack of definitive prognostic significance, these findings highlight the need for further investigation into environmental and genetic factors underlying the tumor-host immune interactions, which have important therapeutic implications.

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68Ga-DOTATATE Imaging versus Fludeoxyglucose Positron Emission Tomography (FDG-PET/CT) in Oropharyngeal Cancer Patients

R. Patel and G. Marano; *West Virginia University, Morgantown, WV*

Purpose/Objective(s): The incidence of oropharyngeal cancer (OPSCC) is increasing, in part due to the human papilloma virus (HPV). OPSCC often presents with an undetectable primary tumor site and has a risk for long-term recurrence. Unfortunately, tumor-specific imaging for head and neck cancer (HNC) is non-existent, making detection and follow-up reliant on surrogate markers for metabolic activity. FDG-PET/CT is the current standard for HNC imaging, but specificity can be limited. Recent studies have correlated HPV infection with increased local expression of somatostatin receptors (SSTR). SSTRs are also differentially expressed in HNC specimens as compared to adjacent normal tissue, suggesting SSTR as a potential target for OPSCC tumor-specific imaging. 68Ga-DOTATATE, a SSTR-specific radiotracer, is widely used for imaging neuroendocrine tumors. We aim to explore this imaging modality to 1) Determine the ability of 68Ga-DOTATATE-PET/CT to detect primary tumors and nodal disease in OPSCC patients, and 2) Evaluate the concordance of 68Ga-DOTATATE-PET/CT imaging with FDG-PET/CT in OPSCC patients.

Materials/Methods: Institutional review board (IRB) approval for a prospective trial was obtained at our tertiary care institution. Treatment naïve patients were enrolled with a known or suspected diagnosis of OPSCC based on p16 and/or HPV testing. Patients underwent FDG-PET/CT imaging, followed by 68Ga-DOTATATE-PET/CT within 24 hours − 7 days. Baseline creatinine values were obtained prior to each scan to monitor for contrast toxicity. Imaging was reviewed by a neuroradiologist blinded to tumor site. Imaging findings on FDG-PET/CT, 68Ga-DOTATATE-PET/CT, and standard CT imaging were recorded and included location, dimensions and standard uptake values (SUV) at suspected sites of primary tumor and nodal disease. Data were compared with t-test and ANOVA ($p > 0.05$).

Results: 5 patients have met inclusion criteria. Both FDG-PET/CT and 68Ga-DOTATATE-PET/CT detected the primary tumor with no significant difference in tumor volume or dimension between imaging modalities. 13 total nodal metastases were identified; of these, 10 were concordant between imaging modalities with no significant difference in nodal size or volume. SUV were significantly lower at both the primary site ($p < 0.006$) and nodal sites ($p < 0.003$) for 68Ga-DOTATATE-PET/CT versus FDG-PET/CT.

Conclusion: 68Ga-DOTATATE-PET/CT has high concordance with FDG-PET/CT in the imaging of both primary tumor site and nodal disease in patients with OPSCC. Our findings present early results from a larger trial examining the utility of 68-Ga-DOTATAE-PET/CT in HNC patients. Future work will focus on evaluation of metastatic disease, as well as pathologic and molecular tissue correlation.

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Low Skeletal Muscle Mass Predicts Discharge Disposition after Free Flap Reconstruction in Head and Neck Cancer Patients

A.J. Jones, V.J. Campiti, M. Alwani, L.J. Novinger, A. Bonetto, M. Sim, M.G. Moore, and A. Mantravadi; *Indiana University School of Medicine, Indianapolis, IN*

Purpose/Objective(s): To determine if preoperative CT-measured skeletal muscle mass is a prognostic indicator for disposition other than home in head and neck cancer free flap reconstruction (HNCFFR) patients.

Materials/Methods: Patients undergoing HNCFFR at our tertiary referral center from 2014 − 2019 with preoperative abdominal imaging were included. Independent factors were retrospectively collected and included: patient demographics, major preoperative comorbidities (modified Charlson Comorbidity Index, mCCI), ECOG score, body mass index (BMI, kg/m^2), skeletal muscle index (SMI, cm^2/m^2), oncologic history, intraoperative data, and 30-day Clavien-Dindo (CD) postoperative complications. SMI was calculated by isolating and measuring the cross-sectional skeletal muscle area (cm^2, Hounsfield Units -29 to +150) at the third lumbar vertebra and dividing by patient height squared (m^2). Binary logistic regression modeling was used to identify significant, independent predictors of patient discharge disposition other than home.

Results: The cohort consisted of 174 patients, 57 (32.8%) of whom were discharged to a rehabilitation or nursing facility. Compared to patients discharged home, these patients were older (64.8 ± 11.8 vs. 57.1 ± 12.7 years, $p < 0.001$) and had lower SMI (39.3 ± 8.8 vs. 46.9 ± 9.0 cm^2/m^2, $p < 0.001$), but no statistical difference was observed between sex or race distributions, BMI, smoking or alcohol abuse rates. These patients had greater incidence of a major comorbidity (mCCI ≥1, 73.7% vs. 30.8%, $p < 0.001$) and functional disability (ECOG ≥1, 75.4% vs. 30.8%, $p < 0.001$). They more frequently had stage IV cancer (80.7% vs. 60.0%, $p = 0.007$) of the aerodigestive tract (86.0 vs. 71.8%, $p = 0.039$), but there was no difference in cancer histology, prior chemotherapy, or prior radiation therapy. Intraoperatively, they utilized fewer forearm flaps (14.0% vs. 30.8%, $p = 0.017$) and received more blood transfusions (64.9% vs. 26.5%, $p < 0.001$). No statistical discrepancy existed between operative times. Postoperatively, they more frequently experienced a major complication (CD ≥3, 36.8% vs. 13.7%, $p < 0.001$). Univariate analysis identified age, SMI, mCCI, ECOG score, stage IV disease, aerodigestive cancer, free flap type, perioperative blood transfusions, postoperative delirium, and CD ≥3 as significant predictors. The final multivariate

binary logistic regression model identified ECOG score ($p = 0.015$), SMI ($p = 0.033$), mCCI ≥ 1 ($p = 0.007$), postoperative delirium ($p < 0.001$), and CD ≥ 3 ($p = 0.036$) as significant, independent predictors of discharge disposition.

Conclusion: CT-measured SMI is independently associated with disposition other than home in HNCFFR and should be considered in preoperative planning.

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Redefine End-of-range RBE of Protons Based on Long-term Clinical Outcome

Y.Y. Zhang,[1,2] J.M. Slater,[3] S.I. Goldberg,[1] J.A. Adams,[4] H.M. Lu,[3] and A.W. Chan[3]; *[1]Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, [2]Department of Oncology, Xiangya Hospital of Central South University, Changsha, China, [3]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Massachusetts General Hospital, Boston, MA*

Purpose/Objective(s): Uncertainty in relative biological effectiveness (RBE) constitutes a major pitfall of the use of protons in clinics. Though it is well-known that RBE is tissue-specific, and it increases over the terminal few millimeters of the spread-out Bragg peak (SOBP), a fixed value of RBE of 1.1 that is based on animal models and cell cultures is currently used in clinical proton planning. The purpose of this study was to determine the end-of-range RBE in brain using long-term follow-up data of patients with nasopharyngeal carcinoma (NPC).

Materials/Methods: Sixty consecutive patients with newly diagnosed non-metastatic NPC received double-scattering proton therapy at our institution between 1997 and 2013. Treatments included a pair of right and left anterior oblique fields, with proton beams invariably ranged out in the left and right temporal lobes, respectively. Proton dose distributions were simulated using Monte-Carlo (MC) method and compared with those obtained from the clinical treatment planning system (TPS). Late treatment effect was defined as development of enhancement of temporal lobe on T1-weighted MRI. The dose-volume histograms (DVHs) of the individual temporal lobe was reviewed. The tolerance dose of temporal lobe was calculated by Receiving Operator Characteristics (ROC) analysis and Youden's index.

Results: With a median follow-up of 72.5 months (range: 6-207), 9 out of 60 patients (15%) developed enhancement in temporal lobe(s), with or without clinical symptoms. All areas of enhancements developed at the end-of-range regions of the anterior oblique fields. There was no significant difference in dose distributions between the MC and TPS plan. The tolerance dose-volume levels of temporal lobe for protons were V10 (25.5%), V20 (17.1%), V30 (10.9%), V40 (7.2%), V50 (3.2%), V60 (2.7%), and V65 (1.3%). Based on the cumulative DVHs generated from significant cut-off points, the D1% of protons was 58.56 Gy. The RBE for protons, using the established D1% of photons of 69.07 Gy, was calculated to be 1.18.

Conclusion: We, for the first time in literature, have determined that the clinical end-of-range RBE in brain is 1.18, a value that is 7.3% higher than the currently one. Considerations in proton treatment planning should be made with this newly clinically defined RBE.

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Prospective Assessment of DCE-MRI Parameters Associated with Advanced Mandibular Osteoradionecrosis after IMRT of Head and Neck Cancer

A.S. Mohamed,[1] R. He,[2] Y. Ding,[2] J. Wang,[2] B. Elgohari,[1] H. Elhalawani,[1] J.M. Johnson,[2] J. Stafford,[2] J. Bankson,[2] V.C. Sandulache,[3] C.D. Fuller,[4] and S. Lai[2]; *[1]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Baylor College of Medicine, Houston, TX, [4]University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Our group recently demonstrated that DCE-MRI can be used to detect alterations in bone vascularity following definitive radiotherapy to head and neck cancer patients. As a part of an active clinical trial to establish DCE-MRI as a biomarker of osteoradionecrosis (ORN), we sought to characterize the quantitative DCE-MRI parameters associated with advanced ORN.

Materials/Methods: Patients with diagnosis of advanced ORN after curative-intent radiation treatment of head and neck cancer were prospectively enrolled after institutional-review board approval and study-specific informed consent. Eligibility criteria included; age>18 years, pathological evidence of head and neck malignancy with history of curative-intent external beam radiotherapy; patients with clinically confirmed high-grade ORN requiring surgical intervention; and no contraindications to MRI. Prior to DCE-MRI, T1 mapping will be performed using a total of 6 variable flip angles. The DCE-MRI acquisition consisted of a 3D SPGR sequence. Extended Toft's pharmacokinetic model was be used for analysis. Motion correction was applied. Manual segmentation of advanced ORN 3-D volume was done using anatomical sequences (T1, T2, and T1+contrast) to created ORN volumes of interest (ORN-VOIs). Subsequently, normal mandibular VOIs were segmented on contralateral healthy mandible of similar volume and anatomical location (i.e. mirror image) to create self-control VOIs. Finally, anatomical sequences were co-registered to DCE sequences and contours were propagated to the respective quantitative parameter maps.

Results: Thirty patients were included. Median age at diagnosis was 58 years (range 19-78), and 83% were men. The site of tumor origin was in the oropharynx, oral cavity, salivary glands, and nasopharynx in 13, 9, 6, and 2 patients, respectively. IMRT was the radiation technique for all patients. Median IMRT prescription dose was 70 Gy in 33 fractions. Using matched pairs analysis, there were a statistically significant higher Ktrans and Ve values in ORN-VOIs compared with controls (0.8 vs 0.25 min^{-1}, and 1.9 vs 0.87, $p<0.0001$ for both). The average relative increase of Ktrans in ORN-VOIs was 3 folds healthy mandibular control VOIs (range 1.3-9.6). Moreover, the relative increase of Ve in ORN-VOIs was 2.6 folds the controls (range 1.2-6.6).

Conclusion: Our results confirm there is a quantitatively significant higher degree of leakiness in the mandibular vasculature as measured using DCE-MRI parameters of areas affected with advanced grade of ORN versus healthy mandible. We were able to measure significant increases in quantitative parameters (3 fold Ktrans, 2.6 fold Ve) compared to values from non-ORN mandibular bone. Further efforts are ongoing to validate these findings to be able to use these DCE-MRI parameter thresholds for early detection of subclinical cases of ORN.

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Near Infrared (NIR) Autofluorescence Image-guided Thyroid Surgery can Prevent Post-thyroidectomy Hypoparathyroidism – a Multicenter RCT

E. Lykke,[1] C.V. Buchwald,[1,2] A. Kjær,[3] and P. Homøe[4]; *[1]University Hospital of Copenhagen, Copenhagen, Denmark, [2]Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [4]Zealand University Hospital, Køge, Denmark*

Purpose/Objective(s): The objective of this ongoing randomized controlled trial is to examine whether the use of intra-operative NIR camera can reduce the number of patients who experience transient or persistent hypoparathyroidism after total thyroidectomy both in malignant and benign thyroid disease. Hypoparathyroidism is the most frequent complication after thyroid surgery and can be divided into transient (>3 month) or permanent (>12 months). Both are associated with significant costs and morbidity for the patient. It is well known that parathyroid glands can be detected intraoperatively due to their ability to autoflouresce when subjected to NIR-light. We hypothesize that NIR Imaging will reduce the frequency of persistent hypoparathyroidism. Several studies have found NIR useful to identify the parathyroid glands during thyroid surgery which has been associated with a reduced risk of transient hypoparathyroidism. To the best of our knowledge this is the first study where the effect on persistent hypoparathyroidism is examined in a randomized controlled setting.

Materials/Methods: 128 patients undergoing total thyroidectomy or completion thyroidectomy are expected to be included from august 2019 till august 2020 from two university hospitals in Denmark (Copenhagen University Hospital and Zealand University Hospital). Participants are randomized to either NIR optic imaging assisted or conventional total thyroidectomy and stratified based on sex and treatment center. All total thyroidectomy patients from either of the two centers who were able to give informed consent and above the age of 18, were invited to participate in the study. Patients with previous surgery on the parathyroid glands were excluded. The primary endpoint was the number of participants that biochemically showed hypoparathyroidism 12-months after surgery (defined as Parathyroid hormone (PTH) <1.6 pmol/L). PTH was measured preoperatively and at 4 hours, 1-, 3-, 9- and 12-months follow-up. The secondary endpoints were changes in ionized-calcium, number of detected parathyroid glands, in the NIR group: number of correctly and in-correctly identified glands (according to the NIR optics camera), duration of surgery and complications (vocal cord paralysis, post-operative bleeding and infections).

Results: The number of participants with hypoparathyroidism after 12-months in the two groups was compared using paired T-test. Changes in PTH and ionized-Ca over time were compared using two-way repeated measures ANOVA.

Conclusion: If NIR Imaging is found to reduce the incidence of hypoparathyroidism post-surgery this would be of major benefit for the patients. If this abstract is accepted I will present preliminary results at the Head and Neck Symposium 2020.

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3D Computational Modeling of Total Glossectomy Reconstruction: a Volume Based Approach by Donor Site

A. Rosko,[1] S.E. Ellsperman,[1] J. Cho,[2] R. Herster,[3] A. Vita,[3] K. VanKoevering,[3] and M.E. Spector[1]; *[1]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [2]University of MIchigan, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Free tissue transfer has become the mainstay for head and neck reconstruction, including total glossectomy reconstruction. The primary goal of total glossectomy reconstruction is to obliterate the oral cavity to rehabilitate speech and swallowing. To accomplish this goal, a number of donor sites have been described and utilized. The purpose of the study was to determine the best donor site to reconstruct the total glossectomy defect using 3D computational modeling using computed tomography (CT).

Materials/Methods: Patients with CT scans of the oral cavity, thorax and lower extremity were identified. Patients were excluded if they had a history of prior tongue surgery or radiation. In total, 130 patients were identified. Neck CT scan were reviewed and 3D modeling was performed to calculate the oral cavity volume necessary for adequate tongue reconstruction. A template was fashioned based on patient specific measurements for free tissue reconstruction. From this, the ideal free flap thickness for each patient was calculated. Whole body imaging was used to calculate the thickness of the anterolateral thigh (ALT), parascapular, latissimus dorsi and rectus abdominus fasciocutaneous free flaps. Free flap thickness was then correlated with Body Mass Index (BMI) as it related to ideal flap thickness. BMI was categorized as less than or equal to 22.5 kg/m^2, greater than 22.5 but less than or equal to 25, greater than 25 but less than or equal to 30, greater than 30 but less than or equal to 35 and greater than 35.

Results: As expected, free flap thickness was highly correlated with BMI. In patients with a BMI of less than or equal to 22.5, only the rectus free flap had adequate volume to reconstruct the oral cavity. In patients with a BMI of 22.5-25 the rectus, parascapular and latissimus flaps all had adequate volume to reconstruct the oral cavity. The ALT approached adequate volume in this group but otherwise had inadequate volume across all BMI groups to reconstruct the volume of the oral cavity. The same was true for those with a BMI greater than 35.

Conclusion: This is the first study to evaluate computed tomography and 3D modeling to characterize head and neck defects and ideal reconstructive options. In this study, rectus flap is the only flap adequate for oral cavity reconstruction in low BMI patients. The ALT appears inadequate to fully reconstruct the oral cavity volume in any BMI.

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Radiation Sensitivity of ADC in Head and Neck Cancers

Y. Cao,[1] M.P. Aryal,[1] C. Lee,[1] C.H. Chapman,[2] D. Owen,[3] A. Dragovic,[3] P.L. Swiecicki,[4] K. Casper,[5] F. Worden,[4] T.S. Lawrence,[6] A. Eisbruch,[1] and M.L. Mierzwa[1]; *[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [2]Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI, [3]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, [6]University of Michigan, Department of Radiation Oncology, Ann Arbor, MI*

Purpose/Objective(s): In head and neck cancers (HNC), prognostic and predictive values of apparent diffusion coefficient (ADC) have been demonstrated. Thus ADC has the potential to guide adaptive RT. However, ADC can be affected by multiple biological and pathological factors. The effect of HPV status on ADC response to radiation is not well understood. We hypothesized that the HPV status affects ADC and its response to radiation as well as its prognostic and predictive values.

Materials/Methods: The first 74 patients (26 p16-) who were enrolled in a randomized phase II multi-center clinical trial for stage III AJCC 8 p16+ OPSCC or p16- advanced HN cancer planned for definitive

chemoradiation (including those in the observation arm) were included in this analysis. Diffusion MRI was acquired before RT and at fx 10 of 2 Gy of RT (2 wk). Gross tumor volume (GTV) of each tumor was defined on post-Gd T1 weighted MR images. Mean ADC and fractional volume of low ADC ($< 1.2\ 10^{-3}$ mm^2/s) in each GTV pre-RT and at 2wk as well as theirs changes were evaluated for significant differences between p16- and p16+ tumors. Their prognostic and predictive values for times to local and regional failure, censored for last follow-up, distant failure, or death, were analyzed using log rank test.

Results: Both p16- and p16+ cohorts of patients had similar and large sizes of total GTVs (median of 74 cc for both). The mean pre-RT ADC values were different between p16- and p16+ primary tumors, but did not reach significant (1.47 vs 1.39 $x10^{-3}$ mm^2/s). The changes in ADC and fractional volume of low ADC at 2wk vs pre-RT were significantly less in p16- (respective 11.3% and 7.0%) than p16+ primary tumors (respective 16.4% and 10.5%) with $p<0.03$. However, for nodal tumors, there was no significant difference of any parameters between p16- and p16+. At the time of this analysis, 14 patients (10 for p16-) had local progression, and 10 patients (6 for p16-) had regional progression. For patients with p16- tumors, high ADC and small fractional volume of low ADC in primary and nodal tumors pre-RT and at 2wk significantly differentiate local and regional progression from control (log rank test, p values of 0.005-0.04), but not their changes. For patients with p16+ tumors, there were large variations in ADC, fractional volume of low ADC and their change in primary (or nodal) tumors, and no significant differences between local (or regional) progression and control.

Conclusion: We found that p16- and p16+ tumors had different ADC response rates to radiation. However, the response rates of ADC cannot predict local or regional progression in either p16- or p16+ tumors. In p16- tumors, high ADC, possibly due to stroma, results in local or regional progression. These together suggest that low ADC, possibly due to cellularity, may not be resistant to CRT in HNC.

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Using Mathematical Modeling and Machine Learning to Optimize Individualized Radiation Response in Head and Neck Squamous Cell Carcinoma Patients

T. Zhang[1] and V. Takiar[2]; [1]*University of Cincinnati Cincinnati, OH,* [2]*University of Cincinnati Department of Radiation Oncology, Cincinnati, OH*

Purpose/Objective(s): Radiation therapy (RT) is a key component of definitive head and neck squamous cell carcinoma (HNSCC) treatment. However, current radiation paradigms are not optimized for the individual patient. Given the high social-economic cost and patient discomfort associated with recurrence, it would be ideal to choose the optimal RT dose for maximal tumor regression and minimal side effects. Since it is unethical to treat any given patient with different radiation schedules for comparative purposes, a practical alternative is to model and simulate with various radiation dosages to identify the optimal plan for that patient. The purpose of this research is to develop a practical computational framework to predict, understand and optimize the radiation response of individual patients with HNSCC.

Materials/Methods: We integrated mathematical modeling and machine learning methodologies to develop a computational framework. The modeling was used to incorporate known biology of HNSCC, while machine leaning allowed us to explicitly address heterogeneity between individual patients as well as uncertain biology. To connect the tumor dynamics, the behaviors of tumor cells and the underlying molecular control network, we undertook a multi-scale modeling approach.

Results: We have developed a computational framework that can guide the personalization and optimization of a radiation plan for individual patients. We accumulated a total of more than 10,000 HNSCC *virtual patients* and their tumor responses based on literature reports and NIH- sponsored databases. Despite inter-patient heterogeneities and the uncertainties with kinetic parameters, our framework can predict optimized treatment plans for each individual patients with high accuracy (>80%). Moving an individual patient to the optimized plan determined by the model results in faster tumor regression and smaller size (30-80% of the control). Machine learning analysis with the virtual patients reveals that the survival rate of tumor cells, as well as the proliferation rates of both tumor cells and resistant cells, are the top three significant components in predicting patient outcomes. The multiscale model also reveals how minimal dosages of chemotherapy agents (cisplatin and BCL inhibitor-263) can be combined to effectively reverse the radiation resistance of tumor cells.

Conclusion: In summary, we have developed and a comprehensive, multiscale framework that faithfully reflect our knowledge and gaps. The framework provides a rational method for searching for optimal dosing regimens for combinations of radiation therapy and chemotherapy for individual patients so that the plan can be "*just right*" for any given patient at that specific time.

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Association between multimodal functional imaging and intratumor heterogeneity of immunohistochemistry in head and neck squamous cell carcinoma

J.H. Rasmussen,[1] A. Olin,[2] G. Lelkaitis,[3] A.E. Hansen,[2] F.L. Andersen,[2] H.H. Johannesen,[2] A. Kjær,[2] B.M. Fischer,[2] L. Specht,[4] S.M. Bentzen,[5] C.V. Buchwald,[1] I. Wessel,[6] and I.R. Vogelius[4]; [1]*Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [2]*Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [3]*Department of Pathology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [4]*Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [5]*Division of Biostatistics and Bioinformatics, University of Maryland Greenebaum Cancer Center, and Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD,* [6]*Department of Otorhinolaryngology, Head & Neck Surgery and Audiology at Copenhagen University Hospital, Rigshospitalet, Denmark, Copenhagen, Denmark*

Purpose/Objective(s): Tumor heterogeneity is furthered by mutation, selection and adaptation as the primary tumor spreads to regional or distant sites. While some similarities may be preserved among individual lesions there is multi-level biological variability between patients, within patients and within lesions. The concept of a more individualized treatment approach, known as precision medicine, is an emergent field and several immunohistochemical (IHC) biomarkers associated with hallmarks of cancer have been identified. Single tumor biopsies cannot detect intratumor heterogeneity for obvious reasons and molecular imaging would, in

principle, offer the ideal solution by providing a non-invasive measurement of the biological properties of the entire extend of the tumor. In this study we perform a lesion level investigation of intratumor heterogeneity on cancer related biomarkers in head and neck tumors and investigate if global tumor measures on functional imaging can predict intratumor heterogeneity.

Materials/Methods: In this prospective study patients with primary or recurrent head and neck squamous cell carcinoma (HNSCC) referred for surgery with curative intend were offered inclusion. All patients were scanned on an integrated PET/MRI scanner prior to surgery with the PET tracer FDG. All tumors were removed en bloc, formalin fixated and sliced contiguously. Six tumor blocks from each lesion were selected for core biopsy and used to construct tissue microarray (TMA) blocks. Immunohistochemical staining was performed with a predefined list of biomarkers: p40, p53, EGFR, Ki-67, Glut1, VEGF, Bcl-2, CAIX, PD-L1. Intratumor heterogeneity of the IHC biomarkers was assessed using the variation in tumor proportion score in the six core biopsies within each tumor lesion. The heterogeneity in the imaging biomarkers was assessed by calculating the coefficient of variation (CV) of the three imaging measurements SUV (FDG uptake), ADC (diffusion) and K^{trans} (perfusion) in each tumor lesion.

Results: Twenty-eight patients with a total of 33 lesions were included. PD-L1, CAIX and Ki-67 is heterogeneously expressed between the lesions but also between the core biopsies from the same lesion. There was a large variation in p53 expression between the lesions, but better concordance in p53 expression within a lesion *(figures illustrating the heterogeneity of all biomarkers will be presented)*. The variation in tumor cell count correlated positively and significantly with the variation in ADC (rho = 0.37) and in the regression analysis ADC were significant for the variation in tumor cell count (p=0.004).

Conclusion: The studied functional imaging biomarkers showed only weak association with heterogeneity IHC. More accurate and specific functional imaging metrics are required for successful imaging-based assessment of intratumor heterogeneity.

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HPV-Positive EBV-Negative Nasopharyngeal Cancer: Prevalence and Impact on Outcomes in a Non-Endemic Population

W.R. Kennedy,[1] A. Srivastava,[1] A. Chundury,[2] P. Cosper,[3] J. Contreras,[4] H.A. Gay,[1] P.J. Parikh,[5] X. Wang,[1] D. Gondim,[6] R. Chernock,[6] and W.L. Thorstad[1]; *[1]Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO, [2]Department of Radiation Oncology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, [3]Department of Human Oncology, University of Wisconsin, Madison, WI, [4]Miami Cancer Institute, Miami, FL, [5]Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, [6]Washington University School of Medicine, Department of Pathology, St. Louis, MO*

Purpose/Objective(s): To determine the prevalence of high-risk human papillomavirus (HPV) in non-endemic nasopharyngeal cancer (NPC), its association with p16 status, and potential influence on clinical outcomes in a cohort treated with definitive chemoradiotherapy (CRT).

Materials/Methods: We identified 24 patients from a prospectively-maintained database treated with CRT for NPC from 1997 to 2014. All patients had paraffin-embedded tumor specimens on which Epstein-Barr virus-encoded small RNAs (EBER) in-situ hybridization and p16 immunohistochemistry (IHC) were performed. All specimens were then reviewed by an experienced head and neck pathologist who isolated and reverse transcribed total RNA from tumor regions, then performed quantitative PCR for E6 and E7 of 13 different high-risk HPV types. Log-rank tests and Cox proportional hazard models were performed to evaluate the impact of clinical factors on patient outcomes. Survival estimates were derived via the Kaplan Meier method.

Results: Of the 24 tumors, 7 were HPV-positive/EBV-negative (29%), 15 were HPV-negative/EBV-positive (63%), and 2 were negative for both HPV and EBV (8%). All tumors positive for HPV mRNA expression were also positive for p16 IHC, and all tumors negative for HPV were also negative for p16, resulting in a 100% sensitivity and 100% specificity of p16 as a surrogate for high-risk HPV expression. Median age of diagnosis was 48 (19 – 68). All but 1 HPV-positive tumor was WHO II and no patients with HPV-positive tumors were WHO III. All patients received concurrent chemotherapy, with 3 patients also receiving neoadjuvant and 16 receiving adjuvant chemotherapy. Median doses to the primary and neck were 70 Gy (69.96 – 72) and 56 Gy (50.4 – 64.6), respectively. Median follow-up was 5.9 years (0.9 – 18.0) and was not different when stratified by HPV status. Local-regional control at 5 years was 100% for HPV-positive versus 81.9% for HPV-negative patients (p=0.171). Distant control at 5 years was 83.3% for HPV-positive versus 70.1% for HPV-negative patients (p=0.414). Overall survival at 5 years was 100% for HPV-positive versus 74.5% for HPV-negative patients (p=0.044). Multivariable analysis revealed that older age (HR 1.15, 95% CI 1.01-1.28) and advanced nodal stage (HR 33, 95% CI 1.19-91.44) remained as independent predictors of OS.

Conclusion: We revealed that in a group of patients diagnosed with NPC in the midwest United States, HPV-driven NPC comprised a significant proportion of NPC cases, and was mutually exclusive from EBV positivity. Importantly, we discovered that p16 IHC is a strong surrogate marker for HPV-positivity in NPC. Patients with HPV-positive NPC had significantly improved overall survival in our cohort.

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Pathologic Analysis of Submandibular Triangle and Jugular Chain Lymph Nodes in Oral Cavity Squamous Cell Carcinoma

T. Gessert,[1] M. Tao,[1] M. Hoffman,[1] R. Hu,[2] and G.K. Hartig[3]; *[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, [3]University of Wisconsin, Madison, WI*

Purpose/Objective(s): The presence of extracapsular extension (ECE) in regional lymph node metastases carries implications for prognosis and treatment in patients with oral cavity squamous cell carcinoma. The following grading system for nodal ECE has been proposed in the literature:

G0: metastatic focus contained within node with normal nodal tissue between tumor and capsule
G1: metastatic focus extending to capsule
G2: ≤ 1mm of extension beyond capsule
G3: >1mm extension beyond capsule
G4: complete replacement of node by tumor

Little is known about the growth patterns of regional metastases that transform an intranodal metastatic focus to a node with ECE. Even less is known about differences in the pattern of that transformation within submandibular triangle nodes (level I) versus jugular chain nodes (levels II-

IV). It has been our impression that even small level one nodes often have ECE and that ECE in level I nodes can be dramatic with gross tumor extension into surrounding structures. The objective of this study is evaluate the first of these impressions by examining the degree of ECE in level I nodes relative to nodal size and comparing this to nodes with ECE in levels II-IV.

Materials/Methods: This is a single institution retrospective review study comparing pathologic characteristics of lymph node metastases within the submandibular triangle and the jugular chain. The institutional head and neck cancer database was queried for patients with both oral cavity squamous cell carcinoma and lymphadenectomy specimens with involved lymph nodes and pathology slides available for review. These specimens were re-reviewed by a pathologist recording various measurements including size of lymph node, size of metastatic focus within node, presence/absence of ECE, distance of extension beyond nodal capsule and grade of ECE. These nodes were stratified by level of origin (I vs II-IV) and pathologic grade of ECE, and mean nodal size for each subset was reported. Mean nodal size for nodes with G1 or G2-4 ECE was compared between level I nodes and level II-IV nodes using independent samples t-tests. $P<0.05$ was considered significant.

Results: 123 patients met inclusion criteria. For G1 ECE, average nodal size was 1.5 ± 0.9 cm ($n=24$) for level I and 2.1 ± 1.2 cm ($n=35$) for levels II-IV ($t=1.884$, $p=0.065$, 95%CI: -0.03 to 1.09). For G2-4 ECE, average nodal size was 1.8 ± 0.9 cm ($n=36$) for level I and 2.2 ± 1.0 cm ($n=46$) for levels II-IV ($t=1.629$, $p=0.107$, 95%CI: -0.08 to 0.78).

Conclusion: Our results did not meet statistical significance, however there was a strong trend towards smaller nodal size at equivalent grades of ECE for level I nodes compared to levels II-IV. Further investigation is required to determine whether level I nodes develop ECE at smaller sizes and earlier time points compared to jugular chain nodes.

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Initial Experience with MR-Guided Adaptive Radiotherapy for Head and Neck Cancers: Daily Setup and Dosimetric Variability on an MR-Linac

B. McDonald,[1,2] S. Vedam,[1] J. Yang,[1] P. Castillo,[1] A. Sobremonte,[1] B. Lee,[1] J. Wang,[1] N. Hughes,[1] M. Mohammedsaid,[1] and C.D. Fuller[1]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX*

Purpose/Objective(s): The recent clinical implementation of a novel integrated MRI/linear accelerator (MR-linac) has enabled daily adaptive radiotherapy treatments for head and neck cancers. We report the inter-fraction variability in patient setup and radiation dose to the tumor and organs at risk (OARs) for the first five head and neck patients at our institution.

Materials/Methods: Five patients (age range: 56-80; treatment sites: 3 larynx, 1 oropharynx, 1 orbit; number of fractions per patient: 4-33) were treated with intensity modulated radiotherapy (IMRT) on a 1.5T/7MV MR-linac, totaling 105 adaptive fractions. Patients were positioned in custom immobilization masks. To assess setup variability, isocenter shifts from the reference plan in the x, y, and z directions were recorded for each fraction and are reported as the absolute distance. Gamma analysis with 3%/3mm criteria was performed for IMRT quality assurance of each adaptive plan. For each patient, the adaptive plans were summed to create a composite plan for dosimetric comparison with the reference plan.

Results: Between the 105 fractions, the median isocenter shift was 0.58 cm (range: 0.15-1.77 cm). The median gamma pass rate was 99.5% (range: 90.9%-100%). Among the 5 patients, the percent difference in dose to the target structure between the reference and composite plans ranged from 0.02% to 1.6%. For OARs, the percent difference in dose ranged from 1.8% to 6.9% for the spinal cord, 0.03% to 6.7% for the brainstem, 0.9% to 6.6% for the ipsilateral parotid gland, 1.6% to 11.0% for the contralateral parotid gland. For all patients, the dose to all OARs was lower in the composite plan than in the reference plan with the exception of the spinal cord for three patients. However, the spinal cord still met the IMRT constraint in two of these three cases.

Conclusion: Daily adaptive head and neck radiotherapy on an MR-linac produces minimal setup variations and reduces dose to nearly all OARs while maintaining consistent tumor dose.

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Method for motion artifact compensation in dynamic optical contrast imaging

Y. Hu,[1] M. St. John,[2] P. Pellionisz,[3] S. Moon,[1] and Y.M. Alhiyari[4]; *[1]UCLA, Los Angeles, CA, [2]Ronald Reagan-UCLA Medical Center, Dept of Head and Neck Surgery, Los Angeles, CA, [3]University of California, Los Angeles, Los Angeles, CA, [4]Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Purpose/Objective(s): It has always been challenging for surgeons to localize offending lesions because of their small size, variable locations and indistinct external features while surgical interventions. Traditional methods include palpating edges and following analysis of biopsied tissues, which are limited in experienced hands or time consuming. Our group was able to innovate an intraoperative imaging system which generates wide-field tissue contrast images using relative differences in autofluorescence lifetimes at the speed of a few seconds per frame. In our technique, due to the relatively long gating time of each frame and intervals between frames, human movements are inevitably reflected in the images, yielded low success rate and required multiple re-runs to achieve satisfying results. This paper presents a way to minimize the influence of movements.

Materials/Methods: Phantoms with different autofluorescence lifetimes, 15% acrylamide (of rhodamine dye) and 10% acrylamide (of fluorescein dye), are co-molded into specific shape and placed on translational stages with pre-set motion patterns to mimic human movements in clinical settings. Images of phantoms are taken with our DOCI (Dynamic Optical Contrast Imaging) system. The blurred images caused by the pre-set movements is deblurred using a blind-deconvolution algorithm, which first computes the blur kernel and then uses the blur kernel to extract the sharpened pixel values. Sharpened frames are auto correlated using Scale-Invariant Feature Transform (SIFT) before calculating the final contrast images. In the process, parameters are optimized for best imaging quality. The above-mentioned method is applied to images of human tumor and surrounding normal tissue in biopsies taken from patients undergoing surgery for head and neck squamous cell carcinoma. The tissue with pre-set movement patterns is imaged using DOCI, and the data is deblurred, auto correlated, the contrast images is generated with optimized parameters.

Results: As the results show, the utilization of motion correction algorithms improves both RGB image quality and reduces the presence of solid red/blue image artifacts observed in the DOCI images.
Conclusion: Although this work has illuminated the value of the motion correction method in DOCI, the few limitations encountered in this work offer equally valuable insights into future DOCI-based research. These regions of interests cannot include non-tissue objects (e.g. metal objects, rubber surgical gloves, etc.). This method only corrects for x and y translation and does not account for z-motion (i.e. breathing) or rotation/torqueing (i.e. motion due to the surgeon's hands). This development is crucial for the future clinical translation of DOCI.
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Intensity-modulated proton therapy (IMPT) for head and neck cancer (HNC): problems encountered and solutions developed in the first six months of patient treatment

C. Henson,[1] Y. Chen,[2] H. Ortega,[3] J. Arntzen,[3] and H. Jin[3]; [1]*University of Oklahoma Health Science Center, Stephenson Cancer Center, Department of Radiation Oncology, Oklahoma City, OK,* [2]*University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States,* [3]*University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Purpose/Objective(s): We anticipated that the first 6 months with a new IMPT unit would challenge our creativity, especially with complex head and neck cancer (HNC) plans. We hypothesized that in working through issues we would formulate novel strategies that may prove helpful to others who encounter similar issues as IMPT becomes more prevalent.
Materials/Methods: Between April and July of 2019, we treated 4 patients with HNC using IMPT and documented our troubleshooting processes.
Results: We encountered several issues that are unique to our machine and have not yet been described in the literature. These include field size and software limitations, setup collisions/small air gap, dental artifact, and bilateral targets. The biggest issue encountered was small field size, 20x20 cm. Our first solution is to adjust couch rotation and beam angle to cover the target with one field. If not possible, we split the plan into 2 plans, upper and lower, with a 2-4 cm junction field between. Multi-field optimization and gradient matching are used to achieve robust dose coverage at the junction area. The second issue is that the spot size for our machine is bigger than other systems, of particular concern for HNC therapy because the target is relatively shallow (all low-energy layers). We turned this disadvantage into an advantage by using Adapted Aperture (AA) MLC-based treatment planning. At first, this increased treatment times drastically, as plans took longer to load/export. The DICOM treatment service would often time out before the plan had successfully transferred. The root cause of this issue is that this new function produces a high number of plan control points (one checkpoint per spot, approximately 300 checkpoints, versus 200 for a typical arc plan) so takes extra time to move between databases. To fix this, we had our service team increase the DICOM transaction timeout setting from 120 seconds to 600. We also try to limit to 4 beam angles if possible. Also unique to our machine, when treating a bilateral target, a couch kick/PA imaging verification is required because our gantry rotation is limited to 195 degrees. Our solution is to do a couch kick to treat more beam angles, then to confirm with one PA film. In addition to the above unique issues, we encountered more typical problems, including setup collisions/air gap. To fix, we do not allow air gaps to be <3 cm. We do a virtual sim with the patient instead of just with the mask so that pitch and roll can be accounted for in adjusting the air gap. If adjusted within 1 cm, we just re-calculate, not reoptimize. If >1 cm, we reoptimize. Lastly, IMPT is sensitive to tissue densities such as dental artifact. We therefore avoid angling beam through artifact, use metal density overwrite, and have teeth extracted as necessary.
Conclusion: We encountered novel problems and here describe novel solutions for issues seen when initiating treatment with a new IMPT unit.
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Clinical Outcomes in Integrated PET-CT Radiotherapy Planning for Radiochemotherapy of Locally Advanced Head and Neck Cancer

F.L. Ampil,[1] T.A. Richards,[1] R.G. Baluna,[2] Y. Ngo,[1] and D. Kim[1]; [1]*Louisiana State University Health Sciences Center, Shreveport, LA,* [2]*Overton Brooks VA Medical Center, Shreveport, LA*

Purpose/Objective(s): Locally advanced head and neck cancer (LAHNC) in patients is generally managed with a combination of treatment modalities to improve patient outcomes. Integrated PET-CT radiotherapy planning (RTP) of LAHNC has gained acceptance because of its improved tumor coverage and reduced exposure of normal tissues to radiation; with the fusion of anatomic (CT) and metabolic (PET) information as a single image, the complementary strengths each modality are utilized. Because of the considerable cost of image integration and sparse information, the goal of this retrospective, observational study was to determine the effects (tumor response, failure patterns and survival) of RTP in the contemporary management of LAHNC.
Materials/Methods: Between June 2010 and August 2016, 29 consecutive patients underwent RTP (which involved the fusion of PET-CT images) for radiochemotherapy of LAHNC. Gross target volume was outlined under the guidance of integrated PET-CT imaging. Patient and tumor characteristics, treatment failure patterns, toxicity and survival were analyzed. The mean follow-up period was 36 months (range 4 to 90 months). Any relapse rate of ≥20% was considered a significant study endpoint.
Results: The overall locoregional and distant relapse and complication rates were 38%, 41% and 21%, respectively; the 3-year crude survival rate (CSR) was 41%. In all patients with locoregional recurrences, the relapses were in the clinical target volume. Of the 25 evaluable patients, the response to radiochemotherapy was complete in 76%, and absent in 24% of the cases. At last follow-up (median 62.5 months), close to half (48%, 14 patients) of the subjects were alive; the other 15 individuals were deceased, and their median survival was 15 months. The 3-year CSRs were 79% and 13% for patients who did not and did experience relapsing disease, respectively ($p<0.001$); the corresponding complication rates were 8% and 13%, respectively ($p>0.30$). After adjusting for potential confounding variables, the occurrence of tumor relapse was found to be the independent predictor of an adverse prognosis.
Conclusion: In this limited experience, recognizing the integration of images is not a form of treatment, PET-CT RTP was not cost-effective given the observed relapse rates of >25%. The measure of RTP usefulness (in our view) can be expressed in the monitoring of response to treatment, frequencies of failure patterns and disease-free survival. These important associations with clinical practice require more data from investigations of larger number of patients.
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Inflammatory and genetic signatures for recurrent oropharynx cancer

R. Garg,[1] C. Yang,[2] K. Fredenburg,[3] J. Kresak,[3] P.T. Dziegielewski,[1] J. Dourado,[4] R.J. Amdur,[5] W.M. Mendenhall,[5] K.E. Hitchcock,[5] F. Kaye,[6] D. Mitchell,[2] E. Sayour,[2] and N. Silver[1]; *[1]Department of Otolaryngology, University of Florida College of Medicine, Gainesville, FL, [2]University of Florida, Department of Neurosurgery, Gainesville, FL, [3]University of Florida, Department of Pathology, Gainesville, FL, [4]University of Florida, College of Medicine, Gainesville, FL, [5]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, [6]University of Florida, Gainesville, FL*

Purpose/Objective(s): There have been advances in our understanding of the immunologic and genetic characteristics of head and neck cancer, including human papillomavirus positive (HPV+) oropharynx cancer (OPC). While more immune rich tumors such as HPV+ tumors have been associated with a better prognosis, there is evidence that inflamed tumors are also subject to increased immunoregulatory influence. Our goal was to assess whether a specific genetic or immune signature is associated with recurrence in OPC.
Materials/Methods: 32 FFPE samples from pretreatment biopsies of OPC patients were retrospectively collected. RNA was extracted and quantitated by the HTG EdgeSeq Path Assay. p16 immunohistochemistry was used as a surrogate for HPV status. Normalized counts of samples were used for single sample geneset enrichment with a predefined human immune cell geneset through the Genepattern ssGSEA portal. Immune cell populations grouped by HPV status and disease recurrence status were plotted with pheatmap. Immune cell population enriched scores of HPV+ recurrent vs non recurrent patients were calculated with GSEA.
Results: For HPV+ patients (22/32): 11 had recurrence, and 11 did not have recurrence. 81% of patients were male and most (73%) were treated with chemoradiation. Higher T stage was the only significant clinical factor associated with the HPV+ with recurrence group (95% CI, 0-0.9, p = 0.035) and all other clinical factors were not significant. The fold-change expression of phenotypic markers for various immune cells was increased in HPV+ patients with recurrence compared to those without recurrence. GSEA and fold change data for gene expression revealed monocytic cell populations (fold change of CD14; 1.26, CD68; 1.55) were higher in the recurrence cohort. Among the immunosuppressive cells, expression of M2 and MDSC markers, including CD163 (1.61), CD33 (1.04), S100 family genes (S100A6; 1.08, S100A8; 1.18), and ROS1 (5.64) was increased in recurrent patients. Despite the increased expression of some immune cell activation markers, innate myeloid cells might be dysfunctional due to lower expression of CD40 (-1.18), LAMP3 (-1.03), HLA (e.g. HLA-DQB1; -1.42), and essential signaling molecules (CD80;-1.16) in the recurrent patients. While the recurrent patients had a higher fold change for CD4 (1.03) and CD8a (1.12), they had lower expression of CD3 T cell co-receptor molecules (CD3E; -1.17, CD3G; -1.18), and signature effector molecules, e.g., perforin (-.157), and granzyme B (-1.17), suggesting T cell exhaustion. Also, recurrent patients had decreased expression of genes associated with CD4 and CD8 memory T cells (CD2; -1.05 and CD27; -1.04).
Conclusion: While overall inflammation may be increased in HPV+ patients with recurrent disease, based on the current study, the tumor associated inflammation may be contributing to an enhanced immunosuppressive environment.
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Spatially optimized radiation therapy for enhanced immune priming of head and neck cancer

J. Sims-Mourtada,[1] F. Mourtada,[1] H. Chen,[1] J. Keller,[2] Y. Yu,[2] B. Lu,[2] and A. Raben[1]; *[1]Christiana Care Health System, Helen F. Graham Cancer Center, Newark, DE, [2]Department of Radiation Oncology, Sidney Kimmel Medical College & Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Purpose/Objective(s): Radiotherapy (RT) primes the immune system due to the release of tumor specific antigens from dying tumor cells and improves responses to PD-1 based immunotherapy in head and neck cancer (HNC). Although hypofractionation (HF) has been shown to be superior to traditional fractionation schedules, the immunostimulatory effects of this regimen may be limited by death of radiation sensitive T-cells. There is a need to optimize RT delivery to induce focal necrosis required for immune priming, while sparing tumor infiltrating T-cells. We propose a novel method of RT delivery, Spatially Optimized Radiation Therapy (SORT), to enhance immune priming. In contrast to HF, which applies uniform dose over the tumor, SORT dose distribution is heterogeneous producing high and low radiation dose regions within the tumor. Here we demonstrate the feasibility and early outcomes of SORT delivery in a mouse model of HNC.
Materials/Methods: SORT was validated for the SARRP irradiator using high spatial resolution radiochromic film absolute dosimetry. The nozzles size was selected to deliver either a uniform dose of 12 Gy or SORT using two abutted nozzles to deliver low (2Gy) and high (12 Gy) HF-like dose regions. C3H/HeJ mice bearing SCCVII/SF xenografts (n = 8/group) were irradiated with either a single fraction of 1) uniform dose of 12 Gy using the 1x1 cm^2 nozzle to cover the entire tumor and 2) SORT (2-12Gy) using 0.5x0.5 cm^2 nozzle. To assess early T cell responses, mice were sacrificed 24 hrs after radiation and the presence of T cell subsets and cytokines was determined by real-time PCR. Statistical differences were determined using a one-way ANOVA followed by a post-hoc Tukey T-Test.
Results: Radiochromic film measurements indicated highly uniform dose profiles with sharp dose fall off region for 0.5x0.5 cm^2 nozzle, allowing abutting of high and low dose fields. Gene expression analysis revealed increases in CD8 in both treatment groups over sham-irradiated mice with a slight but significant increase in SORT treated mice compared to mice treated with 12Gy (7 fold vs 5 fold). Significant increases of IFN-gamma gene expression were observed in SORT treated mice compared to mice irradiated with 12Gy. Mice treated with a uniform 12Gy dose showed a 13.75-fold increase in IFN-gamma over sham irradiated mice. This increase was significantly larger in SORT treated mice in which a 67 fold increase over sham-irradiated mice was observed.
Conclusion: Although increases in CD8 gene expression were observed in both treatment groups, this increase was not proportional to the large increase in IFN-gamma observed in SORT treated mice, indicating enhanced T-cell activation by SORT. Further study is needed to determine if early immune activation in SORT treated mice correlates to a sustained immune response and improved response to immunotherapy.
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Withdrawn

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Real World Treatment Patterns and Time On Treatment in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) Previously Treated with Platinum-Containing Chemotherapy in United States (US)

D. Chirovsky,[1] Z. Liu,[2] S. Baxi,[3] S. Chandwani,[2] S. Joo,[2] and K. Ramakrishnan[2]; *[1]Center for Observational and Real World Evidence (CORE), Merck & Co, Inc., Kenilworth, NJ, [2]Center for Observational and Real World Evidence (CORE), Merck & Co., Inc., Kenilworth, NJ, [3]Flatiron Health, New York, NY*

Purpose/Objective(s): Immuno-oncology (IO) therapies, pembrolizumab and nivolumab, were approved in 2016 as single agents for the treatment of R/M HNSCC with disease progression on or after platinum-based chemotherapy (PbC) in the US. We examined treatment patterns and estimated real-world time on treatment (rwToT) with IO and non-IO based therapies post-PbC in patients with R/M HNSCC.
Materials/Methods: Data from the nationwide Flatiron Health electronic health record-derived database was used in this study. Patients with R/M HNSCC who initiated first-line (1L) therapy with a PbC and received a second-line (2L) systemic therapy between 1/1/2017 and 12/31/2018 were included and were followed until 06/30/2019 (database cutoff). Analysis of rwToT and treatment rate were conducted using the Kaplan-Meier method.
Results: The study population included 449 patients with R/M HNSCC who received 1L therapy with a PbC and received 2L systemic therapy. The study population was 77% male, with median age 63 years (IQR: 57-70), 58%/9%/33% had Eastern Cooperative Oncology Group (ECOG) performance status 0-1/2-3/unknown, and 43% had oropharynx primary tumor. Among prior 1L PbC, a greater proportion of patients received a PbC combination regimen (N = 290, 65%) versus PbC monotherapy; common combination regimens included platinum+taxane (N = 139, 31%) and platinum+cetuximab+ +fluorouracil (N = 47, 11%). Among 2L therapies, majority of patients received IO monotherapy (nivolumab: N = 190, 42%, pembrolizumab: N = 107, 24%) and 2% (N = 10) received IO combination therapy. Fewer patients received non-IO based 2L therapies (N = 141, 31%), which commonly included re-treatment with PbC combinations (N = 85, 19%), and cetuximab monotherapy (N = 31, 7%). For patients who received 2L IO monotherapy, 81% discontinued therapy during study period. Median rwToT was 2.3 months (95% CI: 2.0 - 2.8) with 6-month treatment rate of 24.8% (95% CI: 19.9% - 30.0%). For 2L non-IO based therapy, 92% discontinued therapy during study period. Median rwToT was 1.9 months (95% CI: 1.4 - 2.3) with a 6-month treatment rate of 7.5% (95% CI: 3.8% - 12.9%).
Conclusion: Use of IO therapies in R/M HNSCC previously treated with PbC is common in US oncology practices. Median duration of use was similar with IO monotherapy and non-IO based therapies, but 6-month treatment rates tended to be higher. Additional research exploring the influence of clinical characteristics of R/M HNSCC on treatment practice patterns and longer follow up time, is warranted to further elucidate drivers for these observed trends.
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Analysis of spatial relationships between CD8 and FoxP3 cells using digital imaging in head and neck squamous cell carcinoma

M. Stewart, R. Stapp, D. Amin, R. Ganti, U. Nwagu, T. Richa, M. Crippen, R. Zinner, A. Luginbuhl, J. Johnson, V. Bar-Ad, U. Martinez-Outschoorn, C. Solomides, U. Rodeck, and J.M. Curry; *Thomas Jefferson University Hospital, Philadelphia, PA*

Purpose/Objective(s): T cell-mediated anti-tumor immune responses are gated in part by the relative abundance of cytotoxic T cells (Teffs) and regulatory (Tregs) in the tumor microenvironment (TME) whereby Treg may impair the efficacy of Teffs. Tregs can affect Teff function by direct cell-to-cell contact or by secretion of soluble mediators, consistent with the hypothesis that proximity of Tregs to Teff within tumor tissues may have prognostic significance. Here we used a novel chromogenic multiplex assay to investigate the spatial relationship of these functionally diverse T cell subsets in HPV positive and HPV negative head and neck squamous cell carcinomas (HNSCCs).
Materials/Methods: Twenty head and neck cancer patients with primary tumors of the oropharynx or oral cavity were included in this study of which 10 were HPV positive and 10 HPV negative. Formalin-fixed tissues were stained with antibodies detecting CD8 (Teffs) and FoxP3 (Tregs). At least three different fields at the leading edge of tumor and adjacent stroma were evaluated. Stained tissue sections were digitally scanned at 40x magnification utilizing an iScan HT (Roche, Switzerland) whole-slide imaging scanner. Visiopharm (Visiopharm, Denmark) image analysis software was utilized by a pathologist to analyze the digitized slide images.
Results: HPV positive tumor tissues contained >3-fold higher numbers of both CD8 and FoxP3 expressing cells when compared to HPV negative tumors whereas the ratios between these cell subsets (CD8/FoxP3) were comparable. The differential density of T-cells in the sampled areas was reflected in a significantly shorter mean distance between CD8+ and FoxP3+ cells in HPV positive (29.92 μm) tumors compared to that of HPV negative (52.56 μm) tumors ($p = 0.0045$, 95% CI: 8.17-37.11). The mean frequency of distances <30μm measured in HPV positive tumors was 98.46 contrasted by 39.44 in HPV negative tumors; this difference was statistically different ($p = 0.0194$). The mean frequency of distances >30μm measured in HPV positive tumors was 37.02 and in HPV negative tumors 36.06.
Conclusion: Consistent with earlier reports, HPV positive lesions contained more CD8 and FoxP3 expressing T cells than HPV negative lesions. This difference was reflected in statistically significantly closer proximity of Teffs and Tregs in HPV positive lesions, potentially enhancing functional interaction of these T cell subsets in the tumor microenvironment of HPV positive lesions. The implications of these observations for prognosis and response to immunotherapeutic intervention remain to be investigated.
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Prognosis and Neutrophil-to-Lymphocyte Ratio in Nivolumab-treated Patients with Recurrent/Metastatic Head and Neck Cancer

I. Ota; *Nara Medical University, Kashihara, Japan*

Purpose/Objective(s): Efficient use of nivolumab in recurrent/metastatic head and neck squamous cell carcinoma (r/mHNSCC) has been limited by the lack of a definitive predictive biomarker. We aimed to investigate the association between pretreatment neutrophil-to-lymphocyte ratio (NLR) and outcome of patients with r/mHNSCC treated with nivolumab.
Materials/Methods: We identified 21 patients with r/mHNSCC treated with standard-of-care nivolumab between 2017 and 2019 at Nara Medical University. NLR was determined from complete blood count collected before starting treatment, and imaging was performed to assess progression. The NLR cutoff value of 5 was determined by log-rank test, and the univariate association with overall survival (OS) or progression-free survival (PFS) was assessed by the Cox proportional hazard model and Kaplan-Meier method.
Results: The 21 patients had a median age of 65 years. The PFS and OS for all patients at 12 months was 42.7% and 55.6%, respectively. The median PFS was 3.2 months in the high NLR group but not reached in the low NLR group. Low NLR was strongly associated with increased OS with hazard ratio of 0.26 (95% confidence interval, 0.07-0.93; $P = .0149$). The median OS was 6.83 months in the high NLR group but not reached in the low NLR group. Low NLR was significantly associated with a prolonged OS with hazard ratio of 0.22 (95% confidence interval, 0.05-0.91; $P = .0194$).
Conclusion: Pretreatment NLR < 5 is associated with superior PFS and OS. NLR is a biomarker that can inform prognosis for patients with r/mHNSCC and should be further validated in larger cohorts and in prospective studies.
Author Disclosure: **I. Ota**: None.

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Integrated Biomarker Study of Pepinemab in Combination with Nivolumab or Ipilimumab to Evaluate Immune Cell Composition of TME in Patients with Head and Neck Squamous Cell Carcinoma and Other Solid Tumors

C. Steuer,[1] G.B. Lesinski,[2] E.E. Evans,[3] T.L. Fisher,[3] C. Mallow,[3] B. Olson,[2] D.R. Pastore,[3] J.E. Leonard,[3] E. Smith,[3] M. Zauderer,[3] M. Lowe,[2] R.R. Kudchadkar,[2] C. Wu,[2] M.R. Patel,[4] and N.F. Saba[5]; *[1]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, [2]Winship Cancer Institute of Emory University, Atlanta, GA, [3]Vaccinex, Rochester, NY, [4]Department of Otolaryngology, Emory University School of Medicine, Atlanta, GA, [5]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Immunosuppressive myeloid cells activated in the tumor microenvironment (TME) are a critical limitation to the efficacy of immune checkpoint inhibitors (ICIs) in patients with head and neck squamous cell carcinoma (HNSCC). In preclinical models, antibody blockade of Semaphorin 4D (SEMA4D, CD100) reduced function and recruitment of immunosuppressive myeloid cells, while simultaneously restoring the ability of dendritic cells and cytotoxic T cells to infiltrate the TME. Importantly, this coordinated shift from immunosuppression to tumoricidal activity complemented effects of other immunotherapies in syngeneic tumor models, whereby combinations of anti-SEMA4D with ICIs enhanced T cell activity and tumor regression.

Purpose/Objective(s): Evaluation of immunomodulatory effects of pepinemab, a humanized monoclonal antibody targeting SEMA4D, and combinations with ICI within periphery and TME. Additional objectives include extension of the previously reported safety profile of pepinemab to ICI combination therapies and overall survival in patients with HNSCC.

Materials/Methods: Biomarker-driven window of opportunity studies are recruiting patients to investigate novel combinations of pepinemab with ICIs in HNSCC (NCT03690986, n=36); as well as colorectal cancer with resectable liver metastases and pancreatic ductal adenocarcinoma (NCT03373188, n=32); and metastatic melanoma (NCT03769155, n=36). HNSCC patients will be stratified by HPV status and randomly assigned into cohorts receiving one dose of a combination of pepinemab (20 mg/kg) with nivolumab (480 mg) or ipilimumab (1 mg/kg), single agents, or no treatment. Three to five weeks later, surgically resected tumors are collected under the guidance of a pathologist. Blood is collected for PK, PD, and correlative biomarker assessments. Multiplex flow cytometric (FC) and immunohistochemistry (IHC) panels have been established to phenotype cells in the TME and periphery, including cytotoxic T cells, Tregs, DCs, monocytes, macrophages, and myeloid-derived suppressor cells. Target engagement and expression of SEMA4D and its receptors will be evaluated.

Results: Correlative FC and IHC panels utilizing a sequential probe and strip procedure that allows co-localization and quantification of multiple immune markers have been established. Analysis of liver metastases from three CRC patients demonstrate an increase in CD8 density and reduction in MDSC density in patients treated with pepinemab. Nine HNSCC patients have been enrolled as of 04 SEP 2019 and interim biomarker analysis will be presented.

Conclusion: These studies will provide the first integrated clinical assessment of the use of anti-SEMA4D antibody to reprogram the TME.

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Prognostic value of the modified Glasgow Prognostic Score for head and neck cancer in the era of immunotherapy

Y. Imamura,[1] N. Kiyota,[1,2] C. Suzuki,[3] T. Koyama,[1] S. Kimbara,[1] H. Shinomiya,[4] N. Otsuki,[4] T. Hasegawa,[5] M. Toyoda,[1] Y. Funakoshi,[1] M. Akashi,[5] R. Sasaki,[6] K.I. Nibu,[4] and H. Minami[1,2]; *[1]Department of Medical Oncology/Hematology, Kobe University Hospital, Kobe, Japan, [2]Cancer Center, Kobe University Hospital, Kobe, Japan, [3]Department of Otolaryngology-Head and Neck Surgery, Kyoto University Hospital, Kyoto, Japan, [4]Department of Otolaryngology-Head and Neck Surgery, Kobe University Hospital, Kobe, Japan, [5]Department of Oral and Maxillofacial Surgery, Kobe University Hospital, Kobe, Japan, [6]Division of Radiation Oncology, Kobe University Hospital, Kobe, Japan*

Purpose/Objective(s): The Modified Glasgow Prognostic Score (mGPS) is a well-known prognostic indicator for several malignancies. However, its role in the current era of immune checkpoint inhibitors (ICPi) has not been fully elucidated.

Materials/Methods: We examined mGPS before the start of ICPi and 6 weeks later in 30 platinum-refractory head and neck squamous cell carcinoma (HNSCC) patients (pts) treated with ICPi between Nov 2014 and Sep 2018. We analyzed the efficacy of ICPi and the relationship between survival and mGPS. Total mGPS index was defined as the sum of the mGPS before and at 6 weeks after ICPi.To evaluate consistency, we repeated the analysis using a previous data set for 30 platinum-refractory HNSCC pts treated with salvage chemotherapy from Apr 2008 to Oct 2014 before approval of nivolumab in Japan (without sequential ICPi).

Results: The pts were 26 men and 4 women with a median age of 65 years (range 39 to 78). Major primary tumor sites were the oral cavity (47%) and hypopharynx (30%). Prior surgery and radiation had been carried out in 83% and 90%, respectively. Among 28 evaluable patients, objective response rate was 29% (95% confidence interval, 13-49%). With a median follow-up of 15.7 months (M), median progression-free survival (PFS) and overall survival was 2.3 and 11.3 M, respectively. Median PFS according to mGPS (0/1/2) before and at 6 weeks after ICPi was 3.5/2.5/2.1 M ($P=0.11$) and 3.2/6.4/0.7 M (Landmark analysis, $P=0.06$), respectively. Median PFS according to total mGPS index (0-1/2/3-4) was 5.5/2.8/0.7 M (Landmark analysis, $P=0.04$). For the previous data set, median PFS according to mGPS (0/1/2) before and at 6 weeks after salvage chemotherapy and total mGPS index (0-1/2/3-4) was 3.0/1.1/1.4 M ($P=0.02$), 1.7/1.7/1.6 M($P=0.90$), and 1.7/1.6/1.0 M ($P=0.34$), respectively.

Conclusion: Total mGPS index might have good predictive value for platinum-refractory HNSCC pts who were treated with ICPi. This finding warrants validation in a larger data set and other malignancies.

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Withdrawn

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A Phase 1b Presurgical Window Study to Evaluate Immune Biomarker Modulation in Response to Motolimod and Nivolumab in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN)

D. Adkins,[1] E. Cohen,[2] L. Nabell,[3] D. Zandberg,[4] M. Old,[5] D. Cognetti,[6] D. Blair,[7] X. Wei,[8] A. Wells,[9] A. Patel,[9] T. Foy,[7] K. Hege,[9] and R.L. Ferris[4]; *[1]Washington University School of Medicine in St. Louis, St.*

Louis, MO, [2]Moores Cancer Center, University of California San Diego (UCSD), La Jolla, CA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, [5]The Ohio State University Comprehensive Cancer Center (OSUCCC - James), Columbus, OH, [6]Thomas Jefferson University, Philadephia, PA, [7]Celgene Corporation, Seattle, WA, [8]Celgene Corporation, Berkley Heights, NJ, [9]Celgene Corporation, San Francisco, CA

Purpose/Objective(s): SCCHNs are a complex and difficult-to-treat group of aggressive cancers. Surgery and radiotherapy remain the primary treatments for locoregional SCCHN; however, they are associated with significant morbidity and high recurrence rates. Although immune checkpoint inhibitors such as the anti-PD-1 antibody nivolumab are active in SCCHN, strategies to improve response rate and durability are needed. The development of more effective therapies is hindered by the immunosuppressive nature of these tumors. As such, a better understanding of the tumor microenvironment and identification of predictive biomarkers are needed. Ultimately, therapeutic combinations that leverage both adaptive and innate immunity may be key to improving SCCHN outcomes. This multicenter, window-of-opportunity study, aims to characterize the immunomodulatory effects of nivolumab and the toll-like receptor 8 agonist motolimod in patients (pts) with resectable SCCHN.

Materials/Methods: This open-label study (NCT03906526) will enroll approximately 52−72 pts in 1 of 4 treatment arms (**Table**). The primary objective is to characterize the immunomodulatory effects of nivolumab and motolimod given as single agents and in combination. Secondary objectives include assessing the safety and tolerability of these agents in the setting of resectable SCCHN. Eligible pts are adults with newly diagnosed, resectable SCCHN of the oral cavity, pharynx, or larynx. Pts can be human papillomavirus-positive or -negative. Pretreatment diagnostic tests will include tumor biopsy, imaging, and peripheral blood collection. Enrolled pts will undergo study treatment 3−4 weeks before scheduled surgical resection. Nivolumab will be administered intravenously per product label. Motolimod will be delivered by intratumoral (IT) injection at an initial dose of 2 mg/m^2 (Arm 2). Following an initial safety review, additional cohorts testing IT motolimod at 3 mg/m^2 and the combination of IT motolimod with nivolumab will open. Arm 4 will test subcutaneous motolimod plus nivolumab. Following treatment, pts will undergo definitive resection and will be followed for 90 days from last treatment. Pre- and post-treatment samples will be analyzed for changes in gene and protein expression, IT immune populations, cytokine profiles, and evidence of pathologic response. Enrollment is expected to take approximately 26 months, and the study is expected to continue for 30 months.

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	Nivolumab	Motolimod
Arm 1 (n = 10−15)	IV; days 1 and 15	None
Arm 2 (n = 16−21)	None	IT; days 1, 8, 15, & 22
Arm 3* (n = 16−21)	IV; days 1 & 15	IT; days 1, 8, 15, & 22
Arm 4 (n = 10−15)	IV; days 1 & 15	SC; days 1, 8, 15, & 22

IT, intratumoral; IV, intravenous; SC, subcutaneous.
*Dosing will procede if < 2/6 events occur in Arm 2.

Results: Not applicable/trial in progress

Conclusion: Not applicable/trial in progress

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Fistula Rate after Salvage Laryngectomy with Aggressive Levothyroxine Replacement, A Prospective Phase 2 Clinical Trial

A. Rosko,[1] C.T. Haring,[1] A. Birkeland,[2] E. Bellile,[3] C.C. Jaffe,[2] A. Shuman,[1] S.B. Chinn,[1] C.L. Stucken,[1] K. Malloy,[1] J.S. Moyer,[2] K. Casper,[1] M.E. Prince,[1] C.R. Bradford,[1] G.T. Wolf,[1] D.B. Chepeha,[4] and M.E. Spector[1]; *[1]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Department of Biostatistics, University of Michigan, Ann Arbor, MI, [4]Department of Otolaryngology - Head & Neck Surgery, University Health Network-University of Toronto, Toronto, ON, Canada*

Purpose/Objective(s): Patients undergoing salvage laryngectomy are predisposed to hypothyroidism due to the tissue effects of radiation and due to surgical manipulation of the thyroid during surgery. Hypothyroidism impairs wound healing and has been linked to pharyngocutaneous fistula formation. These effects are compounded by the sequela of prior radiation (XRT) and chemoradiation (CRT), which induces a hypoxic, hypocellular, and hypovascular environment, which also predisposes patients to fistula formation. The hypothesis of this study is that aggressive thyroid hormone replacement after salvage laryngectomy reduces the rate of pharyngocutaneous fistula.

Materials/Methods: An interim analysis of a phase 2 non-randomized prospective clinical trial at a single institution was performed. Patients undergoing salvage laryngectomy after XRT or CRT were included. All patients underwent free tissue reconstruction. Patients who were hypothyroid (defined as a TSH > 5.5 mIU/L) at the time of surgery were excluded. All patients were treated with weight based intravenous (IV) levothyroxine (1.3 mcg/kg/day) for 1 week. This was converted to enteral levothyroxine at day 7. The primary outcome was fistula formation and the secondary outcome was need for re-operation due to fistula. A retrospective cohort of patients undergoing salvage laryngectomy was used for comparison.

Results: In the interim analysis, 41 patient met inclusion criteria. The overall fistula rate was 14.6% (6/41). In this cohort 4.9% (2/41) of patients required re-operation for a fistula. Despite aggressive thyroid hormone replacement 19.5% (8/41) of patients developed hypothyroidism postoperatively (defined as a TSH > 5.5 mIU/L). In contrast, in the historical cohort, there were 94 patients with a fistula rate of 42.6% (40/94; p=0.002) and a re-operation rate of 16.0% (15/94; p=0.09). In the prospective cohort the mean length of stay was 11.2 ± 7.9 days compared to 16.2 ± 14.0 days (p=0.03). In the prospective cohort, the readmission rate for any reason was 22.0% (9/41) compared to 35.1% (33/94; p=0.2). There were no complications attributable to levothyroxine.

Conclusion: This prospective phase 2 trial suggests a protective effect from aggressive post-operative levothyroxine replacement after salvage laryngectomy, with reduced fistula formation and a subsequent reduction in the length of stay. This study lays the foundation for a subsequent randomized trial to validate these results.

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Prognostic Factors in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

C.T. Haring,[1] A. Rosko,[1] M.E. Heft-Neal,[1] A. Shuman,[1] J.C. Brenner,[1] F. Worden,[2] M.E. Spector,[1] and P.L. Swiecicki[2]; *[1]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [2]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Despite the development of novel treatment regimens, survival for patients with unresectable recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) remains poor. Patients have varied treatment responses due to heterogenous clinical factors and tumor characteristics. The ability to prognosticate outcomes and determine likelihood of treatment response for individual patients would allow for tailored therapeutic approaches and avoidance of unnecessary toxicities and costs. The objective of this study is to identify prognostic clinical factors in patients with R/M HNSCC.

Materials/Methods: A retrospective case series was performed of patients diagnosed with R/M HNSCC between 1998 and 2018. Kaplan Meier curves were created to calculate overall survival (OS) estimates. Multivariable regression analysis using Cox proportion hazard modeling identified independent predictors of survival. Covariates were selected from clinically relevant survival predictors, including primary tumor site, smoking status, prior radiation, comorbidities (by Charleston index), organ dysfunction (tracheostomy or gastrostomy tube dependence), location of metastases (locoregional versus distant), interval from primary treatment completion to R/M diagnosis, and tumor bulk. Covariates with > 30% missing data were excluded, including HPV status and ECOG performance status. Tumor bulk was a sum of unidimensional measurements of maximum diameter at all disease sites by CT scan. Linear regression was also performed to determine predictors of time to death.

Results: A total of 500 patients diagnosed with R/M HNSCC were identified. Preliminary analysis of 117 patients is included here. The median OS was 9.8 months (95% confidence interval (CI) 6.9-13.6 months). The 2-year OS rate was 19% and the 5-year OS rate was 3%. On multivariate analysis, independent predictors of worse overall survival include tumor bulk (HR 1.1 (95% CI 1.1-1.2), p<0.001), medical comorbidity (HR 1.7 (95% CI 1.0-2.9), p=0.04), locoregional recurrence (HR 1.8 (95% CI 1.1-2.9), p=0.03), and primary site in the oral cavity (HR 2.6 vs larynx (95% CI 1.2-5.5), p=0.01, HR 2.6 vs other sites (95% CI 1.0-6.8, p=0.04). On linear regression, presence of comorbidity decreased survival time by 5.5 months (p=0.05), locoregional recurrence decreased survival time by 8.7 months (p<0.01), and for every 1 cm increase in tumor bulk, survival time decreased by 1.2 months (p<0.001).

Conclusion: This is the largest retrospective database to date of patients diagnosed with R/M HNSCC. Final analyses are ongoing and will be presented. Preliminary analyses reveal that comorbidity, primary tumor site, pattern of R/M disease, and tumor bulk are important prognostic biomarkers for patients with R/M HNSCC. From these data, we aim to create a nomogram to predict an individual's survival time after a diagnosis of R/M HNSCC.

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Chemotherapy outcomes following immunotherapy failure in advanced squamous cell carcinoma of the head and neck

A.J. Kacew,[1] J. Lorch,[2] J.D. Schoenfeld,[2] D.N. Margalit,[2] J. Kass,[3] R.B. Tishler,[2] R.I. Haddad,[2] and G.J. Hanna[2]; *[1]Dana-Farber Cancer Institute, Boston, MA, [2]Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, [3]Department of Surgery/Otolaryngology, Brigham & Women's Hospital and Dana-Farber Cancer Institute, Boston, MA*

Purpose/Objective(s): Immune checkpoint inhibitors (ICIs) alone or with chemotherapy (CT) is a new standard of care in first-line recurrent, metastatic squamous cell carcinoma of the head and neck (SCCHN). With the growing use of ICIs in this setting, response rates to second-line CT are now being explored. We investigated whether prior ICI therapy associated with more favorable outcomes for SCCHN patients on CT, as ICIs may produce lasting immunomodulation that may influence subsequent CT benefit.

Materials/Methods: We analyzed 60 advanced SCCHN patients who progressed on ICI-containing regimens (as any line of therapy) and who had been treated at our institution between 2014 and 2019. We reviewed best response to immunotherapy and duration of response (DOR), then choice and benefit from next-line CT. We compared these data to historical published trials in which patients had not received ICI previously.

Results: The majority were men (52, 87%) and current or former smokers (39, 65%), with primary oropharyngeal disease (35, 58%; of whom 28,

80% were HPV+). Eleven (19%) initially experienced a response to ICI with an additional 25% having stable disease. Median time on ICI was 3.7 months, with the majority discontinuing for disease progression. Median follow-up time after initiation of post-ICI therapy was 22.7 months (range: 0.9-33+), with 39 deaths. Forty percent received platinum-containing regimens (24/60) after ICI failure. We observed a 50% objective response rate (ORR) to a doublet regimen (DOR 2-15 mos) compared to 39% among controls. ORR was 46% for triplet regimens (DOR 2-6 mos). Response rates were higher for carboplatin/paclitaxel (received by 5/60) following ICI failure vs. controls (60% vs. 39%). Cetuximab-containing therapy (received by 22/60, 37%) yielded an ORR of 32% (DOR 2-6 mos) compared to 13% historically; ORR 0% for cetuximab monotherapy. None of six patients on single-agent cytotoxic therapy (gemcitabine, docetaxel, methotrexate) following ICI had a response. Median overall survival (OS) in our post-ICI failure cohort was 9.8 months from post-ICI therapy initiation (95% CI 6.1-12.1 mos), vs. 6.6 months in the 2+ line setting historically. Patients on platinum-containing regimens experienced longer OS compared to all others in the cohort (HR = 0.46, p = 0.04).

Conclusion: Compared to historical controls, we observed favorable response rates to doublet CT after ICI failure among advanced SCCHN patients, with a signal of improved response to cetuximab-containing regimens. Future studies will help to define the optimal post-ICI regimen.

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The effect of cetuximab and immune checkpoint inhibitor sequence on treatment efficacy

J.C. Park,[1] D. Julia,[2] D. Faden,[2] J.R. Clark,[1] and L. Wirth[1]; [1]*Massachusetts General Hospital, Boston, MA,* [2]*Massachusetts Eye and Ear, Boston, MA*

Purpose/Objective(s): Anti-PD-1 immune checkpoint inhibitors (ICI) have rapidly altered treatment paradigms for advanced head and neck squamous cell carcinoma (HNSCC). However, the optimal treatment sequence of ICI in relation to other treatments remains unclear. Cetuximab has been suggested to have immune modulatory effects and its antitumor effect is in part immune-mediated. Here, we examine both impact of cetuximab on the outcome of subsequent anti-PD-1 therapy and cetuximab efficacy in patients (pts) with prior ICI exposure in a single institution, well annotated cohort.

Materials/Methods: Clinicopathologic data of pts with recurrent or metastatic (R/M) HNSCC who received at least 2 doses of anti-PD-1 therapy between 2015 and 2019 at our institution was retrospectively collected. Patient characteristics, treatment history, response, and survival data were analyzed with descriptive statistics.

Results: A total of 110 pts were identified who met inclusion criteria. Median age was 66 years. 36 (32.7%) of pts had HPV-positive (+) disease. 48 (43.6%) had > 10 PY smoking history. 25 pts received cetuximab prior to ICI (PriorC) and 24 pts had cetuximab after ICI (PostC). PriorC and PostC group included 7 (28.0%) and 9 (37.5%) HPV+ pts, respectively. 36 (32.6%) received ICI as a first-line therapy: 3 (12.0%) in PriorC and 5 (20.8%) in PostC group. Median follow-up was 11.9 months (m). Median overall survival (mOS) of the total group was 15.3 m (95%CI 11.4-19.2). Pts with PriorC had inferior mOS (10.3 m, 95%CI 2.2-18.4) compared to pts who did not receive PriorC (19.8 m, 95% CI 11.8-27.8) with HR 2.91 ($P < 0.001$). Progression free survival was also shorter in PriorC group compared to non-PriorC group (HR 1.94, P = 0.009). Objective response rate (ORR) to ICI in the total population was 25.5% (95% CI 17.6-34.6). ORR in pts with PriorC (20.0%) was lower compared to pts without PriorC (27.1%), P = 0.476. Treatment response to cetuximab (either alone or in combination) after anti-PD-1 therapy (PostC) was higher than historic data with ORR of 40.0% (95%CI 19.1-64.0). mOS for PostC group was 18.6 m (95%CI 10.8-26.4) which was longer than that of pts without PostC (14.8 m, 95%CI 11.0-18.6) with HR 0.81 (P = 0.523) and statistically significant compared to PriorC group (HR 0.38, P = 0.009).

Conclusion: Here we demonstrate that treatment sequence of cetuximab and anti-PD-1 ICI therapy in R/M HNSCC affects the efficacy of both cetuximab and ICI. Cetuximab prior to ICI was associated with worse survival, disease progression, and objective response while the efficacy of cetuximab appears to be enhanced after ICI therapy. Further studies are warranted to elucidate the molecular mechanisms of our findings.

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A multi-center phase II trial evaluating the efficacy of palbociclib in combination with carboplatin for the treatment of unresectable recurrent or metastatic head and neck squamous cell carcinoma

P.L. Swiecicki,[1,2] G. Durm,[3] E. Bellile,[4] C. Brummel,[5] M. Pang,[5] A. Bhangale,[6] J.C. Brenner,[5] and F. Worden[1]; [1]*Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI,* [2]*Department of Internal Medicine, Division of Medical Oncology, Ann Arbor Veterans Administration, Ann Arbor, MI,* [3]*Indiana University, Indianapolis, IN,* [4]*Department of Biostatistics, University of Michigan, Ann Arbor, MI,* [5]*Department of Otolaryngology, University of Michigan, Ann Arbor, MI,* [6]*University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): Metastatic head and neck cancer (MHNC) has a dismal survival and targeted therapeutics have had little success. Cisplatin has been the backbone of therapy with a 10% response rate (RR) and 12 wk disease control rate (DCR) of 20% to single agent regimens. First line treatment has consisted of the EXTREME regimen (36% RR, 10.1 mo OS) but given the performance status at diagnosis and treatment related toxicities, many patients are not candidates and new are needed. Combinations with targeted therapies are one method. Cell cycle alterations are common in MHNC and targetable with CDK 4/6 inhibitors such as palbociclib (P). Preclinical studies evaluating CDK 4/6 inhibitors have suggested both single agent activity and synergy with platinum chemotherapy in several cancer types including HNC. We conducted a multi-institution phase II trial to investigate the clinical activity of combining carboplatin (C) and P in MHNC. Our hypothesis was treatment with CP would have significant synergy in eliciting an antitumor response and hence achieve an improved 12 wk DCR compared to single agent C.

Materials/Methods: Key inclusion criteria included histologically documented MHNC, ECOG 0-2. Previous cytotoxic chemotherapy in the metastatic setting was prohibited. C was administered day 1 and P days 1-14, cycle length of 21 days. Adverse events were graded according to the CTCAE v4.03, response was evaluated by RECIST v 1.1. The primary endpoint was 12 wk DCR . The optimal two-stage accrual design was employed to test the hypothesis that CP could improve historical DCR by 20% with an interim analysis to allow early termination of the trial if there was evidence that the DCR under this regimen was <40%. A planned interim efficacy analysis was performed after enrollment of 19 response-evaluable patients to evaluate for futility which did not demonstrate superiority of CP and the trial was closed.

Results: 21 pts were enrolled, 19 were evaluable for response. The DCR was 32% (6/19) of which 5 had SD and 1 had a PR. The median PFS was 2.8 mo (95% Confidence Interval (CI): 1.5-4.1), and OS was 4.7 mo (95% CI: 2.8-10.7). Grade 3 or greater toxicities were seen in 79% of all patients with the most common being myelosuppression. Exploratory correlative molecular analysis of 8 patients by targeted sequencing identified 3 *CDKN2A* single copy deletions and 1 *RB1* two copy deletion in the cohort.

Conclusion: Despite preclinical evidence, CP is not an active regimen in MHNC and is associated with significant toxicities. Although an isolated prolonged response was noted, the combination of palbociclib and cytotoxic chemotherapy does not appear to be a promising therapeutic approach. Ongoing studies are evaluating synergy with cetuximab and as an immunomodulatory agent.

Age	Median (range)	65 (40-74)
ECOG	0/1/2	8/11/0
p16	+/-/unk	4/9/6
Disease site	Oropharynx	6
	Oral Cavity	6
	Larynx	4
	Nasopharynx	2
	Other	1
Prior PD-1 inhib		3

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Last-line Local Treatment with the Quad Shot Regimen for Previously Irradiated Head and Neck Cancers

D. Fan,[1] M. Fan,[2] H. Wang,[3] A. Lee,[1] Y. Yu,[1] L. Chen,[1] C.J. Tsai,[1] S. McBride,[4] N. Riaz,[1] M.B. Bernstein,[1] B.A. Mueller,[1] D.Y. Gelblum,[1] J. Fetten,[5] L. Dunn,[6] L. Michel,[7] D.G. Pfister,[5] A. Ho,[5] J.O. Boyle,[8] M. Cohen,[8] B.R. Roman,[4] J.R. Cracchiolo,[8] L. Morris,[9] I. Ganly,[4] B. Singh,[10] A. Shaha,[4] S. Patel,[4] J. Shah,[4] R.J. Wong,[8] E. Sherman,[7] N. Lee,[4] and J.J. Kang[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China, [3]Department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China, [4]Memorial Sloan Kettering Cancer Center, New York, NY, [5]Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, NY, [6]Memorial Sloan Kettering Cancer Center, Department of Medical Oncology, New York, NY, [7]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [8]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, [9]Memorial Sloan Kettering Cancer Center, Department of Head and Neck Surgery, New York, NY, [10]memorial sloan kettering cancer center, new york, NY*

Purpose/Objective(s): There are guidelines to assist with patient selection for reirradiation in recurrent head and neck (HN) cancer, but those who are ineligible for definitive retreatment often have limited effective or tolerable locally palliative options before hospice. We report the largest series of the use of the Quad Shot (QS) regimen as a last-line local palliative therapy for patients with prior HN radiation therapy (RT) who were incurable and ineligible for definitive salvage.

Materials/Methods: From 2011 to 2018, 166 patients with prior HN RT (median 70 Gy, IQR 64-81Gy) and locoregional recurrence were treated with palliative intent QS RT (3.7 Gy twice daily over 2 consecutive days at 4 weeks intervals per cycle, up to 4 cycles). The majority had been radiated less than two years before QS, and 27% had received two or more prior full courses of HN RT. Palliative response as defined by subjective relief of presenting symptom(s) or objective reduction of gross tumor volume on radiographic or physical examination. Progression free survival (PFS), and overall survival (OS) were assessed. Outcomes and toxicity between patients treated with photon (n=92) and proton (n=74) RT were compared.

Results: Median age was 66 years (range 21-101). Median follow-up for all patients was 6.0 months (IQR 3.0-10.6) and 10.1 months (IQR 5.5-16.9) for living patients. Sixty-eight percent of patients achieved a palliative response. Predictors of palliative response were > 2 year interval from prior HN RT and 3-4 QS cycles. Median PFS was 4.3 months (95%CI 3.6-5.1), with 1-year PFS 13.9%. Median OS was 6.3 months (95%CI 5.5-7.1), with 1-year OS 26%. On multivariate analysis, proton RT, KPS>70, presence of palliative response and 3-4 QS cycles were associated with both improved PFS and improved OS. The ability to administer 3-4 QS cycles was the only factor that predicted for palliative response, improved PFS, and improved OS. Proton patients were more likely to complete 3-4 QS cycles and receive concurrent chemotherapy, albeit with more recurrences and prior RT courses. Furthermore, Grade 3 toxicity in proton patients was comparable with photon patients (8.1% protons vs. 9.8% photons). No Grade 4-5 toxicities were observed in the entire cohort.

Conclusion: Even in patients with previously irradiated HN cancer, palliative intent QS is an effective last-line local therapy with high response rate, minimal toxicity, and survival outcomes that exceed expectations. The only factor that predicts palliative response in addition to improved PFS and OS is the administration of 3-4 QS cycles. Proton therapy offers advantages in survival with palliative reirradiation.

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Radiotherapy in Metastatic Oropharyngeal Cancer

S. Nguy,[1] C. Oh,[2] P. Wu,[3] Z. Li,[4] M. Persky,[5] K.S. Hu,[1] B. Givi,[5] and M.M. Tam[6]; *[1]Department of Radiation Oncology, NYU Langone Health, New York, NY, [2]New York University School of Medicine, New York, NY, [3]Department of Radiation Oncology, NYU Langone Health and Perlmutter Cancer Center, New York, NY, [4]Department of Medical Oncology, NYU Langone Health, New York, NY, [5]Department of Otolaryngology, NYU Langone Health, New York, NY, [6]NYU Langone Health, Department of Radiation Oncology, New York, NY*

Purpose/Objective(s): The role of locoregional radiotherapy (RT) for metastatic oropharyngeal cancer has not been clearly delineated. We investigated the outcome of locoregional radiation to the head and neck in de novo metastatic oropharyngeal cancers who also received systemic therapy.

Materials/Methods: We queried the National Cancer Database from 2004-2016 for oropharyngeal squamous cell carcinoma patients. We selected all patients who presented with distant metastases initially and received systemic therapy. Demographics, tumor characteristics, treatments and survival were abstracted and analyzed. Kaplan-Meier methods were used to analyze the overall survival. Univariable and multivariable analyses were performed using Cox proportional hazard models to determine the association between covariables and overall survival. The influence of head and neck radiotherapy on survival was analyzed in univariable and multivariable models controlling for age, T stage, N stage, HPV status, insurance status, and income status.

Results: We identified 86,153 patients with OPSCC in NCDB from 2004-2016. A minority (1,471, 1.7%) presented with metastatic disease. Most were male (83%, n=1,216) and half of patients were >60 years (49%, n=721). The median age was 59 with a standard deviation of 9.7. Of those with complete data, 48% (n=187) were HPV+ and 55% staged as T4 (55%, n=182). Of the entire cohort, 57% (n=818) received radiation therapy to the head and neck area. The median RT dose received was 6432 cGy. The median survival was 12.91 months (SD 25.6) With a median follow up time of 12.9 months (IQR 6.9-26.5 months), head and neck RT was associated with improved overall survival with a 1 year OS of 61% (95% CI 0.58-0.65) compared to 51% (95% CI 0.47-0.56) without RT , p<0.0001. On univariable analysis, HPV status, receipt of radiotherapy, radiotherapy dose, race, age >60 years, T stage, N stage, income, and insurance status were predictive of survival outcomes. On multivariable analysis controlling for multiple clinical and social demographic factors, radiotherapy remained a significant predictor of survival (HR 0.74, 95% CI 0.65-0.84, p <0.001). No factors were associated with increased likelihood of receipt of radiotherapy.

Conclusion: The survival of metastatic OPSCC remains limited. In this large series in which more than half of patients received radiotherapy, radiotherapy was associated with longer survival. This data could be of value by head and neck cancer practitioners in guiding decisions regarding management for this challenging group of patients with poor outcomes.

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Survival Following Photoimmunotherapy in Patients (Pts) with Recurrent Head and Neck Squamous Cell Carcinoma (rHNSCC)

A.M. Gillenwater,[1] J.M. Johnson,[2] J.M. Curry,[2] S.T. Kochuparambil,[3] D. McDonald,[3] M. Fidler,[4] K.M. Stenson,[4] N.R. Vasan,[5] M.A. Razaq,[6] J. Campana,[7] G. Mann,[8] and D. Cognetti[2]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Thomas Jefferson University Hospital, Philadelphia, PA, [3]Allina Health, Virginia Piper Center Institute, Minneapolis, MN, [4]Rush University Medical Center, Chicago, IL, [5]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [6]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [7]Colorado Head and Neck Specialists, Denver, CO, [8]Rakuten Medical Inc, San Mateo, CA*

Purpose/Objective(s): Locoregional relapse of HNSCC accounts for approximately 80% of primary treatment failures (Ridge et al, Cancer Management 2016). The primary source of morbidity and mortality in HNSCC is locoregional progression. Prognosis for pts with locally advanced rHNSCC who have failed chemoradiation therapy is very poor. In pts with recurrent or metastatic disease, the 1-year survival rates after anti-PD-1 therapy (nivolumab[N] or pembrolizumab[P]) was 36% to 37% compared to 17% to 27% after treatment with methotrexate, docetaxel, or cetuximab[C] (Ferris et al, NEJM 2016; Cohen et al, Lancet 2018). In a recent phase 1/2a study of Cetuximab-IR700 photoimmunotherapy (PIT)-treated pts with locoregional rHNSCC, 14 of 30 (47%) pts in the Phase 2a portion of the study were alive at 1 year and the median overall survival was 9.3 months (Cognetti et al, ASCO 2019). Here we seek to further characterize the rHNSCC pts that had survival > 22 months following PIT treatment.

Materials/Methods: In the RM-1929-101 trial, 38 pts with locoregional, rHNSCC who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy were treated with Cetuximab-IR700 PIT. Pts with survival > 22 months were identified and a retrospective review was performed that included tumor characteristics, prior treatment history, tumor response, and post-PIT treatment anti-cancer therapies.

Results: Of the 38 pts treated with Cetuximab-IR700 PIT 10 (26%) pts were alive > 22 months post PIT treatment at the time of data cut (08Aug2019). Of the 10 pts, 8 were male and age at study entry ranged from 54 to 86 years. Median time of primary diagnosis to PIT treatment was 28.1 months (range 9.1 to 182.8 months). In these pts, the median number of prior lines of therapy including surgery, radiotherapy and systemic therapy was 2.5 (range 1 to 6). Of the 10 pts, 4 received prior anti-PD 1 therapy (3 N and 1 P failures), 4 received prior C; of these, two received both N and C, and one received concurrent N. While on Cetuximab-IR700 PIT therapy, the best response by central radiology review was complete response (3), partial response (3), and stable disease (4). Of the 10 pts, 4 (11%) did not receive any additional anti-cancer therapy following PIT treatment. Overall survival duration for these 10 pts from start of PIT treatment ranged from 22.2 months to 48.2 months.

Conclusion: Ten of 38 (26%) rHNSCC pts survived > 22 months following Cetuximab-IR700 PIT treatment. These included responders and pts with stable disease. Notably, 4 pts remained treatment free and are still alive as of the data cut. Survival > 22 months was clinically meaningful in these heavily pre-treated pts. Allowing for this study's small sample size and retrospective analysis, further studies with PIT treatment are warranted.

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Outcomes and Predictive Value of Post-Adjuvant Therapy Surveillance PET/CECT for Locally Advanced Oral Squamous Cell Carcinoma

D.C. Qian,[1] K.R. Magliocca,[2] A.H. Aiken,[3] K.L. Baugnon,[3] D.C. Brandon,[3] W.A. Stokes,[1] M.W. McDonald,[1] M.R. Patel,[4] H.M. Baddour,[4] A.S. Kaka,[4] C. Steuer,[5] N.F. Saba,[5] D.M. Shin,[5] and J.J. Beitler[1]; *[1]Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [2]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, [3]Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, [4]Department of Otolaryngology, Emory University School of Medicine, Atlanta, GA, [5]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Purpose/Objective(s): Positron emission tomography/contrast-enhanced computed tomography (PET/CECT) scan is an important tool for monitoring treatment response in head and neck cancer. For locally advanced oral squamous cell carcinoma (OSCC) treated by surgery and adjuvant therapy, consensus has yet to be reached on whether the optimal time to initiate surveillance PET/CECT is before or after adjuvant therapy. We sought to assess the utility of PET/CECT scans obtained 3 months after adjuvant therapy for locally advanced OSCC.

Materials/Methods: This is a cohort analysis of 220 patients with stage III, IVA, or IVB OSCC who underwent surgery, followed by adjuvant radiotherapy or chemoradiotherapy, and PET/CECT scan. Using the American College of Radiology's Neck Imaging Reporting and Data System (NI-RADS), PET/CECT scans were dichotomized as suspicious (primary or neck category ≥ 3, or distant lesion present) versus non-suspicious. We then computed differences in locoregional progression, distant progression, and overall survival; positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity; and success rate of salvage.

Results: PET/CECT scan was performed a median of 13 (SD 6) weeks after adjuvant therapy for 220 patients (123 males, median age 60 years). Sixty-seven patients (30%) had suspicious PET/CECT scans, which were significantly associated with local failure (HR 14.0, 95% CI 7.3−26.6), distant failure (HR 18.4, 95% CI 9.6−35.3), and poorer overall survival (HR 9.5, 95% CI 5.0−17.9). Follow-up over 4 to 103 months yielded estimates of overall PPV, locoregional PPV, NPV, sensitivity, and specificity to be 85%, 79%, 73%, 58%, and 92%, respectively. Among those with biopsy-confirmed progression, 37 patients (65%) underwent salvage therapy; 4 (11%) were without evidence of disease at last follow-up.

Conclusion: For locally advanced OSCC, PET/CECT scan 3 months after adjuvant therapy is strongly predictive of disease recurrence and survival, demonstrating improved performance over post-operative imaging in previous studies. Following a suspicious post-adjuvant therapy PET/CECT scan, cure of locoregional recurrence is possible but unlikely. Prospective comparison of salvage success between post-operative and post-adjuvant therapy surveillance PET/CECT is warranted.

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Oral Tongue Squamous Cell Carcinoma in Young, Non-Smoking, and Non-Drinking Patients

D.F. Villavisanis,[1] D.R. Dickstein,[2] K. Sindhu,[2] J.W. Rutland,[1] K. Misiukiewicz,[3] M. Posner,[3] J.T. Liu,[2] V. Gupta,[2] S. Sharma,[2] M.S. Teng,[1] E. Genden,[1] B. Miles,[1] and R.L. Bakst[2]; *[1]Department of Otolaryngology − Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, [2]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [3]Department of Medicine, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

Purpose/Objective(s): Smoking, alcohol, and old age are known risk factors for oral tongue squamous cell carcinoma (OTSCC). While OTSCC in nonsmoking and nondrinking young patients has been described as having an aggressive phenotype, risk factors and oncological outcomes of this cancer are poorly understood. The purpose of this study was to characterize outcomes of OTSCC in young, non-smoking, non-drinking patients compared to older patients.

Materials/Methods: A retrospective review of patients presenting to our institution with OTSCC between January 2008 and June 2019 was performed. Inclusion criteria were diagnosis of primary OTSCC and no history of alcohol or smoking. The young cohort age threshold was 45 years. Demographic, clinical presentation, surgical, radiotherapeutic, chemotherapeutic, pathological staging, locoregional failure, distant failure, and survival data were evaluated. In-field failure was determined by comparing PET scans and radiation therapy plans. Chi-square and fisher's exact test were used to determine significance.
Results: 61 patients met inclusion criteria for this study (54.0% young and 46.0% old), with mean cohort ages of 40.8 and 61.5 years. All patients were treated with upfront surgery. 16 (26.2%) had surgery alone, 17 (27.9%) had surgery and adjuvant radiation therapy (RT) only, and 28 (45.9%) had surgery and adjuvant chemoradiotherapy. 19 young (57.6%) vs five old (17.9%) patients had pathological stage I-II tumors and 14 young (42.4%) vs 23 old (82.1%) had pathological stage III-IVB tumors ($p < 0.001$). Mean tumor sizes were $2.55 \pm 1.88 cm^3$ (young) and $1.02 \pm 1.71\ cm^3$ (old) ($p = 0.22$). The mean depth of invasion was significantly greater in old patients ($1.37 \pm 0.65\ cm^3$ vs $0.71 \pm 0.63\ cm^3$) ($p < 0.05$). The old cohort 10 (35.7%) demonstrated comparatively higher rates of lymphovascular invasion compared to young patients 5 (15.2%) ($p = 0.079$). The younger cohort had a significantly higher rate of locoregional failure 15 (45.5%) compared with the older cohort 6 (21.4%) ($p < 0.05$). Young patients had a shorter treatment-to-failure interval (15.0 and 18.5 months), although this was not statistically significant ($p = 0.11$). Young patients exhibited a higher rate of distant failure (8, 24.2%) compared with old patients 3 (10.7%), with a shorter time to distant failure after treatment (10.6 vs 11.8 months), with the same length of survival from treatment at 27.7 months. Of patients with locoregional failure who received RT, 100% demonstrated in-field failures.
Conclusion: OTSCC in young, non-drinking, non-smoking patients exhibited a complex disease course, demonstrating greater rates of locoregional and in-field failures compared to similar patients in an older cohort. Future studies are warranted to examine the factors driving these outcomes and determine appropriate treatment intensive strategies in this unique population.
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Long-Term Update of Proton Beam Re-Irradiation for Recurrent Head and Neck Cancer

A. Lee,[1] S. Kitpanit,[1] P.B. Romesser,[1] K. Sine,[2] J.J. Kang,[1] D. Fan,[1] M. Fan,[1] H. Wang,[1] X. Li,[1] E. Sherman,[3] L. Michel,[3] J.O. Boyle,[4] R.J. Wong,[4] K. Zakeri,[1] L. Chen,[1] Y. Yu,[1] S. McBride,[1] N. Riaz,[1] C.J. Tsai,[1] and N. Lee[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]ProCure Proton Therapy Center, Somerset, NJ, [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): Re-irradiation (re-RT) is the only potentially curative treatment option for patients with locally recurrent head and neck cancer (HNC). Given the significant morbidity with head and neck re-irradiation, the utilization of proton beam radiotherapy (PBRT) has increased. We report an update on a single-institutional clinical experience using curative intent PBRT for re-RT in recurrent HNC.
Materials/Methods: A retrospective analysis of patients treated from a single academic proton center was conducted. Patients with recurrent HNC who had at least one prior course of definitive intent external beam RT were included. Acute and late toxicities were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and by the Radiation Therapy Oncology Group late radiation morbidity scoring system, respectively. The actuarial 5-year locoregional failure (LRF), freedom from distant metastasis (FFDM) and overall survival (OS) rates were calculated with the Kaplan-Meier method.
Results: Sixty-three consecutive patients were treated with curative intent re-RT with PBRT between 2011 and 2014. Median follow-up among surviving patients was 41 months (IQR 11-62) and among all patients was 16 months (IQR 8-42). The median time between last RT and PBRT was 34.4 months. There were 76 patients with one prior RT course and 16 with two or more courses. Median PBRT dose was 60.6 Gy (RBE). Eighty-five percent of patients had prior HNC RT for an oropharynx primary and 39% had salvage surgery prior to re-RT. The cumulative incidence of locoregional failure at 5-years, with death as a competing risk, was 26.0%. 5-year FFDM and OS were 87.5% and 25.1%, respectively. Acute grade ≥ 3 toxicities included mucositis (9.9%), dysphagia (9.1%), esophagitis (9.1%), and dermatitis (3.3%). There was one death during PBRT secondary to disease progression. Grade 3 or greater late skin and dysphagia toxicity were noted in 6 (8.7%) and 4 (7.1%) of patients, respectively. Two patients had grade 5 toxicity secondary to treatment-related bleeding.
Conclusion: This updated analysis confirms that proton beam re-irradiation of the head and neck continues to provide effective tumor control with acceptable acute and late toxicity profiles likely secondary to the decreased dose to the surrounding normal, albeit previously irradiated tissue.
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Role of Hypothyroidism on Postoperative Fistula Development following Salvage Oropharyngectomy

Z.M. Huttinger,[1] M.E. Heft-Neal,[2] J.R. Brennan,[3] S.B. Chinn,[2] M.E. Spector,[2] and A. Rosko[2]; *[1]University of Michigan Medical School, Ann Arbor, MI, [2]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [3]Department of Otolaryngology, Vanderbilt University, Nashville, TN*

Purpose/Objective(s): Previous work has demonstrated that postoperative hypothyroidism negatively affects wound healing, though much of this work focused on laryngectomy. The purpose of this study is to evaluate the association between wound healing and hypothyroidism in patients undergoing salvage oropharyngectomy.
Materials/Methods: A single-institution retrospective case series was performed. Ninety-six patients who underwent salvage oropharyngectomy for recurrent squamous cell carcinoma between 2001 and 2017 after radiation or chemoradiation were included. The principle explanatory variable was postoperative hypothyroidism, defined as thyroid stimulating hormone (TSH) greater than 5.5 mIU/L. The primary endpoints of the study were oropharyngocutaneous fistula development and fistula requiring reoperation within 30 days. Binary logistical regression multivariate analysis using backwards Wald test was performed.
Results: In a multivariate analysis, postoperative hypothyroid patients were at a 3.3-fold increased risk of developing a fistula (95% confidence interval [CI] $1.03 - 10.5$, $p = 0.04$) as the postoperative fistula rate among hypothyroid patients was 34.5% compared to 19.4% among euthyroid patients. Additionally, postoperative hypothyroid patients were at 10.7-fold increased risk for development of a fistula requiring reoperation (95% CI 1.35-83.8, $p = 0.03$). In the analysis 20.7% of patients with hypothyroidism developed a fistula requiring reoperation, while only 9.0% of euthyroid patients developed a fistula requiring operative management. Postoperative hypothyroidism was also associated with free flap loss (OR 19.7, 95% CI $1.12 - 343.4$, $p = 0.04$).
Conclusion: Postoperative hypothyroidism in patients undergoing salvage oropharyngectomy is an independent predictor of complications related to wound healing, namely fistula development. Moreover, patients experiencing hypothyroidism are more likely to require operative management after fistula development. These data are in agreement with previously published work demonstrating postoperative hypothyroidism was an independent risk factor for fistula development in patients undergoing salvage

laryngectomy. This current study provides further evidence for a possible role of hypothyroidism and postoperative wound healing complications.
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Multi-institutional study utilizing surgery + cesium-131 brachytherapy in recurrent head and neck cancer

A. Luginbuhl,[1] D. Kutler,[2] C. Zender,[3] T. Wise-Draper,[4] J. Patel,[5] V. Karivedu,[6] T. Zhan,[7] M. Chang,[8] M. Yao,[9] P. Lavertu,[3] J. Johnson,[1] J.M. Curry,[1] D. Cognetti,[1] and V. Bar-Ad[1]; *[1]Thomas Jefferson University Hospital, Philadelphia, PA, [2]Cornell University, New York, NY, [3]University Hospitals Cleveland Medical Center, Cleveland, OH, [4]University of Cincinnati Division of Hematology Oncology, Cincinnati, OH, [5]Thomas Jefferson University, Philadelphia, PA, [6]Ohio State University, Columbus, OH, [7]Dept of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA, [8]Cornell University, New York City, NY, [9]Radiation Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH*

Purpose/Objective(s): Surgery remains the primary modality for resectable, non-metastatic disease. Here, we explore the safety and oncologic benefit of cesium 131 brachytherapy combined with salvage surgical resection.

1. Analyze the recurrence free survival for surgery plus Cesium-131 brachytherapy compared to surgery alone and surgery with adjuvant re-irradiation in patients with recurrent head and neck cancer.
2. Assess the safety and complications of Cesium-131 brachytherapy as compared to surgery alone and surgery with adjuvant re-irradiation.

Materials/Methods: This is a single arm of surgery + cesium-131 multi-institutional prospective phase 1/2 trial with comparison to historical site and stage matched cohorts of surgery alone and surgery + reirradiation with intensity modulated radiation therapy (surg+reIMRT). Inclusion criteria included patients with recurrent squamous cell carcinoma with previous history of radiation. Data was collected on safety, recurrence and survival.
Results: The study included 108 subjects; a) surgery+cesium131 n=49, b) surgery alone n=29, c)surgery+reIMRT n=30 with an overall median follow-up of over 2 years. Cohorts were equivalent for HPV status, with the surgery only group having significantly fewer patients with positive margins and extracapsular extension (ECE). There was no difference of ECE or positive margins between cesium and re-IMRT cohorts. The cesium cohort had a significantly higher rate of peri-neural invasion (PNI) compared to the other two cohorts (p=0.03). The surgery+cesium arm demonstrated fewer locoregional recurrences (37%) compared to the surgery alone (57%) and surg+reIMRT (50%) groups. We did not see a significant difference in the hazards ratios of matched-recurrence, between the three groups determined by Cox proportional hazards models. The generalization of the Wilcoxon rank-sum test did result in a significantly longer matched-recurrence-free survival time in the radiation groups, compared to surgery-alone group. Surgery+cesium was found to have fewer treatment related grade 1-3 adverse events compared to surg+reIMRT (p=0.001). Surg+reIMRT had 5 subjects (17%) with osteoradionecroris compared to 0% in both cesium and surgery alone cohorts (p.002). Major grade 4 and 5 complications were not significantly different between groups. PEG tubes at any time point post salvage surgery were significantly more common in surgery+reIMRT (60%) compared to surgery+cesium(20%) and surgery alone (38%) (p=0.002).
Conclusion: Use of cesium-131 during salvage surgery for the treatment of recurrent head and neck cancer in select patients demonstrates improved safety including lower rates of ORN and PEG tube placement post salvage compared to IMRT re-irradiation with equivalent DFS to reirradiation with IMRT in this matched cohort.
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Reirradiation in patients with locoregional recurrence of head and neck cancer – single institution experience

A. Mikhailov,[1,2] N. Vorobyov,[2,3] N. Martynova,[2] G. Andreev,[2] A. Kubasov,[2] M. Cherkashin,[2] and N. Berezina[2]; *[1]North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russian Federation, [2]Dr. Berezin Medical Institute, Saint-Petersburg, Russian Federation, [3]Saint-Petersburg State University, St.Petersburg, Russian Federation*

Purpose/Objective(s): Locoregional recurrence is a major cause of death in patients with head and neck cancer (HNC). At present time, there are no clear guidelines and standards regarding the timing, total doses and dose tolerance of normal tissues to re-irradiation. Based on limited studies on the re-irradiation with high total doses, we evaluated the tolerability and efficacy of definitive re-irradiation.
Materials/Methods: 33 patients with histologically confirmed locoregional recurrence of HNC, received reirradiation. Median time after primary radiotherapy course was 52 months, total doses of primary radiotherapy were 44-66 Gy. 21 patient was treated in conventional fractionation, using simultaneously integrated boost (SIB). The treatment volumes and total doses were formed as follows: GTV (primary lesion and involved lymph nodes, delineated on CT, MRI and ^{18}F-FDG PET-CT) + CTV (0.5-1.0 cm) + PTV (0.3-0.5 cm) was treated to the total dose equivalent to 66-70 Gy of conventional fractionation, the upper neck (if indicated, CTV + PTV 0.5 cm) to 60 Gy, the lower neck (if indicated, CTV + PTV 0,5 cm) – equivalent to 50 Gy. Single doses to these volumes were 2.14-2.21 Gy, 2.0 Gy and 1.8 Gy, respectively. 10 patients were treated using SBRT with total doses 35-39 Gy, single doses 7-13 Gy, number of fractions 3-5. According to the literature, in a year after primary irradiation almost complete recovery (approximately 75%) of normal tissue tolerances is observed. Tolerances of the eye, lens, optic nerves and chiasm, brain stem, spinal cord, parotid gland, intact mucosa of the mouth and pharynx were not exceeded. Patient positioning accuracy was controlled by kV-imaging daily and cone beam CT weekly (daily for SBRT).
Results: 29 of 31 patients received full course of radiation therapy without a break. Radiation toxicity manifested with grade 2-3 oral and pharyngeal mucositis and grade 2 radiation epidermitis. After one month, almost complete relief of radiation mucositis and dermatitis was observed. Two patient took a break of 5 and 7 days due to the development of grade 3 mucositis and grade 3 dysphagia. To the present time median time of follow-up is 14 months. The first follow-up MRI (4-6 weeks after treatment) revealed partial response in 21 patients, stable disease in 8 patients, and continued growth in 2 patients. At present time, 16 patients are alive. Two patients died from the bleeding from large vessels, 4 patients died from concomitant pathology. In 9 patients, disease progression with distant metastases was revealed. No late radiation damage to the central nervous system by the current observation period was noted.
Conclusion: Stereotactic re-irradiation in patients with locoregional recurrence of HNC is a well-tolerated and quite effective treatment. However, the risk of late radiation injuries and fatal complications requires careful selection of candidates for this type of treatment.
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A Phase I/II, Open-Label, Dose Escalation Followed by Single-Arm Expansion to Assess the Safety and Efficacy of NT219 in Combination with Cetuximab in Patients with Recurrent/Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC)

O. Ronen,[1] M. Shickler,[2] H. Reuveni,[2] I. Israel,[2] I. Haviv,[2] P.J. Waymack,[2] and E. Cohen[3]; *[1]Galilee Medical Center, Naharya, Israel, [2]Kitov Pharma, Tel aviv, Israel, [3]Moores Cancer Center, University of California San Diego (UCSD), La Jolla, CA*

Purpose/Objective(s): FDA recently approved pembrolizumab as first line for R/M HNSCC in combination with platinum and fluorouracil in all patients (pts) or as monotherapy in tumors with a PD-L1 combined positive

score (CPS) ≥1. As a result, the chimeric IgG1 epithelial growth factor receptor (EGFR) monoclonal antibody cetuximab is currently the only FDA-approved targeted treatment option for pts with a progressed disease following both prior platinum-based therapy and pembrolizumab. However, cetuximab monotherapy results in a median response rate of ~13% and an overall survival of ~6 months in platinum-resistant R/M HNSCC, representing an area of unmet clinical need. Cetuximab inhibits EGFR signaling and initiates Natural Killer (NK) cell antibody-dependent cell-mediated cytotoxicity (ADCC). Feedback activation of STAT3 and IGF1R/IRS plays a prominent role in mediating drug resistance to many cancer therapies. Both IRS1/2 and STAT3 are major signaling junctions regulated by various oncogenes, altered during EMT and drug resistance. STAT3 is also known to play an active role in immune-evasion of the tumor. STAT3 and IRS-to-AKT activation contributes to resistance to cetuximab in HNSCC. NT219 is a small molecule, dual inhibitor of STAT3 and IRS1/2, inhibiting STAT3 phosphorylation and targets IRS1/2 to degradation. HNSCC PDX models have shown that the inhibition of both IRS and STAT3 is essential to overcome cetuximab drug resistance.

Materials/Methods: A phase I/II study with an open-label, dose escalation phase followed by single-arm expansion at the MTD to assess the safety and efficacy of NT219 in combination with cetuximab in R/M HNSCC is planned to be initiated by January 2020. Pts with platinum-resistant, HPV-unrelated HNSCC will be treated with cetuximab + NT219. All pts will be administered NT219 as a 60-minute IV fusion followed by cetuximab with an initial dose at 400 mg/m^2, as a 120 minute intravenous (IV) infusion followed by subsequent 250 mg/m^2 cetuximab weekly doses as 60-minute IV until disease progression or unacceptable toxicity. The safety phase I has a single arm dose-escalating design, aiming to establish the safety of NT219 with cetuximab and determine the MTD dose of NT219 within this combination. Up to 24 pts will participate in this phase, allocated to up to 5 dose levels of NT219 with the starting dose of 9mg/kg. In the phase II, 30 pts will be enrolled at the MTD of NT219. The primary endpoint in the phase I will be safety and tolerability and in phase II will be efficacy based on median PFS using iRECIST. Blood and fresh tissues will be collected for exploratory studies, which will focus on the identification of potential predictive biomarkers.

Results: Phase I results are expected in 2021

Conclusion: TBD

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PD-1/PD-L1 blockade as first line systematic therapy in locally advanced cutaneous head and neck squamous cell carcinoma

E. Ho,[1] K.S. Hu,[2] C.Z. Liu,[3] M. DeLacure,[4] M. Persky,[4] A. Jacobson,[1] D. Ratner,[5] Z. Li,[6] and B. Givi[1]; *[1]Department of Otolaryngology, NYU Langone Health, New York, NY, [2]Department of Radiation Oncology, NYU Langone Health, New York, NY, [3]NYU Langone Health, Department of Pathology, New York, NY, [4]NYU Langone Health, Department of Otolaryngology, New York, NY, [5]Department of Dermatology, NYU Langone Health, New York, NY, [6]Department of Medical Oncology, NYU Langone Health, New York, NY*

Purpose/Objective(s): Advanced cutaneous squamous cell carcinomas (cSCC) of the head and neck remain a therapeutic challenge. The current guidelines recommend surgery, radiotherapy and platinum-based chemotherapy as principal treatment. The efficacy of immunotherapy as a first line systemic agent in platinum naïve head and neck cSCC is not well studied. We report a series of patients with advanced head and neck cSCC treated with PD-1/PD-L1 blockade as first line systemic therapy.

Materials/Methods: All patients from 1/2017 to 7/2019 who were diagnosed with head and neck cSCC and treated with PD-1/PD-L1 blockade were reviewed. Demographics, treatment, and outcome were analyzed.

Results: During the study period, 10 patients with locoregionally advanced cSCC were treated with immunotherapy as first line systemic treatment. Majority were male (8, 80%). The median age was 73.5 (59-95). All patients had prior treatments including surgery and radiotherapy, but none had received systemic treatments. Six (60%) were treated with Nivolumab; 2 (20%) with Cemiplimab, and 2 (20%) with Pembrolizumab. The average treatment duration was 14 months and 7 patients are still under treatment. Four (40%) patients experienced complete response, 4 (40%) partial response and two patients (20%) experienced no response or progressed after initial response. The average time to response was 7 weeks, with response documented as early as 2 weeks. The most common adverse reaction observed was fatigue in 5 (50%) patients. No deaths were recorded on treatment. One patient died after treatment stopped due to medical comorbidities. With a median follow up time of 18 months (2-33), survival was 90%, with median survival time 18 months from initiation of treatment.

Conclusion: We bring forth preliminary evidence to the effectiveness of immunotherapy as first line systemic treatment in advanced cSCC of the head and neck. Immunotherapy was associated with a high response rate in our series. The treatment was well tolerated and resulted in long term survival in a significant proportion of patients. These findings may warrant further investigation in a controlled prospective clinical trial.

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Capecitabine for Salvage Treatment of Patients with Heavily Pre-treated Human Papillomavirus-Associated Oropharynx Cancer (HPV-OPC) with Distant Metastases

C. Fazer,[1] A.V. Chintakuntlawar,[2] and K. Price[2]; *[1]Mayo Clinic, Rochester, MN, United States, [2]Division of Medical Oncology, Mayo Clinic, Rochester, MN*

Purpose/Objective(s): Patients (pts) with metastatic HPV-OPC have a median overall survival over two years (Fakhry *JCO*, 2014) and are often eligible for multiple lines of palliative therapy. Given the chemosensitivity of HPV-OPC, we hypothesized that capecitabine could provide benefit for pts with heavily pre-treated HPV-OPC. We describe our experience using capecitabine as salvage treatment for pts with metastatic HPV-OPC.

Materials/Methods: Pts with HPV-OPC with distant metastatic disease were identified from a medical oncology clinical database. Demographic and clinical data was abstracted from the medical record. Descriptive statistics for survival were used for analysis.

Results: Nine pts were identified (100% male). The median age was 69 years (range 62-82). Primary treatment was definitive chemoradiotherapy in 3 pts (2 high-dose cisplatin, 1 cetuximab), surgery followed by adjuvant radiotherapy alone (2) and adjuvant chemoradiotherapy (1, high dose cisplatin), and surgery followed by de-escalated adjuvant therapy on a clinical trial (1). Two pts had distant metastases at diagnosis and both received induction chemotherapy followed by definitive chemoradiotherapy with weekly platinum to the head and neck. No pts had loco-regional failure. Sites of metastatic disease included liver (6), lung (6), lymph nodes (hilar 4, mediastinum 4, porta hepatis 1, retroperitonum 2, periportal 1, portocaval 1), bone (3) and soft tissue (1). Five pts received capecitabine as 4th line treatment, 2 as 3rd line, and 1 each of 5th and 6th line. Prior therapies included platinum/taxane doublet alone (5) and with cetuximab (2), cetuximab alone or with paclitaxel (2), nivolumab or pembrolizumab (7), nivolumab/ipilumumab (1), pemetrexed/gemcitabine (1), and phase 1 clinical trial (1). Five pts received palliative radiotherapy and 3 received liver ablation. Median time from diagnosis of metastatic disease to start of capecitabine was 21 months (range 12-32). Seven of nine pts were eligible for response assessment. Average time on capecitabine was 9 months (range 1-33). Best treatment response was partial response (4 of 7; 57%), stable disease (1 of 7; 14%), and progressive disease (2 of 7; 29%). Clinical benefit rate (PR+SD) was 71%. Reasons for discontinuation were disease progression (5) and side effects (2). One pt notably has had prolonged benefit and continues to be on treatment after 33 months.

Conclusion: Capecitabine is a salvage treatment option for heavily pre-treated pts with metastatic HPV-OPC. A median time on treatment of nine months is significant given that most pts received treatment in the 4th, 5th, or 6th line setting. Clinical or molecular predictors of response would be helpful to identify those likely to benefit.

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Long-read RNA-Seq of human papillomavirus-associated head and neck cancer reveals novel alternatively spliced viral RNA isoforms

J. Pang,[1] N. Nguyen,[2] A. Finegersh,[3] S. Ren,[1] A. Birmingham,[4] G. Xu,[5] K. Fisch,[5] V. Bafna,[2] and J.A. Califano[6]; *[1]UC San Diego, La Jolla, CA, [2]UC San Diego School of Medicine Computer Science and Engineering, La Jolla, CA, [3]UC San Diego School of Medicine Department of Surgery, La Jolla, CA, [4]UC San Diego School of Medicine Center for Computational Biology and Bioinformatics, La Jolla, CA, [5]UC San Diego, Center for Computational Biology, La Jolla, CA, [6]UC San Diego, Division of Otolaryngology-Head and Neck Surgery, La Jolla, CA*

Purpose/Objective(s): The current transcriptome of HPV-related head and neck cancers (HPV-HNC) is limited by putative assembly from short-read RNA-Seq data on cell lines. Our objective is to leverage no-assembly-required long-read RNA-Seq to conduct the most extensive and accurate characterization of HPV16 transcripts from primary tumors to date.

Materials/Methods: Eleven primary HPV-related oropharyngeal squamous cell carcinoma tumor samples (4 non-integrated, 7 integrated) were collected. Integration status was determined by presence of human-HPV16 junctions by short-read RNA-Seq. Short-read RNA-Seq was performed after quality assessment and reads were aligned to the HPV16 genome. Long-read RNA-Seq of full-length transcripts was performed according to the PacBio Iso-Seq pipeline and aligned to HPV16 genome. Non-HPV reads were discarded.

Splice donor to splice acceptor (SD-SA) junctions were viewed in Integrated Genome Viewer for confirmation and normalized and quantified as percent of mapped reads. T-tests were used for statistical analysis.

Results: Regular RNA-Seq analysis of eleven primary tumors confirmed canonical splice junctions. The number of mapped reads between the non-integrated and integrated groups were not different. The non-integrated group had more splice junctions covered by reads than the integrated group [11.0 (0) vs. 6 (2.8); mean (SD); $p=0.007$]. SD226-SA409 ($p=0.069$) was found more frequently in the integrated group, but splice sites SD226-SA3358, SD226-SA3360, SD226-3389, SD880-SA2708, SD880-3360, SD880-SA3389, and SD1302-SA3356 were all found more frequently in the non-integrated group (all $p<0.05$).

Long-read RNA-Seq identified that non-integrated tumors exhibited a stereotypical pattern of full-length viral transcripts across the HPV16 genome, and this differed from that exhibited by integrated tumors. The most common full-length transcript in non-integrated tumors was 1,476 nt long, beginning at the p97 promoter with splicing at SD226-SA409 and SD880-SA3358 extending to the early polyA tail, creating a shortened form of E6 oncoprotein (E6*I), full-length E7, E4, and E5.

Conclusion: Long-read RNA-Seq gives the first-ever full-length transcriptome of HPV16 transcripts in primary HPV-HNC. We identified the most common full-length viral transcript and detected significant differences in the patterns of transcriptomes based on integration status.

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Aurora kinases mediate resistance to PI3K inhibition in head and neck squamous cell carcinoma

V. Sambandam,[1] T. Mazumdar,[2] L. Shen,[2] H. Zhao,[3] S. Peng,[2] J. Wang,[4] and F.M. Johnson[5]; *[1]Mayo Clinic, Jacksonville, FL, [2]University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Sun Yat-sen University Cancer Center, Guangdong, China, [4]Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, [5]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): The new genomic information available for head and neck squamous cell carcinoma (HNSCC) has not been translated into clinical care largely because the landscape is dominated by tumor suppressors including *NOTCH1* that is mutated in ~18% of HNSCC. To address this translational gap, we recently demonstrated that *NOTCH1* mutant HNSCC cell lines underwent significant apoptosis *in vitro* and *in vivo* following PI3K inhibition. This research led to a clinical trial using a PI3K/mTOR inhibitor in *NOTCH1* mutant HNSCC (NCT03740100). Targeting a pathway that mediates resistance is one strategy to achieve a more durable response to therapy. In this regard, the mechanisms of resistance to PI3K inhibitors in *NOTCH1* wt HNSCC remain unknown, and this represents a major gap in knowledge.

Materials/Methods: To investigate potential mechanisms mediating resistance, we measured the levels of 304 proteins and phosphoproteins using reverse phase protein array (RPPA) in three resistant *NOTCH1* wt and three sensitive *NOTCH1* mutant cell lines after treatment with the dual PI3K/mTOR inhibitor omipalisib. Apoptosis was measured using cleaved PARP, cleaved caspase 3 and Annexin V staining.

Results: RPPA identified 16 proteins were differentially regulated (false discovery rate, FDR of 0.01) including expected markers of apoptosis and proliferation. Immunoblotting to validate RPPA results, and related pathways, demonstrated that total levels of both Aurora kinase A and B decreased following PI3K inhibition in *NOTCH1* mutant, but not in *NOTCH1* wt, HNSCC cell lines. Given their differential regulation, we hypothesized that the maintenance of Aurora expression in *NOTCH1* wt HNSCC contributed to their resistance to PI3K inhibition. To test this hypothesis, we combined the pan-Aurora inhibitor danusertib with omipalisib in 56 HNSCC cell lines and then tested cell viability using Cell Titer Glo. At effect sizes (Fa) of 0.5 and 0.75, the combination index (CI) was less than 1, indicating synergy, in 46/56 (82%) and 49/56 (87%) respectively. *NOTCH1* mutant HNSCC cell lines had CI values less than 1 at Fa 0.5 and 0.75 in 12/13 (92%) and 13/13 (100%) respectively suggesting that inhibiting the residual Aurora can also enhance cell death. To test if the maintenance of Aurora expression in *NOTCH1* wt HNSCC contributed specifically to apoptosis resistance, we treated *NOTCH1* wt cell lines with Aurora and PI3K inhibitors. Consistent with our viability assays, the combination led to more apoptosis than the single agents.

Conclusion: To the best of our knowledge, this is the first study to identify Aurora kinases as a mechanism of resistance to PI3K inhibition in any cancer type. The finding that the combination of PI3K and Aurora kinase inhibition led to synergy in both *NOTCH1* mutant and wt HNSCC suggests that this combination will be broadly effective in HNSCC patients who may have heterogeneous tumors.

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The CHK1/2 Inhibitor Prexasertib Suppresses NOTCH Signaling and Enhances Cytotoxicity of Cisplatin and Radiation in Head and Neck Squamous Cell Carcinoma

L. Zeng, D. della Manna, and E.S. Yang; *University of Alabama at Birmingham, Birmingham, AL*

Purpose/Objective(s): Checkpoint kinase 1 and 2 (CHK1/2) are serine/threonine kinases that activate cell cycle checkpoints and serve as critical regulators of the DNA-damage response (DDR). As resistance to cisplatin and radiation may involve a heightened DDR, we hypothesized that prexasertib, an inhibitor of CHK1/2, may enhance the cytotoxicity induced by cisplatin and irradiation in HNSCC.

Materials/Methods: The HPV-negative UM-SCC1 and UM-SCC6 and HPV-positive UM-SCC47 head and neck cancer cells were used in this study. Clonogenic survival was assessed by colony formation assay. Apoptosis was analyzed using Annexin V and cleaved caspase-3. Expression of proteins involved in DNA repair checkpoint and NOTCH

pathways were assessed by Western blot. Gene expression was performed with the Nanostring platform and the PanCancer Pathways Plus panel. DNA repair was investigated using the neutral comet assay and foci staining. In vivo tumor growth delay was analyzed using orthotopic UM-SCC1 or heterotopic UM-SCC47 xenograft models. Statistics was performed using ANOVA followed by Bonferroni post-test.

Results: The addition of prexasertib to cisplatin and radiation (IR) significantly decreased the *in vitro* survival fraction in HNSCC cell lines both with and without radiotherapy. Reduced survival was accompanied by inhibition of DNA repair checkpoint activation which resulted in persistent DNA damage and increased apoptosis. Additionally, genomic analysis revealed that prexasertib downregulated NOTCH signaling target genes (NOTCH1, NOTCH2 and NOTCH3) and their associated ligands (JAG1, JAG2, SKP2, MAML2 and DLL1). Prexasertib also reduced NOTCH1, NOTCH3 and HES1 protein expression. Importantly, a significant tumor growth delay was observed *in vivo* in both HPV-positive UM-SCC47 and HPV-negative UM-SCC1 cell line xenografts receiving prexasertib, cisplatin, and radiotherapy without a concomitant increase in toxicity as assessed by mouse body weight.

Conclusion: Prexasertib reduced NOTCH signaling and enhanced the *in vitro* and *in vivo* response of HNSCCs to cisplatin and radiation, suggesting combination therapy may increase clinical benefit. A clinical trial has recently completed accrual (NCT02555644).

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Splicing, Mutation, and Methylation Alterations Drive Gene Expression in HPV-OPC more than Copy Number Variation: A Network Propagation Analysis

J.R. Qualliotine,[1] B. Rosenthal,[2] G. Xu,[2] A. Mark,[3] C.A. Nasamram,[3] J.S. Gutkind,[4] K. Fisch,[2] and J.A. Califano[1,5]; *[1]UC San Diego, Division of Otolaryngology-Head and Neck Surgery, San Diego, CA, [2]UC San Diego, Center for Computational Biology, La Jolla, CA, [3]UC San Diego School of Medicine Center for Computational Biology and Bioinformatics, La Jolla, CA, [4]UC San Diego Moores Cancer Center, La Jolla, CA, [5]UC San Diego, Moores Cancer Center, La Jolla, CA*

Purpose/Objective(s): Compared with traditional tobacco- and alcohol-associated head and neck cancer, Human papillomavirus-related oropharynx cancer (HPVOPC) tumors have relatively few alteration events. Attention is often directed toward single nucleotide variation (SNV) or gene mutation as a primary driver of carcinogenesis, although there are other potential drivers of oncogenic gene expression, including DNA methylation, alternative splicing events (ASE), and copy number variation (CNV). The relative contribution of these classes of cancer alterations in driving genome wide differential gene expression (DEG) in HPVOPC is unclear. We employed genome wide network analyses to integrate tumor alteration events with gene interaction networks to investigate what classes of alterations drive global DEG output in HPVOPC. We hypothesize that genome wide ASE, methylation, and CNV alterations, in addition to SNV alterations, may be closely correlated with DEG, implicating these alterations as primary drivers of altered gene expression.

Materials/Methods: We applied network propagation analysis to multiple classes of tumor alterations including SNV, ASE, DNA methylation, and CNV, in a discovery cohort of 46 primary tumor samples of HPVOPC and 25 cancer unaffected controls. The differentially expressed genes most proximal to seed alterations from each of the classes of alteration (SNV, ASE, DNA methylation, and CNV) were defined in network space within defined protein interaction biologic networks using network propagation. A graph-based clustering algorithm was applied to these network proximal genes to identify biological functions altered in the tumor state. These clusters were annotated with known biological pathways using over-representation analysis. Individual classes of alterations are ultimately correlated with global DEG in protein-protein interaction network space. Subsequently, to validate our findings, we compare our results using the discovery cohort to an analogous analysis using HPVOPC from The Cancer Gene Atlas (TCGA).

Results: We identified significant overlap between networks of DEG and all alteration classes; this association was highest for methylation and lowest for CNV. When examining the network clusters driving this association between specific alteration classes and DEG, the greatest overlap was seen for a cluster annotated "Immune System," which included PIKA3CA. A similar pattern emerged in the TCGA validation cohort among tumor alteration classes in which ASE, methylation, and SNV alterations had the greatest fraction of significant genes in network space overrepresented in the DEG network.

Conclusion: Methylation, ASE, and SNV alterations are highly associated with network gene expression changes in HPVOPC, suggesting that ASE and methylation alterations have a larger role in driving oncogenic phenotype than previously believed.

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Circulating Tumor HPV DNA Characteristics in High Risk Oropharyngeal Squamous Cell Carcinoma

C.T. Haring,[1] P.L. Swiecicki,[2] B. Jewell,[1] F. Worden,[2] K. Casper,[1] S.B. Chinn,[1] A. Shuman,[1] M.E. Spector,[1] K. Malloy,[1] M.E. Prince,[1] C.R. Bradford,[1] C.L. Stucken,[1] E. McKean,[1] A. Rosko,[1] S. Mclean,[1] A. Eisbruch,[3] C.H. Chapman,[3,4] Y. Cao,[3] M.L. Mierzwa,[3] and J.C. Brenner[1]; *[1]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [2]Department of Internal Medicine, Division of Medical Oncology, University of Michigan, Ann Arbor, MI, [3]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [4]Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI*

Purpose/Objective(s): Human papillomavirus (HPV) circulating tumor (ct) DNA is a putative prognostic biomarker in HPV-related oropharyngeal squamous cell carcinoma (OPSCC). HPV ctDNA levels have been shown to correlate with total disease burden in recurrent/metastatic OPSCC. During definitive chemoradiation, a rapid clearance profile of HPV ctDNA is associated with decreased risk of locoregional recurrence; and an increase in HPV ctDNA after treatment is correlated with disease recurrence. We assessed HPV ctDNA characteristics in high risk stage III p16+ OPSCC treated on a prospective randomized trial.

Materials/Methods: Patients with locoregionally advanced head and neck (HN) SCC including stage III (AJCC 8) p16+ OPSCC were enrolled in a randomized phase II trial where high risk tumor subvolumes defined by DCE-MRI received 70 vs 86Gy EQD2 with concurrent cisplatin or carboplatin (NCT02031250). Blood samples were collected pre-treatment, during chemoradiation (CRT) at weeks 2, 4 and 7, and then in follow-up at 3, 6, 12, 24 months. Plasma was isolated and HPV status typed (16 or 18) by quantitative PCR (qPCR). Digital droplet PCR (ddPCR) was used to quantify HPV ctDNA at each time point using type specific primers. ctDNA levels were correlated with clinical variables and outcomes.

Results: Preliminary HPV ctDNA analyses were performed on 16 patients with p16+ disease. Of these, 10 patients had complete response (CR) and no evidence of recurrence at least 6 months after CRT completion, and 5 patients had persistent disease (PD) or recurrence after treatment. Of patients with CR, baseline ctDNA levels correlated with gross total tumor volumes (GTVtotal) measured by MRI ($R^2=0.7$, $p=0.01$). In patients who had CR and complete longitudinal data available (6/10), there was an early decrease in HPV ctDNA during CRT from a mean of 132 copies/mL pre-treatment, to 49 copies/mL at week 2, 4 copies/mL at week 4, and 0 copies/mL at week 7. All 6 of these patients had undetectable ctDNA at CRT completion. Of patients with PD or recurrence, two had residual HPV ctDNA at CRT completion. 4/5 of these patients had undetectable or very low HPV16/18 ctDNA levels at baseline and longitudinally to the end of treatment.

Conclusion: HPV ctDNA levels correlated with tumor volume and were undetectable at the end of treatment in patients who had complete

response, however remained positive in two patients who developed recurrence. In the majority of patients with recurrent disease, HPV ctDNA levels were undetectable or very low at baseline and throughout their treatment course, suggesting low HPV DNA copy number not detectable by our assay, alternative high-risk HPV strains or other driving mutations. These data corroborate the promise of HPV ctDNA as a noninvasive early prognostic biomarker, although additional work is necessary to analyze p16+ tumors with undetectable HPV ctDNA at baseline.

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Characterization of Chromosomal Instability and its Effect on Radiation Sensitivity in Head and Neck Cancer

P. Cosper,[1] L. Funk,[2] Q. Yin,[3] J. Wan,[3] R.J. Kimple,[1] and B. Weaver[2]; *[1]Department of Human Oncology, University of Wisconsin, Madison, WI, [2]University of Wisconsin, Dept. Cell and Regenerative Biology, Madison, WI, [3]University of Wisconsin, Madison, WI*

Purpose/Objective(s): Chromosomal instability (CIN), an ongoing rate of chromosome missegregation events over the course of multiple cell divisions, is common in cancer. Low CIN can be weakly tumor promoting while high CIN causes rapid cell death due to loss of both copies of one or more essential chromosomes. Combining two independent insults that each cause low CIN results in high CIN, which leads to cell death and tumor suppression. Because radiation causes CIN, we hypothesize that pre-existing CIN, which has not been well characterized in head and neck cancer (HNC) and can be caused by human papilloma virus (HPV), sensitizes HNC cells to radiation therapy.

Materials/Methods: We characterized the CIN in 4 HPV-positive and 4 HPV-negative HNC cell lines, normal oral keratinocytes (NOKS) that overexpress the HPV oncoproteins E6 and E7, 9 patient-derived HNC xenografts (PDX), and a cohort of HPV-positive and -negative HNC patient biopsies. CIN was quantified by scoring lagging, bridge, misaligned/polar chromosomes, and multipolar spindles using immunofluorescence and brightfield microscopy. An *in vitro* model of CIN was created by knocking down Mitotic Arrest Deficient 1 (Mad1), a protein critical for the mitotic checkpoint, in HeLa and FaDu cells. CIN was then quantified and correlated with radiation sensitivity *in vitro* and in PDXs *in vivo*. n>3 biological replicates for each cell line and significance was determined using a two-tailed Students t-test.

Results: NOKS that overexpress E6 and E6/E7 together had significantly increased mitotic defects and polar chromosomes compared to control. Characterization and quantification of mitotic defects in HPV-positive and −negative human HNC cell lines and patient tumor biopsies revealed significantly more polar chromosomes in HPV-positive cells and tumors, and more lagging chromosomes and anaphase bridges in HPV-negative cells, which is concordant with the HPV E6/E7 overexpression data. Knock-down of Mad1 in both HeLa and FaDu resulted in significantly more lagging, bridge, and polar chromosomes compared to wild-type cells. As hypothesized, clonogenic assays revealed significantly increased radiation sensitivity in the Mad1 knock-down cells. To determine if a similar phenomenon occurs in human tumors, 5 HPV-negative and 4 HPV-positive PDX tumors were established in nude mice and treated with 5 x 2Gy of radiation. Pre-existing CIN significantly correlated with radiation response in both HPV-positive and HPV-negative tumors.

Conclusion: Increased CIN prior to treatment increases radiation sensitivity both *in vitro* and in PDX tumors *in vivo*. HPV status appears to dictate the type and maximum tolerated threshold of CIN in HNC, a characteristic that has potential to be exploited to enhance tumor cell death and potentially select patients appropriate for radiation dose de-escalation.

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Quantity of ctDNA by Risk Category for Post-Operative Patients with HPV Associated Oropharyngeal Squamous Cell Carcinoma

D.M. Routman,[1] B.S. Chera,[2] K.R. Jethwa,[1] K. Van Abel,[3] S. Kumar,[4,5] T.A. DeWees,[6] J.J. Garcia,[7] D.L. Price,[8] J.L. Kasperbauer,[8] N.N. Laack, II,[1] A.V. Chintakuntlawar,[9] K.A. Price,[10] M.C. Liu,[10] R.L. Foote,[1] E.J. Moore,[11] G.P. Gupta,[5] and D.J. Ma[1]; *[1]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, [2]UNC Lineberger Cancer Center and Healthcare System, Chapel Hill, NC, [3]Mayo Clinic, Rochester, MN, [4]The University of North Carolina, Chapel Hill, NC, [5]University of North Carolina, Chapel Hill, NC, [6]Department of Biomedical Informatics, Mayo Clinic, Scottsdale, AZ, [7]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, [8]Department of Otolaryngology, Mayo Clinic, Rochester, MN, [9]Division of Medical Oncology, Mayo Clinic, Rochester, MN, [10]Division of Hematology and Oncology, Mayo Clinic, Rochester, MN, [11]Department of Otolaryngology, Mayo Clinic. Author contributed equally to this work., Rochester, MN*

Purpose/Objective(s): We investigated the quantity of HPV ctDNA for patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) following surgical resection and stratified by post-op risk category and cancer recurrence status. The goal was to establish data on quantity of post-op ctDNA to inform future investigations utilizing HPV ctDNA in this setting.

Materials/Methods: HPV positivity was determined by p16 as a surrogate or HPV testing when available. A ddPCR multiplex assay (HPV 16, 18, 31, 33) was used to analyze all samples. Samples from 10 treatment-naïve patients and 46 patients following surgical resection (median 25 days after surgery), but prior to adjuvant RT, were included. Investigators performing the assay were blinded to sample identity. It was run in triplicate for each patient sample and the average quantity (copies/mL) of E6 and E7 was calculated per patient. The average and median E6/E7 copies/mL were then calculated for each group stratifying by risk category and recurrence status. Intermediate-risk patients were defined as patients with PNI, LVSI, T3-T4, or ≥N2 per AJCC 7th edition, whereas high-risk patients were defined by ECE or positive margins.

Results: Circulating tumor DNA was detectable in all 10 treatment-naïve patients with a median quantity of 511.1 copies/mL. Values are summarized and average quantity is additionally reported in Table 1. Detectability for the 46 post-op patients was 43%. 2 of 8 (25%) intermediate risk patients had detectable ctDNA and the median quantity of ctDNA was 22.1 copies/mL for these 2 patients. For high risk patients, the median quantity of ctDNA was 69.2 copies/mL for the 18 of 38 (47%) detectable patients. The median quantity for the 7 of 11 (64%) recurrent patients with detectable DNA was 63.9 copies/mL.

Conclusion: Quantity of pre-op ctDNA was significantly higher than post-op values. Evaluation between risk categories was limited by patient numbers, but intermediate risk patients had nominally lower quantities than high risk patients. These data add to the available reports and will assist investigators in identifying selection criteria as part of prospective trials incorporating ctDNA. Further work investigating quantity is needed, especially evaluations of patient level pre- to post-op clearance kinetics to further inform the potential use of ctDNA for adjuvant treatment decision making.

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Cohort	N	Detection	Mean (copies/mL)	Median (copies/mL)
Treatment-naiive	10	100%	911.7	511.1
Post-operative	46	43%	46.4	0.0
All Intermediate risk	8	25%	5.5	0.0
Intermediate risk (detectable ctDNA)	2	-	22.1	22.1
All High risk	38	47%	55.1	0.0
High risk (detectable ctDNA)	18	-	116.2	69.2
Non-recurrent disease	35	37%	62.1	0.0
Non-recurrent (detectable ctDNA)	13	-	132.4	68.9
Recurrent disease	11	64%	37.8	22.2
Recurrent disease (detectable ctDNA)	7	-	59.4	63.9
High Risk Non-recurrent disease, (detectable ctDNA)	11	-	152.4	69.4

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Effect of the combined treatment with tipifarnib and cetuximab on EGFR and RAS related signaling pathways in H-RAS wild type squamous cell carcinoma of the head and neck (HNSCC)

N.F. Saba,[1] L. Shu,[2] D. Wang,[3] S. Nannapaneni,[4] D.M. Shin,[1] and G. Chen[3]; *[1]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [2]Vanderbilt University, Nashville, TN, [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, [4]Emory University, Atlanta, GA*

Purpose/Objective(s): Tipifarnib is a potent and highly selective inhibitor of farnesyltransferase (FT). It is known that H-RAS, but not K-RAS and N-RAS, is delocalized into cytoplasm and inactivated by farnesyltransferase inhibitors (FTI), such as tipifarnib. Tipifarnib has demonstrated proof of concept activity in H-RAS mutant HNSCC in an ongoing clinical trial (NCT02383927). Previously, we illustrated that combining tipifarnib with the EGFR inhibitor cetuximab had a more potent efficacy as compared with either of the single agents both in vitro and in vivo. In this study, we report how this combination affects EGFR and H-RAS associated signaling pathways in HNSCC.

Materials/Methods: Three *H-RAS* wild-type HNSCC cell lines were used in this study: UMSCC47, UMSCC1-P, and UMSCC1-C. UMSCC1-C was established from UMSCC1-P as its resistant counterpart to EGFR targeted therapy. UMSCC47 is an HPV16 positive HNSCC cell line. These cell lines were treated with tipifarnib, cetuximab, and their combination for 24, 48, and 72 hours in vitro. In addition, the combination was assessed in the UMSCC1-C xenograft as well as an HNSCC PDX model. Western blot analyses were performed to verify the effect of these treatments on EGFR/ERK/AKT and RAS signaling pathways.

Results: Our results revealed that tipifarnib alone could reduce pEGFR in UMSCC47 and UMSCC1-P, but not in UMSCC1-C. Furthermore, tipifarnib induced K-RAS and pERK, while the combination therapy restored K-RAS back to the baseline level and reduced pERK and pEGFR in all three cell lines. Both the UMSCC1-C xenograft and HNSCC PDX models consistently showed a higher potency of growth inhibition with the combination as compared with either of the single agents confirming our *in-vitro* observations.

Conclusion: Our findings are supportive of an enhanced anti-tumor effect when combining EGFR inhibition with tipifarnib in H-RAS wild type HNSCC. The current data supports the rationale for combining tipifarnib with EGFR inhibitors as a possible effective therapeutic approach in HNSCC.

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Inhibition of radiation-induced autophagy improves control of head and neck squamous cell carcinoma

Y.S. Lee,[1] J. Skiba,[1] G. SenthilKumar,[1] S.T. Bradley,[1] K.P. Nickel,[2] and R.J. Kimple[2]; *[1]University of Wisconsin, Madison, WI, [2]Department of Human Oncology, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Despite multidisciplinary care, 5-year survival rates hover around 40-50% for patients with locally advanced HNSCC. We have shown that radiation, a treatment commonly used in the treatment of these patients, induces autophagy, a pro-survival cellular stress response. In this study, we further investigate the molecular mechanism underlying therapy-induced autophagy and examine the consequences of autophagy inhibition.

Materials/Methods: Autophagy was assessed using immunofluorescence for LC3, p62, and acridine orange in multiple HNSCC cell lines and a nano-Luc LC3 reporter assay (Promega). Expression of putative mediators of therapy induced autophagy such as EGFR and LAPTM4B reduced usig RNAi. CMH2DCFDA was used as a measure of reactive oxygen species (ROS). Hydrogen peroxide was used to stimulate ROS production. Trolox, a ROS scavenger, was used to reduce levels of ROS. Radiation was delivered to in vitro cultures using a RS225 cabinet irradiator and to mouse models using a SARRP at a dose rate of approximately 3 Gy/min with dose validation by TLD using custom, geometry specific phantoms. SAR405, a VPS34 inhibitor, was used to determine whether inhibition of autophagy reduces cell survival or represses cancer cell growth in the clonogenic assay. The combination of autophagy inhibition and radiotherapy was tested in vivo using A253 cells in a flank xenograft model.

Results: Radiation caused a two-fold increase in autophagy as assessed using the nano-Luc reporter assay and immunoblotting. Knockdown of EGFR and LAPTM4B, two proteins important in growth-factor deprivation induced autophagy, did not influence radiation induced autophagy. Radiation increased the accumulation of ROS (~50%) and resulted in the dephosphorylation of mTOR (~25%), an effect that could be blocked by ROS scavenging. The combination of SAR405 and radiation resulted in complete loss of cell survival in clonogenic survival assays suggesting a radiosensitizing effect. In vivo, autophagy inhibition improved tumor control when combined with radiation when compared to either treatment alone.

Conclusion: Radiation-induced autophagy is mediated through generation of ROS and controlled by modulation of mTOR. Autophagy inhibition decreased cell survival in vitro and resulted in decreased in vivo tumor growth. These results suggest that inhibition of autophagy may be a viable approach to sensitize HNSCC to radiation therapy.

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Thymoquinone Preferentially Targets Squamous Cell Carcinoma and Demonstrates Radioprotective Effects on Normal Keratinocytes

K. Kwan,[1] Y.M. Alhiyari,[2] F. Barragan,[3] and M. St John[2]; *[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [2]Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [3]University of California Los Angeles, Los Angeles, CA*

Purpose/Objective(s): Many chemotherapeutics indiscriminately damage healthy and cancerous tissue alike. Chemotherapeutics that preferentially target cancer cells while sparing healthy tissue would greatly improve outcomes and quality of life for cancer patients. Several groups have shown that thymoquinone (TQ), the active constituent in the medicinal plant *Nigella sativa,* has anti-cancer properties. Independently, other studies have shown that TQ has potential radioprotector effects. The objective of our study is to determine if TQ can simultaneously show anti-cancer properties in cancerous tissues and radioprotective effects in healthy tissues utilizing a panel of cell lines.

Materials/Methods: To assess TQ's effects, the following cell lines were utilized: OKF cells, healthy immortalized keratinocytes, and a squamous cell carcinoma cell lines, SCC47 and SCC104. In-vitro dose escalation curves were constructed with TQ doses ranging from 0uM to 25uM. In-vitro clonogenic assays were performed combining TQ treatment with ionizing radiation at doses of 0, 2, 4, 6, and 8 Gray (Gy) single x-ray fractions. We assessed cell viability using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Intracellular oxidative stress at 0 and 8 Gy was evaluated with dichlorofluorescein-diacetate (DCF-DA) assay.

Results: Dose escalation demonstrated that SCC47 and SCC104 cells demonstrate significantly increased sensitivity to TQ treatment compared to OKF cells. Clonogenic assays revealed TQ in combination with radiation increases cell killing in SCC47 and SCC104 while OKF remained unaffected ($p < .05$, $n = 3$ at 8Gy). When subjected to 8 Gy ionizing radiation, reactive oxygen species (ROS) decreased in both cancerous and healthy cells treated with TQ when evaluated 30 minutes after radiation.

Conclusion: Our data shows that SCC cells are selectively sensitive to TQ alone and that this sensitivity is amplified by radiation. The observed differences in dose escalation and radiation response between normal keratinocytes and SCC cell lines suggest a unique mechanism in processing TQ that is active in normal tissues but lost in cancerous ones. This capacity of TQ to preferentially target cancer cells while sparing healthy tissue can greatly improve outcomes and quality of life for head and neck cancer patients.

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Correlation of Standard Clinical p16/HPV Testing with Highly Sensitive HPV Subtype Testing, and Association of HPV Subtypes with Outcomes in Oropharyngeal Cancer

M. Echevarria,[1] G.Q. Yang,[2] A. Giuliano,[3] and J.J. Caudell[4]; *[1]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, [2]H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology, Tampa, FL, [3]Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL, [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Purpose/Objective(s): Presence of the human papilloma virus (HPV) in oropharyngeal cancer is a strong prognostic factor. While HPV16 is primarily associated with oropharyngeal cancer, there are over 100 different subtypes. As part of a prospective biomarker study, we analyzed HPV subtypes on tumor samples and in oral gargles. We hypothesized that differences in HPV subtypes may be associated with outcomes.

Materials/Methods: From May 2014 through October 2017, approximately 502 participants were screened at Moffitt Cancer Center as part of an ongoing prospective biomarker study. Eligible patients were 18 or older, with newly diagnosed squamous cancer of the oropharynx. After exclusions, 239 patients had both tumor HPV subtyping data and clinical data for analysis. Tumor samples were tested using *in vitro* reverse hybridization assay RHA Kit HPV LiPA25 for the qualitative identification of HPV DNA, including 6, 11, 16, 18, 31, 33, 35, 39, 44, 45, 51, 52, 53, 56, 58, 66, 68, 70, and 74. Locoregional control (LRC), distant metastasis free survival (DMFS), and overall survival (OS) were estimated according to Kaplan-Meier method, and comparisons made by log rank test.

Results: HPV subtyping demonstrated that 79.0% (n=189) were solely HPV16+, 4.6% (n=11) were both HPV16+ and other HPV Subtype positive (HPV16+other), 9.6% (n=23) were HPVnon16+, and 6.7% (n=16) were HPV-. Interestingly, while only 63 patients had their HPV clinically tested, there were significant discrepancies, with a sensitivity of the clinical tests of 73.3%, and a specificity of 33.3%. Immunohistochemistry with p16 (n=239) performed better with a higher sensitivity of 92.3%, and a specificity of 43.75%. There were no significant differences in patient age, stage, smoking status, or treatment modalities between the different HPV subtype groups. At a median follow up time of 17 months, there were no significant differences in 2-year LRC for HPV16+, HPV16+other, and HPVnon16+ was 89%, 90.9%, and 82.9% respectively ($p > 0.33$), or in 2-year FFDM: 85.7%, 90.9%, and 84.8%, respectively ($p > 0.68$). Actuarial rates of 2-year OS were not significantly different: 83.7% for HPV16+, 88.9% for HPV16+other, and 71.1% for HPVnon16+ ($p > 0.27$).

Conclusion: Interestingly, there was discordance between clinical HPV assay and the highly sensitive HPV LiPA assay used in this prospective biomarker study, though p16 testing remained sensitive for the presence of HPV. Although limited by small numbers of patients without HPV16+, it appears that HPV subtype was not associated with outcome in patients primarily treated with radiation +/- chemotherapy. However, further follow up is necessary to confirm these results.

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Comparison of two approaches to establishing PDXs of head and neck cancer

L. Abel,[1] R. Hu,[2] J.Y. Bruce,[3] K.P. Nickel,[4] and R.J. Kimple[4]; *[1]University of Wisconsin, Madison, WI, [2]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, [3]University of Wisconsin - Madison, Section of Hematology/Oncology, Madison, WI, [4]Department of Human Oncology, University of Wisconsin, Madison, WI*

Purpose/Objective(s): Patient derived xenografts (PDX's) represent a valuable resource for pre-clinical translational oncology. PDXs have the potential to allow investigators to sample the heterogeneity within a population of cancer patients using in vivo and/or in vitro assays. When properly managed, PDXs are a renewable resource that can be made available through biobanking for drug screening against a wide array of tumor types. Traditional approaches to establishing and maintaining PDX's requires a substantial investment in labor and funds even before knowing whether a given PDX will be useful to investigators. We sought to systematically investigate the ability to immediately cryopreserve patient tissue, to be used at a later time after assessing the usefulness of the tissue as set by the goals of the research lab.

Materials/Methods: We examined the viability of patient tissue in two conditions - tissue implanted into NSG mice immediately upon receipt from the OR and tissue from the same patient cryopreserved, thawed, and implanted at a later date. Fresh, viable tissue from 10 patients undergoing surgical resection was obtained through the institutional biobank. Each sample was divided with half immediately implanted into NSG mice and half cryopreserved and implanted at a later time. Tumor nodules were resected, formalin fixed, paraffin embedded, and sectioned for pathologic review of hematoxylin and eosin stained sections. Time to passage and the

number of implantation sites bearing tumors was recorded. Short tandem repeat analysis was used to confirm that all origin of resulting tissues.
Results: Seven of the 10 patient samples produced tumors in NSG mice. One tumor grew only from the cryopreserved specimen and one only from fresh specimen. STR analysis confirmed that all tissues matched the donor patient. Pathologic review of H&E stained slides demonstrated strong correlation in multiple histologic features between approaches.
Conclusion: Immediate cryopreservation and later implantation produced viable PDX tissue at a rate that was not different from implantation of fresh tissue. This would permit investigators to perform key molecular analysis before investing time and resources in establishing PDXs that do not represent their scientific question. We believe this approach is a cost- and labor-efficient approach to establishing PDXs for correlative and translational science.
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LSD1 Inhibitor and Cisplatin Combination Treatment of Sinonasal Squamous Cell Carcinoma Cell Lines

L. Weatherford,[1] D. Kuhnell,[1] S. Palackdharry,[1] R. Vachon,[1] V. Takiar,[2] S. Langevin,[1] and T. Wise-Draper[3]; *[1]University of Cincinnati, Cincinnati, OH, [2]University of Cincinnati Department of Radiation Oncology, Cincinnati, OH, [3]University of Cincinnati Division of Hematology Oncology, Cincinnati, OH*

Purpose/Objective(s): Sinonasal squamous cell carcinoma (SNSCC) is relatively rare, accounting for less than 3% of all head and neck cancers. Despite intensive treatment, SNSCC is aggressive, with only approximately 50% of patients surviving beyond five years after diagnosis. Treatment typically involves a combination of surgery and radiation with or without cytotoxic chemotherapy, such as cisplatin. Little is known about genetic mutations that occur in SNSCC, and even less is known about potential driving mutations. Next-generation whole-exome sequencing on SNSCC tumor samples and adjacent normal tissue revealed that eight out of ten tumors contained mutations in the lysine methyltransferase gene *KMT2C,* which has specificity for H3K4 methylation, a mark associated with transcriptionally active promoters. We hypothesized that somatic mutations in a H3K4 methyltransferase may result in loss or reduction of function, which would decrease H3K4 methylation, giving SNSCC cancer cells a proliferative advantage via silencing of tumor suppressor and DNA damage response and repair genes. We aimed to indirectly target these mutations in SNSCC cells through inhibition of KMT2C's druggable demethylase counterpart, LSD1, which has specificity for demethylation of H3K4me1/2. Given the high prevalence of *KMT2C* mutations observed in SNSCC tumors, we hypothesized that inhibition of LSD1 would prevent loss of H3K4 methylation and deactivation of key tumor suppressor genes in SNSCC and thus synergize with the cytotoxic drug cisplatin due to increased response to DNA damage.
Materials/Methods: Six SNSCC cell lines (SCCNC1, SCCNC4, SCCNC5, SCCNC6, SCCNC7, and UMSCC33) were treated with the indicated doses of cisplatin (Tocris) and the LSD1 inhibitor GSK2879552 (GlaxoSmithKline) alone or in combination. Proliferation was determined using the CellTiter 96® Aqueous One Solution Cell Proliferation Assay kit (Promega).
Results: LSD1 inhibitor treatment alone did not result in decreased cellular proliferation. As expected, we observed varying sensitivity of the different cell lines to cisplatin alone. LSD1 inhibitor in combination with cisplatin resulted in an enhanced decrease of proliferation for several cell lines compared to cisplatin or the LSD1 inhibitor alone.
Conclusion: Inhibition of LSD1 sensitized several SNSCC cell lines to cisplatin. We are currently in the process of genotyping the SNSCC cell lines for mutations in H3K4 methyltransferase genes. If it is confirmed that a high proportion of SNSCC tumors harbor mutations in H3K4 methyltransferases, further testing of LSD1 inhibitors or inhibitors of other H3K4 demethylases in *in vivo* models would be warranted with future possible translation to clinical trials.
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Molecular Profile of Early Stage Laryngeal Squamous Cell Carcinoma with Radiotherapy Resistance

E. Yilmaz,[1] T.M. Schroeder,[1] D.Y. Lee,[1] B.J. Liem,[1] M.H. Turquie,[1] M.A. Ozbun,[1] D.J. McCance,[2] M. Spafford,[3] A. Cowan,[3] and G.N. Gan[4]; *[1]University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, [2]Department of Pathology, University of New Mexico, Albuquerque, NM, [3]Department of Surgery, University of New Mexico, Albuquerque, NM, [4]Department of Radiation Oncology, University of Kansas, Kansas City, KS*

Purpose/Objective(s): Early stage laryngeal squamous cell carcinomas (LSCC) are treated with radiotherapy or surgery with the intent of larynx preservation. Despite high cure rates with radiotherapy, local failure can be seen in 15-20% of the cases. Therefore, identifying underlying molecular determinants associated with local failure following radiotherapy may allow identification of patients needing escalation in therapy. Here we reviewed next-generation DNA sequencing analysis of 3 patients with early stage LSCC with rapid progression following local recurrence, and then analyzed the TCGA database on early stage LSCC to confirm the relevance of our findings.
Materials/Methods: Next-generation sequencing was performed in a CLIA-certified platform following local recurrence in 3 patients with T1-2 LSCC treated with definitive radiotherapy. Clinical characteristic of these patients were reviewed. Promising gene targets were validated using early stage LSCC in the TCGA and analyzed using the cBioPortal web page.
Results: All three patients demonstrated a similar mutational profile: CDKN2A loss, low tumor mutational burden (TMB) and microsatellite stable status (MSS). Two patients had co-alteration with CCND1 amplification. All three patients had rapid progression in the neck with no distant metastasis. Two of the patients had progression after platinum based chemotherapy and one of these patients also received immunotherapy without response. The third patient had a rapidly enlarging lesion requiring total laryngectomy and adjuvant chemoradiotherapy to the nodal basin. Analysis of the TCGA data for the early stage LSCC identified 14 patients with stage I-II LSCC. CDKN2A alteration with mutation or deletion was observed in 6 patients; however, CCND1 amplification was observed only in 2 patients. The radiotherapy data were limited, and CDKN2A and CCND1 co-alteration was found in just one patient; that patient did not receive radiotherapy. Overall survival was shorter in the patients with CDKN2A alteration (22 months vs. 60 months), although it was statistically not significant due to the small number of the patients ($p = 0.13$).
Conclusion: Mutational signature of CDKN2A loss, low TMB, and MSS with CCND1 amplification may be associated with radiation resistance in early stage LSCC. However, the role of the TMB and radiotherapy has yet to be established. CDKN2A alterations are associated with poor outcome in early stage LSCC. Large scale comprehensive genomic analysis may help to identify mutational signatures capable of predicting response to radiotherapy in early stage LSCC.
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Integrative proteomic and transcriptomic analysis define adenoid cystic carcinoma subgroups with distinct therapeutic targets

R. Ferrarotto,[1] Y. Mitani,[2] T. Karpinets,[3] S.J. Frank,[1] X. Song,[2] Y. Fan,[2] B. Liu,[2] D. Bell,[1] M.E. Kupferman,[4] P.A. Futreal,[3] J. Zhang,[3] J. Heymach,[5] and A.K. El-Naggar[6]; *[1]University of Texas MD Anderson Cancer Center, Houston, TX, [2]MD Anderson Cancer Center, Houston, TX, [3]UT MD Anderson Cancer Center, Houston, TX, [4]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, [5]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [6]The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Adenoid cystic carcinoma (ACC) is a biphasic tumor arising from the secretory glands with high biological variability. We conducted an integrative analysis of DNA, RNA sequencing and quantitative assessment of total and post-translationally modified proteins in a well-characterized cohort of ACC patients to identify molecular characteristics associated with distinct phenotypes and propose a classification with potential therapeutic implications.

Materials/Methods: RNA sequencing and targeted DNA deep sequencing were performed in 54 fresh-frozen primary ACC tumors. Reverse phase proteomic array (RPPA) was used to measure (phospho)proteins expression in 37 samples. Hierarchical clustering followed by the Gene Set Enrichment Analysis and by manual curation was used to group the tumors and to compare the groups in terms of their biological and clinical characteristics.

Results: Unsupervised clustering of ACCs by similarity of genes expression profiles revealed three distinct subgroups. Based on the pathways most significantly enriched in each subgroup, they were named "Notch", "Epithelial-myoepithelial" (Epi-Myo) and "Transition". The Notch group represented 37% of the samples with strong upregulation of MYC target genes (q=3.53 e-10), NOTCH signaling (q=4.28 e-4), mRNA splicing pathway (q=1.83 e-3), and enrichment of *NOTCH1* activating mutations (p=5.7 e-5). Most tumors in the Notch group arose from the lacrimal and minor salivary glands (p=0.002), had solid histology (p=1.28e-7), and comprised of patients with poor survival (p<0.001). The Epi-myo group included 44% of the samples and was characterized by upregulation of apical junction complex (q= 9.26 e-20), epithelial to mesenchymal transition (q=2e-18), and myogenesis associated genes (q=3.4 e-8). This group was enriched for trachea and major salivary gland primary (p=0.002), cribriform histology (p=1.28 e-7), and included patients with better survival (p<0.001). The Transition group (19% of samples) shared features of both, Notch and Epi-myo, but was more similar to the latter group. An analysis of the tumor immune environment revealed that the Epi-myo group is more infiltrated with immune cells as compared to the Notch and Transition groups. There was no difference among the groups with regards to the presence of *MYB/MYB-L1-NFIB* fusions. The three groups were validated by protein expression using RPPA. Distinct potential therapeutic targets by subgroup were inferred from similarity of gene and protein expression profiles and include Notch1/3, BCL2, CHK1/2, for the Notch group and AXL, MET, and IGFBP2 for the Epi-myo.

Conclusion: A comprehensive, integrative molecular analysis of ACC samples revealed three major subgroups (Notch, Epi-myo, and Transition) with distinct RNA and protein expression profiles, biological behavior and unique potential therapeutic targets.

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Tumor Volume is a Predictor of Distant Metastases and Overall Survival in Sinonasal Mucosal Melanoma

S. Flukes,[1] S. Lohia,[1] C.A. Barker,[1] J. Cracchiolo,[1] I. Ganly,[1] S. Patel,[1] J. Shah,[1] A. Shoushtari,[1] V.S. Tabar,[1] A. Shah,[1] and M. Cohen[2]; *[1]Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Sinonasal mucosal melanoma is an aggressive cancer with high mortality, due in part to the significant proportion of patients who develop distant metastases. The standard of care is surgical resection followed by post-operative radiotherapy. Recently, immunotherapy has been added as adjuvant treatment. Identifying patients at increased risk of distant metastasis is important for both management and prognostic reasons. Calculation of tumor volume (TV) has been described in other head and neck cancer types to assist with predicting disease progression and survival. To date, there has been no evaluation of the impact of TV in mucosal melanoma. Our objective was to define the relationship between TV and the risk of distant metastases and overall survival.

Materials/Methods: A retrospective review was conducted of all patients with sinonasal mucosal melanoma who we treated at a single institution over a twenty-one-year period. Although patients were treated heterogeneously, most were treated with surgery when resectable, post-operative radiation, and systemic therapy in the presence of distant disease. Pre-treatment structural imaging was reviewed, and triplanar imaging was used to measure tumor diameter in three axes. Ellipsoid tumor volume was calculated using the method described by Dejaco et al. Survival analysis was performed using Kaplan-Meier and Cox regression models.

Results: Tumor volumes of 61 patients were measured. TV was associated with both development of distant metastases (p=0.018) and overall survival (p=0.022). For each 1 cubic centimeter (cc) increase in tumor volume, the risk of metastases increased 1.5% and the risk of death increased 1.8%. Tumor volume of 5cc was found to be a cut-off over which the risk of both metastases and death increased significantly (p=0.049 and 0.009, respectively). The risk of developing distant metastases within 5 years in patients with small tumors (<5cc) was 45.5% compared to 66.7% in those with larger tumors (>5cc). The 5-year overall survival was 59.1% for small and 30.8% for larger tumors respectively, with a median survival of 80 months compared to 30 months. Advanced T-stage on AJCC staging correlated with increased risk of distant metastases (p=0.005) but not with overall survival (p=0.072).

Conclusion: Calculation of TV assists in quantifying the risk of distant metastases and overall survival in sinonasal mucosal melanoma. These patients are potential candidates for adjuvant immunotherapy for prevention or reduction in the risk of distant metastases, and possibly improvement in survival. Clinical trials using these parameters are

indicated to show the impact of adjuvant immunotherapy in high risk patients.

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Site of initial metastasis is associated with survival in salivary gland cancers

W.T. Turchan,[1,2] M.C. Korpics,[1,2] M.K. Rooney,[1,2] M. Koshy,[1,2] and M.T. Spiotto[1,2]; [1]*Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, IL,* [2]*Department of Radiation Oncology, University of Illinois Hospital and Health Sciences System, Chicago, IL*

Purpose/Objective(s): The extent to which the site of initial metastasis influences survival in patients with cancer remains unclear. Here, we assessed the association of initial metastatic site with the survival of patients with newly diagnosed salivary gland cancers using the National Cancer Database (NCDB).

Materials/Methods: Using the NCDB, we identified 1,049 patients with metastatic major salivary gland cancers with metastasis limited to a single anatomic site at time of diagnosis. Anatomic sites of metastasis included bone (n=317), lung (n=392), and other sites (n=340). Comparisons between site of metastasis and clinicopathologic variables were estimated using logistic regression. Overall survival (OS) was estimated using Kaplan-Meier methods. Cox proportional hazard regression was used to estimate hazard ratios (HRs).

Results: Median follow up was 13.5 months. Bone metastasis only at time of diagnosis was associated with male gender, parotid primary, and adenocarcinoma histology; these patients were also more likely to receive radiotherapy. Patients with lung metastasis only were more likely to have submandibular gland primaries and adenoid cystic histologies. 3y OS of patients with lung metastasis only was 29.1% compared to 22.4% for patients with bone metastasis only ($P = 0.032$). On multivariate analysis, lung as the only site of distant metastatic disease predicted for better OS compared to bone only (HR 0.80; 95% CI 0.65-0.97; $P = 0.027$). When stratified by histology, lung as the only site of metastasis remained associated with improved survival in patients with adenoid cystic and squamous cell histologies. In patients with adenoid cystic carcinoma, improved OS was associated with lung metastasis only (HR 0.50; 95% CI 0.29-0.89; $P = 0.021$) compared to bone metastasis only, as well as lower Charlson-Deyo comorbidity index, receipt of surgery, and receipt of chemotherapy. In patients with squamous cell carcinoma, improved OS was associated lung metastasis only (HR 0.43; 95% CI 0.25-0.73; $P = 0.002$) and metastasis to a single non-lung, non-bone site (HR 0.45; 95% CI 0.26-0.79; $P = 0.006$) compared to bone metastasis only, as well as younger age, receipt of surgery, and receipt of chemotherapy.

Conclusion: Site of distant metastasis is a significant predictor of OS in patients with salivary gland cancers, particularly those with adenoid cystic and squamous cell histologies. Site of metastasis may help guide treatment decisions in patients with limited metastatic disease.

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Treatment patterns and survival outcomes for odontogenic cancers

M.K. Rooney,[1] W.T. Turchan,[2] M.C. Korpics,[2] M. Koshy,[2] and M.T. Spiotto[2]; [1]*Department of Radiation Oncology, University of Illinois Hospital and Health Sciences System, Chicago, IL,* [2]*Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, IL*

Purpose/Objective(s): Odontogenic cancers comprise a rare subgroup of head and neck cancers including ameloblastic carcinomas and odontogenic carcinomas. Given the limited data to guide treatment decisions, we report the treatment patterns and survival outcomes of patients with odontogenic cancers using the National Cancer Database (NCDB).

Materials/Methods: We identified 437 patients in the NCDB having ameloblastic fibrosarcoma (n=10), ameloblastic odontosarcoma (n=1), ameloblastoma carcinoma (n=203), clear cell odontogenic tumor (n=2), odontogenic carcinosarcoma (n=2), odontogenic ghost cell tumor (n=2), and odontogenic carcinoma (n=217). Patients with metastatic disease at presentation or who did not receive at least part of their care at the reporting institution were excluded. Multivariate logistic regression was used to identify factors associated with receipt of surgery and presence of lymph node metastasis. Cox proportional hazard regression was used to identify factors associated with overall survival and the Kaplan-Meier method was used to generate survival curves.

Results: Median follow up was 44.8 months. On multivariate analysis, improved survival was associated with age <57y (HR 0.40; 95% CI 0.20-0.80; P=0.001), lower comorbidity scores (HR 0.44; 95% CI 0.23-0.86; P=0.02), surgical resection (HR 0.08; 95% CI 0.03-0.19; P<0.0001) and absence of lymph node metastasis (HR 0.23; 95% CI 0.11-0.51; P=.0002). Although surgical resection was associated with improved survival, there was no difference in survival between type of resection, as radical resection or debulking were associated with similar survival outcomes (HR 1.00; 95% CI 0.53-1.87; P=0.99). The 5-year overall survival was 87.1% for debulking surgery, 88.6% for radical resection and 26.6% for no surgical resection (P <.001). Non-surgical treatment was associated with age ≥57y (HR 0.24; 95% CI 0.06-0.95; P=0.04) and patients living ≥ 30 miles from the treatment center (HR 0.18; 95% CI 0.03-0.93; P=0.04). On univariate analysis, lymph node metastases were associated with tumor size ≥ 5cm (P= 0.03) and moderate/poorly differentiated histology (P=0.003). In patients with clinical or radiographic lymph node metastasis, the 2-year overall survival was 81.8% in patients receiving radiotherapy compared to 33.3% in patients not receiving radiotherapy (P = 0.04).

Conclusion: We report the largest outcome series for odontogenic cancers. Improved survival was associated with any type of surgical resection as debulking surgeries provided similar outcomes as radical resections. Furthermore, radiotherapy may benefit patients with lymph node metastasis.

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Assessment of Lymph Node Evaluation in Patients with Clinically Node Negative Merkel Cell Carcinoma of the Head and Neck

D. Jacobs,[1] H.S.M. Park,[2] M.R. Young,[2] K. Olino,[3] R. Rahmati,[4] S. Mehra,[4] B. Burtness,[1] and B.L. Judson[4]; [1]*Yale School of Medicine, New Haven, CT,* [2]*Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT,* [3]*Department of Surgery, Yale School of*

Medicine, New Haven, CT, [4]Department of Surgery, Section of Otolaryngology, Yale School of Medicine, New Haven, CT

Purpose/Objective(s): Lymph node evaluation with sentinel lymph node biopsy is indicated by the NCCN for Merkel cell carcinoma (MCC) of the head and neck. The aim of the study is to evaluate the effect of receipt of lymph node evaluation (LNE) on potential survival impact and pathologic staging of patients with clinically node negative, non-metastatic disease of the head and neck. We hypothesized there to be a mortality benefit with LNE.

Materials/Methods: The National Cancer Database (NCDB) was queried for MCC of the head and neck between the years 2004 and 2016. Surgical LNE was defined by the NCDB as removal, biopsy or aspiration of one or more lymph nodes. Kaplan-Meier survival analysis with log-rank tests, multivariable Cox proportional hazard regression and binary logistic regression were performed. Hazard ratios (HR), odds ratios (OR), and 95% confidence intervals (CI) are reported.

Results: 4,159 patients were included, among whom 3,347 had a facial primary site and 812 had disease of the scalp or neck. The median age of diagnosis was 78 years (IQR: 71, 84) and men represented 64.1% of cases. Most tumors were ≤2 cm (66.1%) and LNE was performed in 52.5% of cases. Patients with LNE had superior survival than those without LNE for those with disease of the face (median survival 93.9 months (CI: 84.4, 103.4) vs. 40.4 months (CI: 35.7, 45.0); p-value <0.001) and for those with disease of the scalp or neck (median survival 45.3 months (CI: 35.1, 55.5) vs. 25.8 months (CI: 21.9, 29.7); p-value <0.001). Patients with pathologically confirmed node negative (pN0) disease had superior survival to those who were node positive (pN+) after LNE for disease of the face (median survival 104.1 months (CI: 91.2, 116.9) vs. 49.3 months (CI: 37.8, 60.7); p-value <0.001), and for disease of the scalp or neck (median survival 53.6 months (CI: 25.6, 81.7) vs. 24.2 months (CI: 16.5, 31.9); p-value <0.001). Multivariable analysis revealed higher survival for patients receiving LNE vs. no LNE (HR 0.74; CI: 0.66, 0.83) after adjusting for age, sex, Charlson-Deyo comorbidity score, treatment facility type, geographic location, urban-rural location, tumor size, and disease location. Patients who are pN+ were more likely to be male (OR 1.63; CI: 1.19, 2.22) and have positive margins on resection (OR 2.27; CI: 1.41, 3.65), and were less likely to have tumor size of 2-5 cm (OR 0.40; CI: 0.17, 0.94) compared to smaller or larger tumors.

Conclusion: Surgical LNE is associated with improved survival in clinically node-negative, non-metastatic MCC of the head and neck, supporting its routine use in patients who are surgical candidates.

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Withdrawn

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PIK-ing out an intermediate-risk subgroup in advanced adenoid cystic carcinoma

G.J. Hanna,[1] J.E. Bae,[1] J. Lorch,[1] J.D. Schoenfeld,[1] D.N. Margalit,[1] R.B. Tishler,[1] R.I. Haddad,[1] and N. Chau[1,2]; *[1]Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, [2]BC Cancer's Vancouver Centre, Vancouver, BC, Canada*

Purpose/Objective(s): Adenoid cystic carcinoma (ACC) is a locally aggressive salivary gland neoplasm with a propensity for distant recurrence in the lungs. Little is known about the impact of local and systemic therapies for advanced ACC. We explore the long-term natural history of advanced ACC and the clinical utility of molecular alterations.

Materials/Methods: We identified 123 ACC patients from our institution (89% initially diagnosed between 2001-2019), of which 72 had recurrent (R), locoregionally incurable or metastatic (M) disease. We report long-term outcomes (Kaplan-Meier method), clinicopathologic predictors of recurrence and survival (regression model), and explore the impact of sequential cancer-directed therapy (CDT) or surveillance among R/M patients. We integrate genomic data for 36 ACC patients who underwent tumor sequencing.

Results: Median overall survival (OS) for 72 R/M ACC patients was 35.1 ys (95%CI: 25.8-37.3) with 84.8% 10-y, 71.8% 20-y OS rates (11 deaths). 66 (92%) received definitive surgery ± adjuvant therapy for their initial disease. Median disease-free interval (DFI) was 3.7 ys (range: <1-35.9). Survival was worse for R/M patients with extra-pulmonary disease sites (p=0.02); but did not differ by primary tumor site (p=0.67), or locoregional vs. distant recurrence (p=0.17). The only clinical predictor of recurrence was stage of initial disease (OR 1.69, p=0.03). 48 R/M patients (67%) received systemic or local CDT (median 2 lines) after R/M diagnosis. Longer time to first R/M treatment was associated with improved survival (HR 0.93, p<0.01); Those treated within 3 years of their R/M diagnosis had poor outcomes (p=0.01). There was no survival difference among R/M patients who received systemic therapy vs. active surveillance only for R/M disease (p=0.35), and locally ablative therapy or palliative RT (33, 69%) did not improve survival among R/M patients (HR 0.78, p=0.69). 12/48 (25%) received systemic therapy matched to their tumor mutational profile, without improved OS from the time of R/M diagnosis (HR 3.5, 95%CI: 0.8-15.5, p=0.11). *MYB*-rearrangement or expression was common (22/36, 61%), followed by *PI3K* (22%) pathway alterations among sequenced tumors; with significantly improved survival among *MYB* altered patients (10-y OS: 100% *MYB*, 53.3% *PI3K*, 32.1% *NOTCH1*, p=0.03). *PI3K* mutations were associated with a longer DFI (OR 1.28, 95% CI: 1.21-1.35, p=0.04).

Conclusion: Palliative CDT for R/M ACC did not appear to improve survival suggesting that underlying disease biology remains the strongest predictor of outcomes and newer treatments are needed. Shorter time to therapy initiation predicts poor outcomes in this setting despite variation in clinical practice. *PI3K* mutations may identify an intermediate-risk subgroup among R/M ACC patients.

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Inhibition of BRAF induces PD-L1 expression in BRAF-mutated papillary thyroid carcinoma

A. Mohanty,[1] M. Afkhami,[2] R. Pharaon,[1] H. Yin,[2] J. Sun,[3] A. Nam,[1] S. Chang,[2] T. Gernon,[4] R. Kang,[4] A. Amini,[5] S. Sampath,[5] N.L. Vora,[5] B. Salehian,[6] R. Pillai,[2] R. Salgia,[1] E. Maghami,[4] and E. Massarelli[1]; *[1]Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA, [2]Department of Pathology, City of Hope National Medical Center, Duarte, CA, [3]Department of Internal Medicine, Huntington Memorial Hospital, Pasadena, CA, [4]Department of Surgery, City of Hope National Medical Center, Duarte, CA, [5]Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA, [6]Department of Diabetes, City of Hope National Medical Center, Duarte, CA*

Purpose/Objective(s): Papillary thyroid carcinoma (PTC) represents approximately 90% of all the thyroid carcinomas. Curative surgical resection, followed by radioactive iodine treatment according to risk assessment strategy, is the standard of care with a median overall survival of 10 years. Approximately 20% of PTC recur, and about 5% develop distant metastases. *BRAF* gene, which encodes for a serine/threonine protein kinase, driving the downstream MAP kinase signaling pathway, is one of the commonly mutated genes in PTC patients. The most frequent *BRAF* activating mutation, V600E, is associated with worse overall survival in PTC and is correlated with lymph node metastasis, which confers the worst disease free survival with higher recurrence rate after definitive treatment. In melanoma patients, PD-1 expression is increased after combination of BRAF and MEK inhibition, however, there is little knowledge about this association in PTC. Therefore, we investigated the correlation between PD-L1 expression and BRAF inhibition in *BRAF*-mutated PTC tumor specimens and *in vitro*.

Materials/Methods: High risk and low risk PTC cases (N = 19) from 2013 to 2018 with available paraffin-embedded archived tumor tissue were identified. RNA was extracted from the tumor tissue and analyzed by NanoString to evaluate their immune gene expression profile. We used 3 PTC cell lines, 1 without and 2 with *BRAF* V600E mutations, to validate the NanoString results by qPCR and Western blot. BRAF inhibitors dabrafenib and vemurafenib and ROCK inhibitor Y27632 were used in the 2-D *in vitro* cultures. BRAF-specific siRNAs were transfected in the *BRAF*-wild type and the *BRAF*-mutated cell lines.

Results: 13 tumors harbored *BRAF* V600E activating mutations, 1 tumor harbored *BRAF* V600R activating mutation and the remaining 5 were *BRAF* wild-type. A significant higher expression of PD-L1 and CTLA-4 was detected in the *BRAF*-mutated PTC cases by Nanostring analysis. We then confirmed *in vitro* the association of high PD-L1 expression in the 2 PTC *BRAF*-mutated cell lines. Dabrafenib or vemurafenib treatment of the *BRAF*-mutated cell lines induced PD-L1 expression, measured by Western blotting, without affecting cell viability. Knocking down *BRAF* in the *BRAF*-mutated cell lines, using the *BRAF*-specific siRNA, confirmed PD-L1 upregulation *in vitro*. In addition, we identified AKT-mTOR signaling activation after BRAF knock down as a potential mechanism of PD-L1 expression. mTOR inhibition by ROCK inhibitor, Y27632, caused a strong reduction of PD-L1 expression in the *BRAF*-mutated cell lines.

Conclusion: Our data suggest that BRAF inhibition treatment can induce PD-L1 expression in *BRAF*-mutated PTC via mTOR pathway activation. *In vivo* immunocompetent models are ongoing and results will be presented at the meeting.

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Predictors of Survival in Resected Head and Neck Soft Tissue Sarcoma

N.C.J. Lee,[1] A. Eskander,[2] A. Hosni,[3] C.S. Shah,[4] M.S. Rutenberg,[5] and Z.A. Husain[6]; *[1]Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT, [2]University of Toronto Institute of Health Policy, Management and Evaluation, Toronto, ON, Canada, [3]Radiation Medicine Program, University Health Network and Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [4]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [5]University of Florida, Jacksonville, FL, [6]Sunnybrook Health Sciences Centre Department of Radiation Oncology, Toronto, ON, Canada*

Purpose/Objective(s): The AJCC 8th edition proposed a new dedicated staging system for head and neck sarcomas (HN-STS). The most prominent adjustment occurred in the tumor classification schema with pT1 comprising ≤2cm tumors, pT2: >2cm and ≤4cm, pT3: >4cm, and pT4 representing "invasion of adjoining structures." We sought to validate the new AJCC 8 pT classification, both in terms of tumor size and invasion and also assess predictors of overall survival.

Materials/Methods: Patients with HN-STS were identified from the SEER database using ICD-O codes as specified by the *AJCC Cancer Staging Manual, 8th Ed* and the WHO Classification of Tumors. Patients were included if they had no evidence of metastatic disease at diagnosis and underwent primary surgery without neoadjuvant therapy. The primary endpoint was 5yr overall survival.

Results: 565 HN-STS patients were identified with a median follow-up of 12 years. The median age was 62, and most patients were male (64.3%). The most common histologic grade was moderately differentiated. The median tumor size was 4.0cm, and 105 patients (18.6%) had structurally invasive tumors (pT4). Examination of overall survival according to AJCC 8 pT1-3 classification demonstrated substantial overlap between stage groups ($P = 0.40$). However, pair-wise comparison of individual categories demonstrated significant separation of pT4a and pT4b from pT1-3 and each other (pT4a v pT4b: $P = 0.048$). Nodal involvement was present in 39 patients (6.9%). Interestingly, assessment by nodal category did not show worsened outcomes in pN1 patients compared to pN0 (58.3% vs 55.1%, $P = 0.66$). Histologic grade was an important predictor of survival with five-year overall survival was 79.3% for well-differentiated, 62.2% for moderately-differentiated, 42.9% for poorly-differentiated, and 46.6% for undifferentiated ($P < 0.01$). Multivariable analysis was performed and demonstrated factors associated with worsened overall survival were pT4a classification (HR 2.41, 95% CI 1.50-3.89, $P = 0.001$) and pT4b classification (HR 4.17, 95% CI 1.84-9.45, $P = 0.001$). Grade was also significant: moderately-differentiated (HR 1.76, 95% CI 1.04-2.98, $P = 0.04$), poorly-differentiated (HR 3.30, 95% CI 1.98-5.49, $P < 0.001$), and undifferentiated (HR 3.05, 95% CI 1.86-5.03, $P < 0.001$) were associated with worse overall survival compared to well-differentiated tumors. Nodal positivity was not associated with worsened outcomes.

Conclusion: The AJCC 8 T classifications have overlapping prognoses, and may require further refinement. Tumor invasiveness and grade remain important predictors of survival. Nodal positivity was seen in a minority of patients and did not adversely impact prognosis. Further research should focus on refining T classification criteria, and combining T, N, and grade classifications to create stage groupings.

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Elective Nodal Irradiation for Locally Advanced Cutaneous Squamous Cell Carcinoma of the Head and Neck

K.N.B. Nguyen,[1] B. Harris,[2] A.F. Bewley,[2] and S.S.D. Rao[3]; *[1]University of California, Davis, Department of Radiation Oncology, Sacramento, CA, [2]University of California, Davis, Sacramento, CA, [3]University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Purpose/Objective(s): Cutaneous squamous cell carcinomas are among the most common malignancies worldwide, with the majority occurring in the head and neck area. Patients with locally advanced disease can be at high risk of microscopic spread to regional lymph nodes. However, limited published data exist to guide optimal management in this setting, particularly regarding optimal management of the neck in patients with node negative disease. We report our institutional outcome of elective nodal irradiation in this cohort

Materials/Methods: We reviewed records of patients with cutaneous squamous cell carcinoma treated with curative intent between January 2001 and December 2018. We included patients with T3-T4, N0 disease according to AJCC 8th staging manual. Patient (sex, age,

immunosuppressive status), tumor (PNI, LVI, T stage), and treatment characteristics (prior surgery, radiation dose, receipt of elective nodal irradiation) were recorded. Tumor control and survival rates were calculated using Kaplan-Meier methods and compared using log rank test.

Results: We identified 117 patients meeting the inclusion criteria. The majority (101/117) were male with median age of 73 at the time of diagnosis. PNI was noted in 47% and LVI in 11.1% of all patients. The mean follow-up time was 32 months. There were 34 documented recurrences (28 local and 6 regional recurrences). 5-years local control, regional control, disease free survival, and overall survival rates for the entire cohort were 70.4%, 93.8%, 60.8%, 52% respectively. 26 patients received elective nodal irradiation to a median dose of 54Gy covering at least the first and second nodal echelons. 5-years neck control rate was 100% for the nodal irradiation group versus 87.7% in patients who only received treatment to the primary site. In patients who received elective nodal irradiation, there was no difference in neck failure rate between treating the first echelon nodal compartments versus comprehensive nodal coverage. One patient who received elective nodal irradiation developed grade 3 osteoradionecrosis. There were no grade 4 or 5 toxicities.

Conclusion: Our result suggests potential regional control benefit of elective nodal irradiation in patients with locally advanced, clinically node negative head and neck cutaneous squamous cell carcinoma. Treatments were well tolerated with limited toxicity. Additional studies are needed to guide treatment decision making.

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Outcomes of Major Salivary Gland Tumors Treated with Proton Beam Radiation Therapy

K. Zakeri,[1*] H. Wang,[1*] J.J. Kang,[1] A. Lee,[1] D. Gelblum,[1] E. Sherman,[2] L. Dunn,[3] J.O. Boyle,[4] R.J. Wong,[4] L. Chen,[1] Y. Yu,[1] C.J. Tsai,[5] S. McBride,[5] N. Riaz,[1] and N. Lee[5]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [3]Memorial Sloan Kettering Cancer Center, Department of Medical Oncology, New York, NY, [4]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, [5]Memorial Sloan Kettering Cancer Center, New York, NY*

*indicates co-first authorship

Purpose/Objective(s): Proton beam radiation therapy has dosimetric advantages compared to photon radiation therapy for the treatment of major salivary gland tumors (MSGTs), due to the typically unilateral pattern of disease spread requiring only ipsilateral irradiation. However, clinical data on treatment outcomes and the potentially reduced toxicity with proton beam therapy is lacking.

Materials/Methods: Patients with non-metastatic MSGTs treated at a proton therapy center from October 2013 to October 2018 were retrospectively reviewed. Patient demographics and tumor characteristics were retrieved from medical records. Locoregional and distant recurrence were determined from imaging reports and oncology clinic notes. The Kaplan-Meier method was used to estimate time-to-event outcomes and the Cox proportional hazards model was used to determine the effects of covariates.

Results: Ninety patients with MSGTs were included and the most common site and histology were the parotid gland (74.4%) and adenoid cystic carcinoma (22.2%), respectively. Most patients (91.1%) were treated postoperatively and most had either positive (45.6%) or close (27.8%) margins. The median dose of proton beam radiation therapy was 66.07 CGE and 28.9% of patients received concurrent chemotherapy. With median follow up of 26.4 months, the 2-year rates of locoregional control, progression-free survival, and overall survival were 94.8%, 73.6%, and 92.2%. On multivariable analysis, advanced age and poor performance status were associated with worse survival ($p<0.05$ for both), but gender, T and N category, margin status, LVI, PNI, and receipt of chemotherapy were not. Grade 3 or higher acute dermatitis or mucositis occurred in 11.1% of patients. There were no grade 5 toxicities.

Conclusion: In the largest reported cohort of MSGTs treated with proton beam radiation therapy, the rates of locoregional control were high and treatment was well tolerated.

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Primary Surgery for Locally Advanced Sinonasal Cancer: Influence of Dural and Orbital Resection

N.M. Woody,[1] J. Imamura,[2] H. Li,[3] P.F. Recinos,[3] P. Soni,[3] V. Kshettry,[3] R. Sindwani,[3] T. Woodard,[3] D. Tang,[3] D.J. Adelstein,[4] J.L. Geiger,[4] N.P. Joshi,[1] S. Koyfman,[1] and E. Lamarre[5]; *[1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Case Western Reserve University, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [5]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Locally advanced sinonasal cancer (LA-SC) is often managed with primary surgery and adjuvant therapy to achieve optimal control. Such resections can require orbital exenteration and dural resection which has prompted interest in alternatives to primary surgery. However, endoscopic techniques and combined skull base surgery continue to improve. We report outcomes of LA-SC patients undergoing primary resection.

Materials/Methods: From a single institution IRB approved registry of head and neck cancer we identified all patients (Pts) with a first sinonasal cancer diagnosis of LA-SC (T3/T4 or equivalent primary tumor) treated with primary surgical resection. Sinonasal histologies including squamous, adenocarcinoma, sinonasal undifferentiated carcinoma, NUT midline, teratocarcinosarcoma and neuroendocrine tumors were included excepting sinonasal minor salivary gland tumors, melanomas and sarcomas. Patients were categorized based on extent of surgery performed and separated into those requiring dural resection or orbital exenteration (DR/OE) vs those who did not (SINUS). Operative complications, local control (LC), distant metastasis (DM), event-free survival (EFS) were compared between DR/OE and SINUS groups.

Results: A total 61 Pts (Median age 64.1 yo) with a median (IQR) follow up of 2.2 (0.9, 4.3) years were identified with 37 (60.7%) undergoing SINUS and (39.3%) requiring DA/OE. The primary surgical approach was endoscopic in 37.1% of cases and 53.2% of cases involved skull base neurosurgery. Age was younger for DR/OE (Median 58.4 vs 67.0, $p=0.01$), no significant differences in comorbidity (ACE-27), or nodal involvement were noted between the two groups. Pts undergoing DR/OE were more likely to be clinically T4 (78.3% vs 51.4%, $p=0.003$) and receive adjuvant chemoradiation (79.2% vs 32.4%, $p<0.001$). There were no significant differences in LC (3-Yr: 82.0% vs 91.7%), DM (3-Yr: 15.6% vs 27.3%) or EFS (5-Yr: 60.3% vs 67.9%) between SINUS and DR/OE. More prevalent CSF leak (45.8% vs 2.7% $p=0.001$) and longer length of hospitalization (6.5 days vs 5.0 days $p=0.04$) were observed the DR/OE pts with all CSF leaks successfully repaired.

Conclusion: Primary operative management using modern surgical techniques followed by adjuvant therapy is associated with excellent oncologic outcomes even when DR/OE is needed and forms a standard against which

alternative strategies such as neoadjuvant chemotherapy/radiation will need to be compared.

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Retrospective Review of Clinic-Pathological Characteristics and Overall Survival of Patients with Adenoid Cystic Carcinoma

J. Macias,[1] N. Seetharamu,[2] N. Kohn,[2] L. Pereira,[2] D. Kamdar,[2] E. Gabalski,[2] D. Frank,[2] M. Ghaly,[2] B. Parashar,[2] and P. Goncalves[2]; [1]*Northwell Health, Manhasset, NY,* [2]*Northwell Health, New Hyde Park, NY*

Purpose/Objective(s): Adenoid cystic carcinoma (ACC) is a rare tumor, with variable growth pattern and propensity for distant metastasis. Factors affecting prognosis are under-studied. In this retrospective study, we describe a population of ACC patients (pts) treated at our institution and identify factors associated with survival.

Materials/Methods: We retrospectively reviewed charts of pts with a diagnosis of ACC between 1999-2018. Demographics, histopathology, staging, perineural invasion (PNI) and development of metastasis was recorded. Survival at 24 and 60 months (m) was estimated using the Kaplan-Meier product-limit method, and compared using the log-rank test. Pairwise comparisons were carried out using Tukey's test.

Results: Analysis was performed on 76 pts. The median age was 64 years (22-93). Pts were mainly white (57%) and female (66%). Initial TNM staging was documented in records for 50 pts-32 were local (defined as TNM stages I-III (T3N0 only)), 12 were locally advanced (LAD, TNM stages III with N1, IVA/IVB), and 6 *de-novo* metastatic (defined as stage IVC). 24 pts developed metastasis at some point during the time of the review; with lung as most common site (77%).All pts with localized and loco-regional disease had surgical resection. 5/6 pts with *de-novo* metastatic disease also had resection of the primary disease. 35 pts with localized and loco-regional disease received adjuvant radiation. Histopathological details were available for 40 pts. Survival did not differ significantly according to histopathology ($p<0.2085$)- cribriform only ($n=7$), solid only ($n=7$), any solid component ($n=8$), or cribiform/tubular ($n=18$). Survival at 24 m was 83.3%, 0.0%, 85.7%, and 94.4% respectively, and at 60 m; 83.3%, 0.0%, 57.1%, and 84.0% respectively ($p<0.2085$). 6/7 pts with tumors with solid only pattern were censored prior to 24 m. Survival differed significantly by staging at diagnosis ($p<0.0071$). Survival at 24 m was 95.8%, 51.9%, and 80.0% respectively for local, LAD and metastatic; and at 60 m, was 95.8%, 34.6%, and 80.0% respectively. There was no difference in survival for pts with PNI at diagnosis (41/50) ($p<0.4103$).

Conclusion: Our study demonstrates the variable clinical course of pts with ACC. TNM staging used for other head and neck cancers may not be applicable for ACC, with our limited data showing LAD tumors having shorter survival compared to local or even metastatic ones. One hypothesis could be that distant metastases can be indolent for years whereas regional lymph node metastases can be associated with worse outcomes due to local symptoms or complications from treatment. Our study is limited by small sample size but given the rarity of the condition, a multi-institutional prospective natural history study is warranted and should be pursued.

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Intensity Modulated Proton Therapy (IMPT) to the Parotid Gland: A Seven-Year Experience

A.N. Hanania,[1] G.B. Gunn,[2] D.I. Rosenthal,[2] A.S. Garden,[2] C.D. Fuller,[2] J. Phan,[2] J.P. Reddy,[2] A.C. Moreno,[2] N. Ausat,[2] J.N. Myers,[2] R. Ferrarotto,[2] and S.J. Frank[2]; [1]*Baylor College of Medicine, Houston, TX,* [2]*University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Intensity modulated proton therapy (IMPT) employs the dose-sparing potential of the proton beam to further improve the therapeutic ratio. We report our dosimetric and clinical outcomes in terms of disease control and toxicity in patients with parotid gland malignancies treated with IMPT.

Materials/Methods: Clinical and dosimetric characteristics of patients with parotid malignancies treated at our institution from August 2011 to May 2018 with IMPT (single and multi-field optimization) on an observational, prospective, institutional protocol with weekly assessments of toxicity were abstracted. Local control (LC), locoregional control (LRC), progression free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier method. Logistic regression and receiver operating characteristic curves were used to investigate dosmetric and clinical correlates.

Results: Forty-eight patients were identified with a median follow-up of 36 months. Median age was 53 years (range: 23-87) and most common histologies were mucoepidermoid (19%) and adenoid cystic carcinoma (19%) followed by squamous cell carcinoma (17%). Thirteen patients (27%) were treated for recurrent disease including seven patients (15%) who had received prior RT. Forty-three patients (90%) received post-operative IMPT, five patients (10%) were treated definitively and 18 patients (38%) received concurrent chemotherapy. All but one patient received unilateral IMPT with a median dose of 6390cGyRBE (IQR: 6000-6600). For all cases, minimum dose to 95% of the prescription volume (CTV D95) exceeded prescription dose. Median oral cavity mean dose was 240cGyRBE while median brainstem max dose was 424cGyRBE. On a post-hoc dosimetric analysis, we found that the volume of skin receiving greater than 30Gy (V30) correlated with clinically significant dermatitis ($p=0.02$) and a V30 > 50cc to be predictive (AUC 80%). Three-year rates of LC, LRC, PFS and OS were 95%, 93%, 76% and 85%, respectively. Acute toxicities are reported with radiation dermatitis being the primary grade three toxicity (Table). No late grade three toxicities were reported.

Conclusion: Our institutional experience suggests that IMPT for treatment of the parotid gland manifests in low rates of acute and chronic toxicity while maintaining dosimetric coverage and high rates of biological control. Skin V30 may predict for radiation dermatitis.

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Acute Toxicities	Grade 1 (n, %)	Grade 2 (n, %)	Grade 3 (n, %)	Total
Dermatitis	5 (10%)	29 (60%)	14 (29%)	100%
Pain	19 (40%)	13 (27%)	0	67%
Fatigue	23 (48%)	4 (8%)	0	56%
Xerostomia	20 (42%)	2 (4%)	0	46%
Mucositis	14 (29%)	5 (10%)	1 (2%)	41%
Nausea/Vomiting	14 (29%)	3 (6%)	0	35%
Dysgeusia	12 (25%)	4 (8%)	0	33%
Dysphagia	9 (19%)	5 (10%)	0	29%
Headache	5 (10%)	1 (2%)	0	12%
Trismus	2 (4%)	0	0	4%

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Proton Therapy for Non-Skull Base Head and Neck Adenoid Cystic Carcinoma

A. Lee,[1] S. Kitpanit,[1] K.E. Marqueen,[1] K. Sine,[2] J.J. Kang,[1] D. Fan,[1] M. Fan,[1] H. Wang,[1] X. Li,[1] D. Gelblum,[1] L. Michel,[3] J.O. Boyle,[4] R.J. Wong,[4] K. Zakeri,[1] L. Chen,[1] Y. Yu,[1] S. McBride,[1] N. Riaz,[1] C.J. Tsai,[1] and N. Lee[1]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]ProCure Proton Therapy Center, Somerset, NJ, [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): To report control and toxicity outcomes for patients with adenoid cystic carcinoma (ACC) of the non-skull base head and neck treated at a single institution with proton therapy.

Materials/Methods: Patients with non-skull base head and neck adenoid cystic carcinoma treated with proton therapy from November 2013 to June 2019 were retrospectively reviewed. Patient demographics and clinical characteristics were retrieved from medical records. Local control (LC), distant metastasis free survival (DMFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Acute and late toxicities were graded using CTCAE version v5.0.

Results: Forty-six patients with non-skull base head and neck ACC were included and the most common primary sites involved were the parotid gland (n=15, 33%), submandibular gland (n=12, 26%) and oral cavity/ oropharynx (n=10, 22%). Nine (20%) patients had metastatic disease at the time of local primary treatment with a median Karnofsky performance status of 90%. 7 (15%) patients had recurrent disease of which 4 had prior radiation therapy to a median dose of 60Gy. Among those who received definitive proton therapy, the median dose was 70CGE while the median dose for those who received postoperative radiation therapy was 66CGE. Twenty-one (46%) patients received concurrent systemic therapy. Thirty-one (67%) patients were treated with passively scattered proton therapy (PSPT), 11 (24%) patients were treated with intensity-modulated proton therapy (IMPT), and 4 (9%) received a combination of both. With a median follow up of 34 months (IQR 15-49) for non-metastatic ACC, the 2-year LC, DMFS and OS were 100%, 82.5% and 96.7%, respectively. With a median follow up of 27 months (IQR 4-35) for patients with metastatic ACC, the 2-year LC was 100% and 2-year OS was 87.5%. Grade 3 acute mucositis and dermatitis occurred in 4 (9%) patients and grade 3 late trismus, cranial neuropathy and hearing impairment occurred in 6 (13%) patients. There were no grade 4-5 toxicities.

Conclusion: Proton therapy is a feasible option for ACC of the non-skull base head and neck in the definitive and postoperative setting offering low rates of acute and late toxicity. Patients with metastatic disease also had acceptable outcomes and local treatment was well tolerated.

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Outcomes of Locally Advanced Sinonasal Cancer in the Modern Era: Surgery and Adjuvant Therapy remains an Optimal Treatment Strategy

J. Imamura,[1] N.M. Woody,[2] P.F. Recinos,[3] P. Soni,[3] R. Sindwani,[3] T. Woodard,[3] V. Kshettry,[3] D. Tang,[3] E. Lamarre,[4] D.J. Adelstein,[5] J.L. Geiger,[5] N.P. Joshi,[2] S. Koyfman,[2] and H. Li[3]; *[1]Case Western Reserve University, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH, [5]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Locally advanced sinonasal cancer (LA-SC) remains a challenge to manage given the lack of prospective studies and the rarity of these lesions. Surgical resection and adjuvant radiation has traditionally been associated with improved outcomes over primary radiation/chemoradiation (RT/CRT). Advances in systemic therapy, radiation, endoscopic surgery and skull base resection as well as increasing use of induction chemotherapy in some centers necessitates re-evaluation of outcomes between surgery and primary RT/ CRT approaches.

Materials/Methods: From an IRB approved registry of head and neck cancers we identified all patients treated at a single tertiary care center with a first diagnosis of LA-SC (T3/T4 or equivalent primary tumor) between 2006 and 2018. We included squamous, adenocarcinoma, neuroendocrine and undifferentiated carcinoma histologies and excluded sinonasal minor salivary gland tumors melanomas or sarcomas. Patients were categorized as either primary surgical resection with adjuvant therapy or as a primary RT approach. Outcomes of local control (LC), distant metastasis (DM), event free survival (EFS) were compared between primary RT/CRT and primary surgery options.

Results: A total 85 patients (median age 62.1 yo) meeting study criteria with a median (IQR) follow up of 2.1 (0.9, 4.1) years were identified with 61 (71.8%) undergoing a primary surgery approach and 24 (28.2%) with RT/CRT for local therapy. Patients undergoing primary RT/CRT trended to be younger (52.5 vs 64.1, p=0.099), had fewer comorbidities (median ACE 27 of 0 vs 1 p=0.01), and had more advanced T-stage (T4: 91.7% vs 61.7% p=0.02). Local control trended in favor of surgical patients (HR=2.05 95% CI 0.71-5.91 p=0.17) with 3 year local control of 85.6% vs 70.1%. No significant difference in DM was observed between the two groups and only 3 regional recurrences were observed in the entire cohort. EFS was significantly better in the primary surgery group (3-year EFS: 66.1% vs 48.1%), with age and comorbidity adjusted HR (95% CI) of any event for RT/CRT was 2.4 (1.2-4.9).

Conclusion: Primary treatment decision making in locally advanced sinonasal cancer remains challenging. Despite advancements in radiation techniques and systemic therapy, surgical resection and adjuvant therapy may still provide the best oncologic outcome.

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Use of Post-Operative External Beam Radiation Therapy in Patients with Differentiated Thyroid Cancer

A. Brown,[1] A. Kellogg,[2] Z. Mirza,[1] T. Sears,[3] G.A. Krempl,[3] and C. Henson[4]; *[1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Stephenson Cancer Center, Oklahoma City, OK, United States, [3]University of Oklahoma Health Sciences Center, OKLAHOMA CITY, OK, [4]University of Oklahoma Health Science Center, Stephenson Cancer Center, Department of Radiation Oncology, Oklahoma City, OK*

Purpose/Objective(s): The incidence of thyroid cancer has been on the rise in recent decades with approximately 90% of these being differentiated thyroid carcinomas (DTCs) (including papillary and follicular). The majority of DTCs have a good prognosis and are potentially curable with standard treatment, the cornerstone of which is thyroidectomy. Commonly, patients may also receive adjuvant thyroid stimulating hormone suppression or radioactive iodine-131 (RAI). Due to a lack of randomized clinical trials, the role of adjuvant external beam radiation therapy (EBRT) in DTC is not well-established. Currently, we rely on retrospective studies and limited prospective data to guide clinical practice. Treatment guidelines have been developed through retrospectives studies of EBRT. Two major treatment centers, MD Anderson and Memorial Sloan Kettering, that both concluded that the use of EBRT provided durable locoregional control (LRC) in high risk DTC patients. The American Thyroid Association (ATA) currently approves the consideration of EBRT in selected high-risk patients, however, there is not a clear consensus about what defines this group or regarding the use of this therapy outside of this scope. Here, we analyze outcomes of adjuvant EBRT in patients with differentiated thyroid cancer post- thyroidectomy treated with EBRT at our institution to add to the knowledge on the topic of EBRT use in DTC in order to help solidify treatment guidelines and inform clinician decision making.

Materials/Methods: We reviewed the records at our institution of 52 patients with differentiated thyroid carcinoma and treated with EBRT following thyroidectomy 2008-2017. We excluded anyone who received a seemingly palliative dose of radiation, 4000 cGy or less, leaving 49 patients for evaluation. Surgical pathology, radiation treatment information, post-treatment imaging and follow up visit documentation were recorded.

Results: At the time of this analysis, complete follow up data was available for 31 of 49 patients. 25% of patients were treated in the recurrent setting. The median radiation dose administered was 6000 cGy. Median follow up was 42.5 months from completion of radiation; many patients were lost to follow up after 3 years of follow up. 3 patients experienced progression in this time period. Median OS was 54.2 months. Median PFS was 49 months.

Conclusion: Adjuvant radiation following surgical management of thyroid cancer, in the recurrent and primary adjuvant setting, provides durable local control. Our report will provide an analysis of the variables that make this cohort high risk and suitable for adjuvant treatment.

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Combination Immunotherapy and TKI in Metastatic Refractory Thyroid Cancer, a Case Series

A. Porter,[1] A. Zeh,[1] E. Cohen,[2] W. Chai-Ho,[1] and D.J. Wong[1]; *[1]David Geffen School of Medicine at UCLA, Dept of Medicine, Division of Hematology/Oncology, Los Angeles, CA, [2]Moores Cancer Center, University of California San Diego (UCSD), La Jolla, CA*

Purpose/Objective(s): Patients with metastatic thyroid cancer (mTC) have limited options for effective therapies. Tyrosine kinase inhibitors (TKIs) remain the mainstay of treatment, often at the expense of significant systemic side effects without a proven survival benefit. The use of immunotherapy has revolutionized the treatment of cancer, however, its specific utility in mTC is not yet known.

Materials/Methods: This single institution retrospective case series examined 6 patients with mTC who had progressed on prior therapies, including treatment with TKI or immunotherapy, and were subsequently treated with TKI in combination with an immunotherapeutic agent. Clinical characteristics, histopathology, prior treatments, and outcomes were collected.

Results: Of the 6 patients, 4 were female and 2 were male. The median age was 62.5 years (range 57-72). Pathologic subtypes included 2 patients with follicular thyroid cancer, 2 patients with papillary thyroid cancer, and 2 patients with anaplastic thyroid cancer. Only 1 patient had presented with metastatic disease at the time of diagnosis. The median number of prior systemic therapies was 3.5 (range 1-5), with the median number of prior TKIs being 2 (range 0-4) and prior immunotherapies being 1 (range 0-1). Five of the 6 patients had drug-related adverse events (83%) all attributed to TKI. Significant AEs included diarrhea (66%), hypertension (33%), and transaminitis (33%). One patient with transaminitis developed significant drug-induced liver injury that ultimately required discontinuation of TKI despite continued response to therapy. The median time on treatment with TKI used in conjunction with immunotherapy was 255 days (range 126-532) with 3 of the 6 patients remaining on therapy at the time of this analysis. The 3 other patients had expired.

Conclusion: TKIs may be used in conjunction with immunotherapy as a potential effective treatment modality in mTC, even in the setting of independent prior single agent TKI or immunotherapy failure. The synergistic effects of TKIs and immunotherapy in mTC should be explored in future studies.

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Declining efficacy of definitive radiotherapy (RT) for T4 non-melanoma skin cancers (NMSC): a reverse Will Rogers phenomenon

A. Price,[1] A. Kellogg,[2] and C. Henson[3]; *[1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Stephenson Cancer Center, Oklahoma City, OK, United States, [3]University of Oklahoma Health Science Center, Stephenson Cancer Center, Department of Radiation Oncology, Oklahoma City, OK*

Purpose/Objective(s): Locally advanced NMSC is an uncommon disease characterized by a lack of robust data. Classical outcomes cited for T4 NMSC treated with definitive RT are 50% 5y LC. Most publications describing this therapy are from the pre-IMRT era. Simultaneous with major advancements in RT technology (and resultant improved outcomes across disease sites with the ability to dose escalate), T staging has evolved dramatically. In AJCC 6, a T2 NMSC was defined as tumor >2 cm but

</= 5 cm; T3 as >5 cm; and T4 as invading deep extradermal structures (cartilage, skeletal muscle, or bone). Contrast this with our current edition, AJCC 8: T2 is defined as >/=2 cm, <4 cm; T3 as >/= 4 cm or minor bone erosion or PNI or deep invasion (beyond subcutaneous fat or >6mm); and T4 as gross cortical bone/marrow, skull base, &/or skull base foramen invasion. Current T staging bears very little resemblance to previous systems. Approximately 70% of NMSC that previously would've been T4 based on invasion of cartilage or muscle would now be called T3. This leaves the current T4 strata containing the worst of the worst - the skull base invasive and often inoperable. How does this affect prognosis and treatment recommendations? Here, we analyze outcomes of locally advanced NMSC staged as T4 by AJCC 8 and treated with definitive RT at our institution.

Materials/Methods: We reviewed the records of patients with T4 NMSC evaluated by Radiation Oncology at a high-volume academic center from 2013-2019 (29 patients). After excluding those who were T3 by AJCC 8, had prior treatment, received only palliative doses, or declined treatment, we were left with 6 evaluable patients. BED ranged from 68-88 Gy.

Results: Of the 6 evaluable patients, 3 had persistent disease at the end of treatment (EOT). One was diagnosed with lung metastases 29 months after EOT but had no recurrence of the primary site. (This was the only patient who was clinically N1.) One is NED 38 months after EOT. One had a cCR and is now 3 months out from treatment. Only one patient had BCC, and this patient had persistent disease at EOT.

Conclusion: T4 NMSC who are referred for definitive RT tend to be surgically unresectable or medically inoperable. Many are not deemed healthy enough for definitive doses. Despite a low evaluable number of patients, our data indicate that high-dose RT is moderately effective for these tumors, with a 50% complete clinical response rate and 2 of 6 patients with durable local control (NED at 29 and 38 months at time of evaluation). As aggressive multimodality management of NMSC involving the skull base, including radical surgery and adjuvant therapy, results in 5y OS in the range of 30-40% according to modern literature, our data show that RT is a reasonable alternative for patients disinclined toward, or not candidates for, radical surgery.

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Clinical Outcomes of different management modalities of Anaplastic Thyroid Cancer: A single Center Experience

M. Al-Jumayli,[1] H. Kawsar,[2] and P. Neupane[3]; *[1]University of Kansas School of Medicine, Department of Hematology and Oncology, Kansas City, KS, [2]Kansas Univeristy Cancer Center, Kansas, KS, [3]The University of Kansas School of Medicine, Kansas City, KS*

Purpose/Objective(s): Anaplastic thyroid cancer is decimal disease with a poor prognosis due to its aggressive and rapid metastasis with median survival of less than 6 months. Multimodal treatment involving surgery and chemoradiotherapy has been used to improve the survival of patients. Here, we retrospectively review of treatment outcome of 28 consecutive patients who were treated at a single center.

Materials/Methods: We retrospectively reviewed medical records of 28 Anaplastic thyroid cancer patients in our cancer registry, who received multidisciplinary treatment between 2009 and 2018. Kaplan-Meier survival curve was used to analyze progression-free survival and overall survival of patients who had and who had not had surgery.

Results: The median patient age at diagnosis was 70 years. 3 patients had stage IVc disease.10 patients received primary surgery followed by radiotherapy or concurrent chemoradiotherapy (CRT), 9 patents have chemo radiation, 4 patients received radiation, 2 patients received chemotherapy only and 3 patient opted best supportive care. One patient received weekly doxorubicin-based definitive CCRT, while the rest received Taxol with radiation. By comparing the groups of patients who had surgery followed CRT to other group who received CRT/ RT with no surgery, the median progression-free survival was 2.6Ms in surgery arm (95% CI, 1.2-4.4) compared to non surgery arm 2.4 Ms (P value 0.6), and the median overall survival was 3.2Ms in surgery group compared to 3.6Ms in CRT (95% CI, 3.0-4.6) (P value 0.8). Our study didn't show a statistical difference between the two groups in the progression-free survival and overall survival

Conclusion: Patients with Anaplastic Thyroid Cancer showed poor prognosis despite multimodality treatment. Therefore, all patients should be enrolled in clinical trial with novel agents. Identification of novel therapeutic targets is warranted to take an improvement on existing dismal prognosis.

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Airway, Voice, and Swallowing Functions after Surgical Management of Multilevel Chordoma of the Cervical Spine Using Fibula Osteocutaneous Free Flap

A.Y. Han,[1] F. Buen,[1] J.E. Alonso,[1] N.F. Jones,[2] F.J. Hornicek,[2] D.K. Chhetri,[1] and M. St. John[1]; *[1]Ronald Reagan-UCLA Medical Center, Dept of Head and Neck Surgery, Los Angeles, CA, [2]Ronald Reagan-UCLA Medical Center, Dept of Orthopaedic Surgery, Los Angeles, CA*

Purpose/Objective(s): Chordomas of the cervical spine present unique challenges for treatment due to nearby critical neurovasculature. Surgical planning requires coordination with surgical, radiation, and medical specialists to achieve oncologically sound surgery and functional preservation. The post-operative airway, voice, and swallowing functions of a patient with fibula free flap reconstruction after a cervical chordoma resection have not yet been characterized.

Materials/Methods: We herein present a case of a multilevel chordoma of the cervical spine that was resected in planned multi-stage surgery with fibula free flap reconstruction. The patient was evaluated postoperatively by a senior expert laryngologist for evaluation of airway, voice, and swallowing functions.

Results: A 33-year-old otherwise healthy male presented for resection of multi-level cervical spine chordoma. His presenting symptom was dysphagia since 12 years of age that had progressively worsened in the past year. Associated symptoms included choking, hoarseness, and snoring. MRI showed a heterogenous, expansile, T2 hyperintense, enhancing mass 52 x 52 mm in size centered in the C4 vertebral body and extending through the posterior elements bilaterally with involvement of the spinous process. Prominent anterior extension into the prevertebral soft tissues extending from C3 to C5 was observed. The tumor encased the bilateral vertebral arteries. Following neoadjuvant radiotherapy (20Gy), the patient underwent embolization of the bilateral vertebral arteries and tracheostomy as the first-stage surgery. As the second-stage surgery, posterior resection of cervical chordoma with bilateral vertebral arteries and posterolateral fusion were performed. The third stage included an anterior approach to the cervical spine, bilateral modified radical neck dissection, tumor resection, and C3-5 corpectomy. The defect was reconstructed with a fibula free flap spanning the vertebral bodies of C2-5. The patient did well postoperatively. Surgical pathology revealed a low-grade chordoma of the conventional type with negative margins. He was decannulated prior to discharge. One month after surgery, the patient was found to have a normal vocal cord movement with complete glottic closure during phonation. Post-op FEES revealed trace residue consistent with pharyngeal weakness, and patient was advanced to teaspoons of liquids. The patient was referred to adjuvant proton therapy.

Conclusion: Successful surgical management of a chordoma of the cervical spine requires a team-based approach involving multiple expert specialists. Despite the complex nature of surgery, outstanding airway and voice preservation were achieved in our case. Postoperative swallowing function remains reassuring without laryngeal aspiration or penetration. Pharyngeal weakness found on exam may improve with continued therapy.

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A Phase II Prospective Trial of Photobiomodulation in Limiting Oral Mucositis in the Treatment of Locally Advanced Head and Neck Cancer Patients

L.J. Mady,[1] U.K. Iheagwara,[2] J. Ohr,[3] K. Holeva,[2] A. Quinn,[4] and D.A. Clump II[2]; *[1]UPMC, Pittsburgh, PA, [2]UPMC Hillman Cancer Center, Department of Radiation Oncology, Pittsburgh, PA, [3]Department of Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [4]Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Purpose/Objective(s): Oral mucositis (OM) is a major side effect in head and neck cancer (HNC) patients receiving definitive chemoradiotherapy (CRT). Severe mucositis leads to decreased oral intake, pain, and treatment delays resulting in inferior oncologic outcomes. Narcotic pain medication, oral anesthetics and nutritional support via PEG tube and IV hydration are commonly deployed supportive modalities. Photobiomodulation (PBM) is one modality that shows potential in decreasing OM rates. This study compares historical rates of grade 3+ OM (35-40%) in HNC patients undergoing definitive concurrent CRT versus our cohort of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) treated with prophylactic PBM.

Materials/Methods: A phase II institutional clinical trial was initiated in 50 patients (age ≥18yrs; KPS>60) with locally advanced HNSCC receiving definitive or adjuvant RT with concurrent platinum-based chemotherapy. PBM was delivered 3-times per week (2.5 Hz; 660-nm wavelength; 75 mW, 4.5 J) throughout RT. Each treatment involved an extra-oral probe to the bilateral buccal mucosa for 1-minute and an intra-oral probe to the tongue and soft palate for 1-minute. If any area of mucositis was identified, the intraoral probe would be used to treat that specific site. The primary outcome measure was incidence of severe OM (WHO grade 3+); secondary outcome measure was time to onset of severe OM (NCI CTCAE v4 toxicity scale, grade 3+) following the initiation of therapy.

Results: Of 50 subjects enrolled, 47 (mean age 57±7 years) were eligible for analysis of primary clinical trial endpoints The oropharynx was the most common primary site (n=34, 72%) followed by larynx (n=8, 17%), nasopharynx (n=2, 4%), unknown (n=2, 4%), and hypopharynx (n=1, 2%). Subjects were treated to a mean cumulative RT dose of 6600cGy (±500cGy) and 486 mg/m^2 of platinum-based chemotherapy. At baseline, all patients had grade 0 mucositis by WHO scale assessment. The mean time to onset of severe OM (CTCAE grade 3-4) following the initiation of therapy was 34±12 days. During week 4, the incidence of severe OM (WHO grade 3+) was 4.5% (n=2/44). At week 6, the incidence of severe OM was 10.5% (n=4/38). Of 44 patients evaluated at 2-weeks after therapy, 4.5% (n=3) demonstrated severe OM (WHO grade 3+). According to visual analog scale assessment in which 0 is the absence of pain and 10 is maximum pain, among patients with severe OM at 2-weeks after therapy, mouth pain was 6±1 and throat pain was 4±2.

Conclusion: Compared to historical outcomes, PBM aides in decreasing severe OM in patients with locally advanced HNSCC. PBM represents a minimally invasive, prophylactic intervention to decrease OM as a major treatment-related side effect.

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Weekly Versus Tri-Weekly Paclitaxel and Carboplatin in Combination with Cetuximab in Recurrent/Metastatic Head and Neck Cancer Patients: a Toxicity Analysis

L. Geraghty,[1] S. Hoffman,[1] T. Schultz,[2] K. Porter,[2] M. Issa,[2] R. Rupert,[3] P. Bhateja,[2] M. Old,[4] J.W. Rocco,[5] D.M. Blakaj,[6] and M. Bonomi[1]; *[1]Ohio State University, Columbus, OH, [2]The Ohio State University, Columbus, OH, [3]The Ohio State University Wexner Medical Center, Division of Medical Oncology, Columbus, OH, [4]The Ohio State University Department of Otolaryngology - Head & Neck Surgery, Columbus, OH, [5]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, [6]Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, OH*

Purpose/Objective(s): The combination of paclitaxel, carboplatin, and cetuximab (PCC) is efficacious in patients (pts) with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Unfortunately, two thirds of patients will experience grade 3/4 (G3/4) toxicity. This study assesses the incidence of G3/4 toxicity for patients receiving weekly or tri-weekly PCC for R/M HNSCC.

Materials/Methods: This single institution, retrospective analysis, included 74 pts who received either tri-weekly or weekly PCC. Cetuximab was administered as a loading dose at 400mg/m2 in week 1, followed by 250mg/m2 weekly until disease progression. Tri-weekly PCC was administered as follows: paclitaxel 175mg/m2 followed by carboplatin area under the curve (AUC) 5 every three weeks for six cycles. Weekly PCC was administered as paclitaxel 45 mg/m2 followed by carboplatin AUC 1.5 weekly until disease progression. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events v4.03. Response to therapy was assessed by computed tomography every 12 weeks (sooner if clinically indicated). To account for group differences, we used inverse probability of treatment weighting (IPTW), and to estimate propensity scores for stabilized IPTW weights, a logistic regression model was used with the following variables: age ≥65 years, baseline ECOG performance status, PCC initiation within 6 months of chemoradiation, line of therapy, sex, race, tobacco use, previous radiation, and previous surgery.

Results: 48 pts (65%) received tri-weekly PCC, and 26 pts (35%) received weekly PCC. 30 pts (65.7%) in the tri-weekly PCC arm experienced G3/4 toxicity vs 6 (25.4%) in the weekly PCC arm (OR 0.18: 0.05-0.64; P=0.01). The most common G3/4 side effects were neutropenia (52.5% vs 7.6%), anemia (31.7% vs 15%), and fatigue (10% vs 2.7%). In both treatment arms, most patients experiencing G3/4 toxicity required chemotherapy dose modifications (77% vs 74%). The overall response rate was 27% in the tri-weekly regimen vs 39% in the weekly PCC arm. The progression free and overall survival at 1 year was 13.4% and 44% for the tri-weekly regimen, and 27.4% and 46% for the weekly arm.

Conclusion: Weekly PCC has a reduced risk of G3/4 toxicity when compared with tri-weekly PCC. Both regimes have similar anti-cancer activity.

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Can patient reported quality of life predict locoregional recurrence in oropharyngeal cancer?

L.A. Gharzai,[1] P. Li,[2] E. Jaworski,[1] M. Schipper,[2] N. Burger,[3] J.R. Wilkie,[1] C.H. Chapman,[1] C.A. Schonewolf,[1] K. Casper,[3] and M.L. Mierzwa[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 Otolaryngology, University of Michigan, Ann Arbor, MI*

Purpose/Objective(s): The excellent prognosis of p16+ oropharyngeal squamous cell carcinoma (OPSCC) invites efforts to reduce surveillance burden after treatment. Current surveillance guidelines suggest frequent clinical examination, demanding time, costs, and discomfort with nasopharyngoscopy. Recent publications demonstrated low rates of asymptomatic locoregional recurrence (LRR) detection in these frequent visits, but no alternatives exist. We sought to assess correlation of changes in patient reported quality of life (QOL) forms with LRR to evaluate feasibility of using such forms in an individualized surveillance approach.

Materials/Methods: Patients with QOL forms treated on a single institution randomized trial and patients on a prospective registry were evaluated (74 and 102 patients respectively). Patients completed EORTC C30 and

HN35 at baseline, 1, 3, 6, 9, 12, 18, 24, and 36 mos after end of treatment. Patients were grouped by time to LRR, and QOL forms from the two time points prior to LRR were evaluated for changes in the following pre-specified EORTC QOL subscales: from C30, physical functioning, role functioning, fatigue, pain; from HN35, pain, swallowing, social eating, feeling ill. A minimal clinically important difference (MCID) of 10 for each subscale was considered significant, and area under the curve (AUC), sensitivity (sens) and specificity (spec) were calculated for each subscale for each group of failures.

Results: With a median follow up of 12.4 mos, 176 patients experienced 29 failures. 71.1% of patients had OPSCC. Baseline forms were completed by 157 patients, with increasing attrition over time. Combining all eight subscales led to a prediction tool with average sensitivity of 80% for detection of LRR, with failures from 3-6 mos (AUC 0.69, sens 83%, spec 34%) and 6-12 mos (AUC 0.78, sens 100%, spec 49%) most significant. Failure within 1-3 mos was best predicted by MCID changes in C30 role functioning (AUC 0.85, sens 100%, spec 62%). Failure within 3-6 mos was best predicted by MCID changes in HN35 pain (AUC 0.71, sens 67%, spec 84%). Failure within 6-12 mos was best predicted by MCID changes in C30 pain (AUC 0.90, sens 80%, spec 82%), HN35 swallowing (AUC 0.80, sens 60%, spec 90%), HN35 social eating (AUC 0.72, sens 40%, spec 88%), and HN35 feeling ill (AUC 0.71, sens 40%, spec 91%). Assessment from 12-24 mos was complicated by low numbers of events.

Conclusion: MCID changes are present in 8 subscales of EORTC C30 and HN35 QOL forms prior to clinical presentation of LRR, and the implementation of a rule assessing MCID changes in any of these subscales led to a tool with 83% sensitivity of detecting LRR. Utilization of QOL forms to prompt closer surveillance in integration with a novel less burdensome monitoring paradigm for good-prognosis OPSCC could represent a new option for individualized surveillance. Further validation and study is needed.

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Prophylactic Gabapentin Results in Dramatic Reduction Of Narcotic Utilization In Head and Neck Cancer Patients Undergoing Radiotherapy

J.J. Mandia,[1,2] H. Wang,[3] R. Padmanabhan,[4] Z. Ferguson,[5] A.R. Chaurasia,[1,2] A.K. Brennan,[1] C. Solano,[5] K. Skoczylas,[6] P. Lee,[7] J. Deeken,[8] and G.K. Bajaj[5,9]; *[1]Walter Reed National Military Medical Center, Bethesda, MD, [2]Radiation Oncology Branch, National Cancer Institute, NIH, Bethesda, MD, [3]Georgetown University, Washington, DC, [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, [5]Center for Advanced Radiation Oncology and Proton Therapy, Inova Schar Cancer Institute, Fairfax, VA, [6]Life with Cancer, Inova Schar Cancer Institute, Fairfax, VA, [7]Otolaryngology Associates, Fairfax, VA, [8]Inova Schar Cancer Institute, Fairfax, VA, [9]University of Maryland Medical Center, Baltimore, MD*

Purpose/Objective(s): Several investigations into the use of gabapentin as an adjunctive therapy for pain management in head and neck squamous cell carcinoma (HNSCC). However, there is limited adoption of gabapentin with radiotherapy (RT) or chemoradiotherapy (CRT), likely due to lack of comparison with a control. We report a retrospective single institution experience of the impact of prophylactic gabapentin (PG) on narcotic utilization in comparison to a historical non-PG control group.

Materials/Methods: Records of HNSCC patients treated 12/15-3/19 with RT or CRT and PG with a tapered regimen of 100mg-300mg tid (max 1200mg tid) starting week 1 of therapy. 139 patients were retrospectively analyzed after intensity-modulated radiation therapy (IMRT) median dose of 69.96 Gy (range: 54-70 Gy), with induction chemotherapy in 7.2% and concurrent chemotherapy in 69.1% of cases. This was compared to a matched historical cohort of 49 patients treated without PG. PG use, opioid use in morphine equivalents (ME), pain score, and toxicity scores were recorded at weekly on-treatment and follow-up evaluations.

Results: Opioid utilization was not significantly different between the cohorts at the outset of treatment 8.2% vs 5.8% ($p=0.38$), but was significantly reduced in the PG cohort for all subsequent time endpoints. During the second week of RT, narcotic utilization was 18.4% in the non-PG vs 7.2% for the PG group ($p=0.03$). This difference in opioid utilization increased and remained statistically significant through the remainder of treatment and the first three recorded follow-ups, peaking at week 6 of treatment with a 60% relative reduction in overall opioid usage (77.6% vs 31.7%, $p<.0001$). PG was also associated with a reduction the median dosage of opioids required during treatment at week 3 (16mg ME vs 2.7mg ME, $p=0.009$) and remained significant through the first 2 follow-up visits, peaking at week 7 with a 71% relative decrease in narcotic utilization in the PG group (100mg ME vs 29.1mg ME, $p=0.009$). Mucositis rates and pain scores did not different between the groups. PEG tube placement rate was 11.5% in the PG Group. PG was well tolerated with 98.6% of patients compliant with the regimen. 8.0% reported side effects specific to PG with 96.4% of patients able to continue PG with dosage adjustment. The most common side effects were grade 2 imbalance, dizziness, and fatigue. None of these effects required significant medical intervention beyond tapering or discontinuing PG.

Conclusion: Our data show that PG can be can safely and effectively be administered to HNSCC patients undergoing RT or CRT and results in a significant decrement of opioid requirement throughout RT, while achieving similar pain score improvement as narcotics. In the context of a global opioid crisis, these data would support PG as a widespread clinical standard in this patient population upon prospective verification of these findings.

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Comparison of the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging for oropharyngeal squamous cell carcinomas (OPSCC): A Surveillance, Epidemiology and End Results Program (SEER) database analysis

P. Vijayvargiya,[1] S. Trivedi,[2] H. Song,[3] Y. Liu,[4] C. Steuer,[5] W.A. Stokes,[6] A.S. Kaka,[7] M.R. Patel,[7] G. Chen,[8] D.M. Shin,[5] J.J. Beitler,[9] A.H. Aiken,[10] and N.F. Saba[5]; *[1]Emory University, Atlanta, GA, [2]Department of Medicine, Emory University School of Medicine, ATLANTA, GA, [3]Department of Biostatistics & Bioinformatics, Rollins School of Public Health, Atlanta, GA, [4]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, [5]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [6]Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, [7]Department of Otolaryngology, Emory University School of Medicine, Atlanta, GA, [8]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, [9]Emory University School of Medicine, Atlanta, GA, [10]Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA*

Purpose/Objective(s): The recently released eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section, incorporates significant changes to the prior seventh edition. These changes reflect the improved understanding of tumor biology, prognostic factors and molecular markers that effect outcomes in Head and Neck cancers. A key update restages OPSCC by human papilloma virus

(HPV) positivity as data demonstrates that these tumors have markedly improved prognostic outcomes compared to HPV negative tumors, which is reflected by the differentiation of HPV positive and negative disease in eighth edition staging.

Materials/Methods: Using SEER data from 2004 − 2014, we identified male patients with squamous cell carcinomas of the tonsil, base of tongue and soft palate aged between 21 and 64 years old (these clinical characteristics were used as surrogate markers for HPV positive status). We re-classified them by the AJCC 7th edition staging for HPV positive OPSCC as well as by AJCC 8th edition staging. The prediction performance by two staging editions were compared regarding overall survival (OS) and Disease free survival (DFS). Kaplan-Meier method and Cox proportional hazard model were applied, and the discrimination performance was measured by the concordance statistics (C-statistics).

Results: A total of 8202 eligible patients were included in the analysis with a median follow up period of 51 months. 7415 (90.4%) patients had previously received radiation and 7038 (85.8%) patients had previously received chemotherapy. The median age of patients was 56 years. Upon restaging, distribution of stage I disease increased from 2% to 19.6% in AJCC 8th edition while Stage IV decreased from >59% to 3.54%. After comparing the change of 7th edition and 8th edition staging groups, the clinical staging changed for 93.9% of patients. 10-year overall survival (OS) for AJCC 8th stages I (74%), II (78%), III (55%) and IV (32%). Using Stage I as reference, the hazard ratio for stage II, III, and IV is 0.98 (95% CI: 0.87-1.09), 2.29 (95% CI: 2.04-2.57), and 5.88 (95% CI: 4.96-6.98). Similar results were noted for ten year disease free survival. The C-statistics measured overall discrimination for 8th edition is 0.68 and 0.63 for the 7th edition (P<0.001).

Conclusion: Based on this SEER analysis, the overall performance of discrimination improved from AJCC 7th to 8th edition incorporating HPV status more effectively, most notably to distinguish stage III and IV disease. However, this study population does not distinguish stage I and II as conclusively as it does for the latter stages. Further limitations include the use of surrogate markers for p16 status and under reported data.

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Cost-Effectiveness of Radiation Therapy by High-Volume Versus Low-Volume Radiation Oncologists for Head and Neck Cancer

T.Q. Huang,[1] R.K. Chin,[2] and A. Raldow[2]; [1]*David Geffen School of Medicine at UCLA, Los Angeles, CA,* [2]*Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA*

Purpose/Objective(s): Intensity-modulated radiation therapy (IMRT) administered by high-volume radiation oncologists (ROs) provides a survival benefit for patients with head and neck cancers (HNC) compared to treatment by low-volume ROs. However, geographic proximity is often a factor in choosing providers. Additional costs can be associated with relocating to a higher-volume center, but may be worthwhile with respect to treatment outcomes. Our objective was to determine the cost-effectiveness of IMRT by low- versus high-volume ROs for patients with HNC.

Materials/Methods: A cost-effectiveness model was developed to simulate the 4-year outcomes of 1 million hypothetical patients with HNC treated by low- or high-volume ROs. Incremental cost-effectiveness ratios were determined using utilities and probabilities from the literature and costs from National Medicare fee schedules. To account for uncertainty, sensitivity analyses were run varying costs, probabilities of developing adverse events, and probability of death when treated by low- and high-volume ROs.

Results: Treatment by high-volume ROs was the dominant strategy as compared with treatment by low-volume ROs (incremental cost-effectiveness ratio, -$106,598.01/quality-adjusted life year). One-way sensitivity analyses revealed that the cost-effective approach was not dependent on variations in cost or probability of developing adverse events. One-way sensitivity analyses for the costs of travel revealed that IMRT by high-volume ROs was the most cost-effective approach even with an additional travel cost of up to $1,530.13.

Conclusion: Treatment by high-volume ROs was the cost-effective strategy compared with treatment by low-volume ROs for patients with HNC. High-volume RO treatment was the most cost-effective approach even with an additional travel cost, suggesting that traveling to a high-volume RO should be considered when making treatment decisions. The results of this economic analysis should be used to inform patients and referring providers when making decisions about where to undergo treatment.

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Ameliorating radiation-induced hyposalivation and xerostomia with Adipose-derived Mesenchymal Stem/stromal cells (MESRIX-II)

C.D. Lynggaard,[1] C. Grønhøj,[2] and C.V. Buchwald[3]; [1]*Department of Otolaryngology, Head and Neck Surgery, University Hospital Rigshospitalet, Copenhagen, Denmark,* [2]*Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,* [3]*Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): Salivary gland hypofunction and xerostomia remain major obstacles after radiation of head and neck cancers. There is large unmet need for new treatment strategies as only insufficient symptomatic therapies exits. The randomized controlled MESRIX-trial indicates that autologous adipose-derived mesenchymal stem/stromal cells (ASCs) can safely restore function of the irradiated submandibular glands in former oropharynx cancer patients. Allogeneic ASCs from healthy donors as a ready-to-use therapies have been proved safe for several diseases and may be a new intervention for radiation-induced xerostomia. We have commenced a Phase I study with allogeneic ASCs with encouraging results. We plan to start in 2020 a randomized controlled trial with allogeneic ASCs for radiation-induced xerostomia (MESRIX-II).

Materials/Methods: MESRIX-II is an investigator-initiated, single-centre, randomized, stratified and analyst-blinded trial. 240 patients with radiation-induced hyposalivation and xerostomia will be allocated to receive ASCs or placebo ultrasound-guidance injections into the parotid and submandibular glands. Primary outcome is day-120 change in unstimulated whole salivary flow rate (UWS) measured with sialometry. Secondary endpoints are severe adverse events (SAEs), severe adverse reactions (SARs), change in HRQoL with EORTC QLQ-H&N35 and Xerostomia Questionnaire (XQ), change in uptake rate and washout fraction with 99mTc-Pertechnetate salivary gland scintigraphy and development of donor-specific antibodies. The study will be monitored according to the Good Clinical Practice standards.

Results: Will be analyzed according to the predefined statistical analysis plan.

Conclusion: Allogeneic ASCs may be a future "off-the-shelf" therapy to mitigate the implications of radiotherapy to the major salivary glands. The MESRIX-II trial will provide evidence of the efficacy and safety of allogeneic ASCs for regeneration of the damaged major salivary glands in patients suffering from radiation-induced hyposalivation and xerostomia.

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Quality of Life Impact and Dosimetric Predictors of Radiation-induced Fibrosis of the Neck in Patients Treated for Head and Neck Cancer

G. Azzam,[1] H. Perlow,[2] D. Cerbon,[3] Z. Sargi,[3] M.C. Abramowitz,[3] N.M. Elsayyad,[4] L.M. Freedman,[3] E. Nicolli,[5] D. Kwon,[3] L.Y. Huang,[6] M.A. Samuels,[7] and S. Samuels[8]; *[1]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, [2]University of Miami Miller School of Medicine, Miami, FL, [3]University of Miami, Miami, FL, [4]University of Miami, Miami, FL, United States, [5]Department of Otolaryngology, University of Miami / Sylvester Comprehensive Cancer Center, Miami, FL, [6]University of Miami, Physical Medicine and Rehabilitation, Miami, FL, [7]Department of Radiation Oncology, University of Miami / Sylvester Comprehensive Cancer Center, Miami, FL, [8]Department of Radiation Oncology, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL*

Purpose/Objective(s): Skin and soft tissue fibrosis of the neck is a common late toxicity of H&N cancer treatment. To date, no comprehensive patient(pt)-reported outcome (PRO) survey specifically addresses this toxicity and no dose constraints have been established for radiation-induced fibrosis (RIF) in this context. This study documents a PRO metric adapted from research in scleroderma that identifies and categorizes pts with symptomatic fibrosis. Further, we identify novel organs at risk (OAR) and corresponding doses that correlate with QOL detriment after H&N radiotherapy (RT).

Materials/Methods: Participants completed the EORTC QLQ-C30 and QLQ-H&N43 PRO surveys, in addition to a survey validated to assess symptom severity in pts with systemic fibrotic symptoms (Scleroderma Skin PRO, SSPRO). A correlation between the QLQ-C30 and QLQ-H&N43 scoring against SSPRO was performed using Pearson's correlation coefficient statistical analysis. Dosimetry parameters from novel OAR's including the skin, sternocleidomastoid (SCM) muscle and subcutaneous tissue (SCT) were calculated from administered RT plans. Univariate linear regression analysis was performed using these data points with scoring from the QLQ-C30, QLQ-H&N43 and SSPRO questionnaires. False discovery rate (FDR) was used to obtain adjusted p-values for multiple testing correction.

Results: A total of 58 pts are included in this analysis. Using Pearson's correlation coefficient, correlations were significant between the SSPRO survey scores and QLQ-C30 ($r=0.546$, $p<0.0001$) and QLQ-H&N43 ($r=0.656$, $p<0.0001$). In non-surgical pts, positive dosimetry correlates were observed for all novel OAR. SCM V70Gy percentage correlated with SSPRO score (0.86, $p=0.048$). A dose-dependent skin dose to SSPRO score was observed from V50Gy (0.6, $p=0.00067$) to V70Gy (7.08, $p<0.0001$) and for SCT from V50Gy to V70Gy (0.12 to 0.99, $p<0.05$). In this exploratory analysis, no skin dose parameters correlated with QLQ-H&N43 scoring, although SCM and SCT parameters were positively correlated with similar coefficient magnitudes. Importantly, *no* correlates were identified in surgerized pts.

Conclusion: Comparison of the SSPRO to the QLQ-C30 and QLQ-H&N43 indicates significant positive correlations in scoring with moderate strength. Dosimetric parameters for the skin were positively correlated with SSPRO scoring in a dose-dependent manner but not with QLQ-H&N43 scores. We propose the SSPRO more adequately captures fibrosis-related QOL detriment after H&N RT because it provides more detailed fibrosis information. Further we identified dose metrics of the SCM, subcutaneous tissue and skin that are associated with a decrease in fibrosis QOL for H&N pts treated with primary RT +/- chemo. No such associations were found with surgically treated pts. Future studies will focus on decreasing the dose to these structures to prevent or mitigate RIF.

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Prevalence of Comorbidities and Effect on Survival in HPV-related Head and Neck Cancer Survivors and Matched Non-Cancer Controls in the United States

E.O. Bigelow, A. Blackford, D.F. Eytan, D. Eisele, and C. Fakhry; *Johns Hopkins University School of Medicine, Baltimore, MD*

Purpose/Objective(s): The prevalence of human papillomavirus-related (HPV) head and neck cancer (HNC) survivors is increasing. While elderly HPV-related HNC (HPV-HNC) survivors are known to have a high burden of comorbidities, it is unknown how this compares to a similar cohort without a history of cancer.

Materials/Methods: This retrospective cross-sectional study included individuals with first incident primary diagnosis of HPV-HNC from 2004-2011 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Linked Databases and matched controls. Baseline prevalence and subsequent incidence of comorbid conditions were identified. Association between comorbidity and overall survival was evaluated.

Results: A total of 2,497 HPV-HNC patients were eligible and were matched to 4,994 non-cancer controls. Baseline comorbidity was higher in cases (Charlson Comorbidity Index >0 for 48.5% of cases versus 35.8% of controls). At five years, cases were more likely than controls to develop comorbid conditions. HPV-HNC survivors were at high risk (≥20% cumulative prevalence by 5 years) to develop several comorbidities including cardiovascular diseases, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and tobacco abuse, and were at moderately high risk (10-19% cumulative prevalence) to develop conditions including carotid artery occlusive stroke, alcohol abuse, depression, and anxiety. In both cases and controls, the presence of most comorbidities either at diagnosis or during the follow-up period was associated with worse survival.

Conclusion: HPV-HNC patients have a higher comorbidity burden than matched controls, both at baseline and during survivorship, most of which are associated with decreased survival. Oncologic surveillance of HPV-HNC patients should include screening for highly prevalent conditions.

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Late Oral Toxicity after Photon Radiotherapy for Oropharyngeal Cancer Patients with Tongue-lateralizing and Tongue-depressing Oral Stents

S. Stieb,[1] I. Perez-Martinez,[2] S. Rock,[3] A.S. Mohamed,[1] N. Bajaj,[1] T.S. Deshpande,[1] A.S. Garden,[1] J.P. Reddy,[1] J. Phan,[1] W.H. Morrison,[1] S.J. Frank,[1] D.I. Rosenthal,[4] E.J. Koay,[1] C.D. Fuller,[1] and G.B. Gunn[1]; *[1]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]University of Puerto Rico - Rio Piedras Campus, San Juan, PR, [3]Brigham Young University, Provo, UT, [4]The University of Texas MD Anderson Cancer Center Institution *, Houston, TX*

Purpose/Objective(s): Tongue-depressing stents improve positional reproducibility and the use of a lateralizing oral stent diverts the mobile tongue to the contralateral side in order to minimize dose-dependent oral toxicities. However, data on long-term clinical outcome is still lacking. Since dosimetric studies already showed a benefit of stent use during photon RT, our hypothesis is that these stents decrease late oral toxicities and should routinely be applied. The aim of this study was therefore to evaluate the use of these stents regarding the association with late symptom burden in a large IRB-approved prospective longitudinal toxicity survey of oropharyngeal cancer (OPC) patients.

Materials/Methods: Radiation-induced oral toxicity was assessed in 426 disease-free OPC survivors with the MD Anderson Symptom Inventory (MDASI) Head and Neck module. Questions had to be answered on an

Abstract 359; Table 1 Mean MDASI scores separate for OPC patients receiving uni- or bilateral head neck RT with or without dental stent.

		Xerostomia	Dyshagia	Mucus	Taste impairment	Appetite	Oral sores
Unilateral RT	Tongue-lateralizing stent (n=49)	3.08	1.83	1.54	0.51	0.17	0.65
	No stent (n=43)	3.38	2.81	1.33	1.74	1.02	0.69
Bilateral RT	Tongue-depressing stent (n=205)	4.20	2.53	2.25	2.20	0.96	0.37
	No stent (n=97)	4.04	3.28	2.58	1.92	1.12	0.55

11-point Likert scale from 0 (no symptoms) to 10 (worst clinical outcome). All patients received IMRT or VMAT. Descriptive statistics have been used for description of patient population and oral complications. Mann-Whitney U and Kruskal-Wallis test was performed for non-parametric analyses between groups. A p-value <0.05 was considered significant.

Results: 248 tonsil (54%) and 214 BOT (45%) cases were queried. Median prescribed CTV1 dose was 66.0 Gy (57.6 − 72.5), administered in 27 − 40 fractions. Median follow-up from end of RT to MDASI assessment was 68 months (13 − 158). Patients suffered most often from xerostomia (mean MDASI score: 3.89), followed by dysphagia (2.70), mucus (2.15), taste impairment (1.82), loss of appetite (0.90) and oral sores (0.49). There was a highly significant correlation between all oral toxicities. 20% of the patients received unilateral RT and showed an improvement in late taste impairment, loss of appetite (both significant) and had better mean MDASI scores for xerostomia, dysphagia and oral sores with the use of tongue-lateralizing stents. Patients with tongue-depressing stents had better swallowing function, less oral sores (both significant), and improved mucus and appetite. However, taste and xerostomia were worse with tongue-depressing stent, although not significant.

Conclusion: Patients with unilateral irradiation for tonsil cancer should be immobilized with a tongue-lateralizing stent during RT as standard-of-care. A tongue-depressing stent should be considered in case of bilateral RT of OPC patients to reduce late oral toxicity.

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Mid-treatment assessment of dose to parotid gland stem cell region and change in parotid gland volume predicts for long-term patient-reported xerostomia

R. Kabarriti,[1] P. Brodin,[1] S. Ahmed,[2] W.A. Tome,[1] C. Guha,[1] S. Kalnicki,[1] and M.K. Garg[1]; *[1]Department of Radiation Oncology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, [2]Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY*

Purpose/Objective(s): To determine whether the radiation (RT) dose to the parotid gland stem cell (SC) region or pre- and mid-treatment CT scans as well as change in parotid gland volume is associated with long-term patient-reported xerostomia after definitive head and neck cancer (HNC) RT.

Materials/Methods: The SC region of the parotid gland, defined as being located next to the dorsal edge of the mandible, near the Stensen's duct at the anterior border based on pre-clinical investigations, was delineated on CT scans with a 0.5 cm isotropic margin for 65 HNC patients that had undergone definitive RT between 2009 − 2014. Prospectively collected EORTC QLQ-H&N35 quality-of-life questionnaires with minimum 9 months follow-up were used to score xerostomia on a 4-grade scale, where chronic grade 3/4 was considered severe xerostomia in this analysis. The SC regions were delineated on pre-treatment as well as mid-treatment CT rescans (15th RT fraction) to determine the best model for predicting xerostomia. The association between the mean dose to the spared parotid gland or SC region of the spared parotid and the risk of severe xerostomia was examined using logistic regression and receiver operating characteristics (ROC).

Results: Increasing RT dose to either whole parotid or the SC region was associated with an increased risk of patient-reported xerostomia ($p=0.003$ and $p=0.005$). Importantly, the mid-treatment analysis showed that the dose to the SC region was more predictive of xerostomia than that of the pre-treatment or using the whole parotid dose, as per the ROC areas under the curve (AUCs) in Table 1. For every 1 Gy increase in radiation dose to the SC region evaluated at mid-treatment, we observed an 8% increase in the odds of xerostomia. We furthermore found that the parotid volume of patients with xerostomia was on average 27% reduced at mid-treatment, compared to only 15% for patients without xerostomia.

Conclusion: Increased radiation dose to the SC region of the spared parotid gland was associated with an increased risk of patient-reported xerostomia, especially when evaluated at mid-treatment. This supports the hypothesis that targeting the SC region reduces regenerative capacity of the gland, which is also supported by the large reduction in parotid size. These results provide rationale for adapting RT mid-treatment based on dose to SC region of the spared parotid gland as well as volume of parotid gland on mid-treatment rescan to optimize patients' post treatment quality-of-life. Logistic regression models predicting patient-reported xerostomia.

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Abstract 360; Table 1

	OR per Gy (95% CI)	p-value	ROC AUC (95% CI)
Spared parotid mean dose pre-RT	1.08 (1.03, 1.13)	0.003	0.72 (0.60, 0.85)
Spared parotid SC mean dose pre-RT	1.07 (1.02, 1.12)	0.005	0.70 (0.57, 0.83)
Spared parotid mean dose mid-tx	1.07 (1.01, 1.13)	0.026	0.72 (0.54, 0.90)
Spared parotid SC mean dose mid-tx	1.08 (1.02, 1.14)	0.012	0.76 (0.60, 0.93)

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Dysphagia After Primary Tors vs Non-surgical Therapies for Low-to-Intermediate Risk Tonsil Cancer: A Prospective Registry Analysis

C.E. Barbon,[1] C.M. Yao,[1] C.L. Warneke,[2] B. Elgohari,[3] R.P. Goepfert,[1] A.C. Hessel,[1] M.E. Kupferman,[1] S. Lai,[1] C.D. Fuller,[3] G.B. Gunn,[3] A.S. Garden,[3] G.M. Chronowski,[3] F.M. Johnson,[4] J.S. Lewin,[1] N.D. Gross,[1] and K.A. Hutcheson[1]; *[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]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): The primary course of treatment for patients with low-to-intermediate risk tonsil cancer has evolved with a shift toward either primary transoral robotic surgery (TORS) or radiation therapy (RT). While favorable outcomes have been reported after de-intensification strategies using TORS or unilateral RT (uniRT), comparisons of functional outcomes between these treatment options are lacking. The purpose of this secondary analysis was to compare clinician-graded and patient-reported swallowing outcomes based on primary treatment strategy: TORS, uniRT, or bilateral RT (biRT).

Materials/Methods: 135 patients with HPV/P16+ T1-T3, N0-2b, and N0-1 (AJCC VII) SCCA of the tonsil were sampled from a prospective registry. Modified barium swallow (MBS) studies graded per DIGEST, feeding tube (FT) placement, and MD Anderson Dysphagia Symptom Inventory (MDADI) questionnaires were collected. Patients were stratified by primary treatment: TORS (n=38), uniRT (n=37), or bilRT (n=60). Dysphagia grade (per DIGEST) and 19-item composite MDADI were compared between groups using Kruskall-Wallis test with post-hoc Dunn's test and sidak correction. We tested the association between dysphagia prevalence (DIGEST grade>0 vs. 0) and FT placement (yes/no) using chi-square test.

Results: T-classification differed by treatment group ($p<0.001$) with T2 or 3 disease more likely in TORS (19/38, 50%) and biRT (43/60, 68%) compared with uniRT (9/37, 24%). Concurrent chemotherapy differed by group ($p<0.001$) and was commonly combined with uniRT (28/37, 76%) and biRT (52/60, 87%) regimens over TORS (8/38, 21%). At baseline, DIGEST grade significantly differed between treatment groups, with higher dysphagia prevalence in the TORS group: (proportion, 95% CI): 34% (20-51) vs. biRT: 12% (5-23). At 3-6 months sub-acute recovery, we found no significant group difference in dysphagia prevalence ($p = .22$): TORS 42% (26-59); uniRT 24% (12-41); biRT 38% (26-52). Patient reported MDADI scores were similar between groups both at baseline (mean±SD: TORS 87 ± 9, uniRT 88 ± 9, biRT 82 ± 8, $p = .90$) and at 3-6 months (TORS 63 ± 17, uniRT 74 ± 10, biRT 73 ± 15, $p = .38$). Rates of FT placement did not differ between groups (TORS 2/38, 5%, uniRT 3/37, 8%, biRT 12/60, 20%, $p=0.06$).

Conclusion: Results suggest that the 3 primary treatment strategies for low-intermediate risk tonsil cancer − TORS, unilateral RT, and bilateral RT − did not have statistically significant differences in clinician-graded or patient-reported dysphagia outcomes. Statistically significant group differences in T-classification, use of concurrent chemotherapy, and baseline dysphagia merit further assessment with longitudinal modeling and multivariate analysis; these analyses are underway.

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Hospitalization During Radiation Therapy for Head and Neck Cancer Portends Poor Prognosis: Single Institution Review and Matched Pair Analysis

H.R. Han,[1] G.M. Hermann,[2] S.J. Ma,[2] A.J. Iovoli,[1] K.E. Wooten,[2] H. Arshad,[2] V. Gupta,[3] R. Mcspadden,[2] M. Kuriakose,[2] W.L. Hicks,[2] J.M. Chan,[2] M.E. Platek,[4] and A.K. Singh[2]; *[1]Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, [3]Roswell Park Cancer Institute, Buffalo, NY, [4]Buffalo State College, Buffalo, NY*

Purpose/Objective(s): Radiotherapy (RT,) often given with chemotherapy, is effective but morbid treatment of head and neck cancer (HNC) and some patients must be hospitalized. Our aims were to catalogue reasons for admission and evaluate survival outcomes associated with rate of hospitalizations in patients undergoing RT for HNC.

Materials/Methods: We retrospectively reviewed hospitalization record of HNC patients treated at Roswell Park Comprehensive Cancer Center with definitive or post-operative RT between 2003 and 2017. Patients who were admitted secondary to complications during treatment period and 90-day post-RT were identified. Reasons for admission were identified. Admissions prior to start of and >90-day post-completion of RT were excluded. Inpatient stays for pre- and post-operative monitoring were excluded. Univariate (UVA), multivariate (MVA) analyses using backward selection ($\alpha<0.20$), Kaplan-Meier statistics, and match-pairing were done utilizing R software. Length of follow-up was defined as time between date of diagnosis to death or last date of follow-up visit.

Results: This retrospective analysis included a total of 857 patients. All patients received either definitive (n=608, 71%) or adjuvant (n=249, 29%) RT and 203 patients (24%) did not receive any chemotherapy. 682 (80%) patients received concurrent chemoradiotherapy (CRT) and 85 patients (10%) received induction chemotherapy. Median follow-up was 34.8 months (range, 1.2-164.4 months). 167 patients (19%) had at least one admission during or within 90 days of CRT. Very low hemoglobin (less than 10 gm/dl) ($p=0.0451$), artificial nutrition support ($p<0.0001$), and weight loss ($p=0.0021$) were significant predictors of hospitalization. 129 patients (77%) had single admission and 38 (23%) had more than one admission. Most frequent reasons for admission included pneumonia, dehydration, fever, altered mental status, and deep venous thrombosis/pulmonary embolism. Patients who were hospitalized were less likely to have a complete response to treatment ($p=0.0023$) and had significantly worse overall survival ($p=0.0018$) and worse cancer-specific survival ($p=0.039$). Match pair analysis of 164 patients in 1:1 ratio, with all variables well balanced, showed that being hospitalized is associated with worse OS ($p=0.0018$) and worse CSS ($p=0.039$). In the same analysis, nutrition support also showed association with worse OS ($p=0.013$) and CSS ($p=0.026$).

Conclusion: This study demonstrates worse overall survival and cancer specific survival for patients hospitalized during CRT for HNC. As newer agents are studied concurrently with radiation therapy, hospitalization (causes and rates) should be monitored as it may be an early marker for worse overall survival.

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Chemosensory Outcomes in Nasopharyngeal Cancer Patients Treated with Proton Beam Therapy: A Prospective Longitudinal Study

J. Slater,[1] L. Liu,[1] D. Sui,[1] E.A. Weyman,[2] and A.W. Chan[2]; [1]*Massachusetts General Hospital, Boston, MA,* [2]*Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Purpose/Objective(s): Chemosensory loss after treatment for nasopharyngeal cancer (NPC) is common, but prospective data assessing impact on quality of life (QOL) are lacking. Proton beam therapy (PBT) has potential to reduce chemosensory loss due to lack of low-dose radiation to the chemosensory structures. The purposes of this study were to assess patient-reported QOL outcomes after PBT and to determine dosimetric predictors of toxicity and QOL outcomes.

Materials/Methods: Twenty-five patients with biopsy-confirmed stage IIB-IVB nasopharyngeal carcinoma were enrolled on a prospective, phase II, NCI-funded study. The primary endpoint was QOL outcomes. Patients were treated with concurrent PBT/cisplatin and adjuvant cisplatin/5-fluorouracil. EORTC-HN43 and ChemoSensory Questionnaire (CSQ) were performed before PBT and at 1.5, 3, 6, 12, and 24 months following completion of CRT. CSQ—a validated tool that assesses patient's olfaction and gustatory senses on a scale of four (greatest detriment in QOL) to 20 (no QOL detriment) for each sense. Analysis of variance (ANOVA) and Pearson's correlation statistical tests were completed.

Results: Twenty-three patients had complete baseline and follow-up CSQ data. The median baseline CSQ taste score was 18, post-treatment CSQ taste score had a significant decrease 1.5, 3, and 6 months with a median of 8.5 (95% CI 7-10), 11 (95% CI 8-13), and 14 (95% CI 10-16), respectively ($p<0.001$ at 1.5 months). At 12 months, median CSQ taste score was 16 and at 24 months it was stable at 15.5. CSQ smell score demonstrated a similar but not statistically significant decrease from baseline (median 20) at 1.5 months (median 14.5), with a gradual increase at 3, 6, 12, and 24 months post-treatment (median 15, 17, 18.5, and 17.5, respectively) ($p=0.35$ at 1.5 months). CSQ taste score had significant correlation with all but four of the metrics of EORTC-HN43 scale, and CSQ smell score had significant correlation with all but six of the metrics. The correlation coefficient between CSQ and Senses Problem metric of EORTC was -0,802 ($p<0.001$). Dosimetric predictors of sensory loss on olfactory system and gustatory system will be presented.

Conclusion: This study marks the first study prospectively assessing the chemosensory QOL outcomes of nasopharyngeal cancer patients. This study demonstrates that with proton beam radiation therapy, the long-term chemosensory outcomes are preserved. These data provide a foundation for further studies phase III involving proton beam therapy and quality of life.

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Withdrawn

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Ninety Day Mortality As A Measure of Quality of Care in Head and Neck Cancer Patients Treated with Radical (Chemo) Radiotherapy: A Single Centre Experience

R. Lyus,[1] Z. Elcioglu,[2] M. Cunnell,[2] J. Kovarik,[2] C.G. Kelly,[2] and M.S. Iqbal[2]; [1]*Newcastle University, Newcastle upon Tyne, United Kingdom,* [2]*Northern Centre for Cancer Care, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom*

Purpose/Objective(s): Thirty day mortality is a recognised measure to assess the quality of care provided. It has been suggested by NHS Department of Health England that post-radical radiotherapy 90 day mortality could be used as another clinical indicator to assess quality of care provided [1]. The primary aim of this study was to assess the 90 day mortality rate for head and neck cancer (HNC) patients treated with radical intent in our centre.

Materials/Methods: From January 2010 to December 2016 (7-year period), 883 patients with HNC were referred to our centre for primary or adjuvant radiotherapy ± chemotherapy. Of these 883 patients, 353 patients have died. Ninety day mortality was defined as 'those patients who died either on or within 90 days of last fraction of primary or adjuvant radiotherapy'. For analysis, the patients were divided in to two groups; group 1 consisted of those patients who died either during or within 30 days of the last fraction of radical radiotherapy and group 2 involved patients who died 31 − 90 days post radiotherapy. Comparison of groups was performed using either Chi squared analysis or T-test.

Results: Thirty eight patients (4.3%) died during or within 90 days of last fraction of radical radiotherapy. The median age of this 38 patient cohort was 67 years (range: 45 − 88 years), WHO performance status was 0 to 2 (0 = 34%, 1 = 42% and 2 = 24%). Adult Co-morbidity score (ACE) was 0 to 3 (0/1 50% and 2/3 50%). The range of patient mortality days was from 0 to 86 days (mean 45.32 with SD 27.75). A comparative analysis between group 1 (n=11) and group 2 (n = 27) showed nutritional status (as defined by requirement for tube feeding) was a significant prognostic factor ($p=0.026$). Age ($p=0.461$), gender ($p=0.578$), smoking status ($p=0.407$), performance status ($p=0.694$), ACE co-morbidity score ($p=0.238$), treatment intent i.e. primary versus adjuvant ($p=0.634$), stage ($p=0.398$), disease subsite ($p= 0.211$) and the addition of chemotherapy (0.309) were not found to be significant factors. The patients who completed radiotherapy were less likely to die within 30 days (24% vs 76%) but this wasn't statistically significant ($p=0.066$).

Conclusion: Our findings show that poor nutritional status is strongly associated with ninety day mortality in HNC and should potentially be considered as an indicator of quality of care provided. A more pro-active approach to nutritional management should be considered in HNC patient being radically treated. However, we recognise the limitations in this study.

References: 1. Department of Health. Improving Outcomes: A Strategy for Cancer. 2011. [Online]. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213785/dh_123394.pdf

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Which Patients Benefit from Prophylactic Gastrostomy Tube in p16-positive Oropharyngeal Squamous Cell Carcinoma Treated with Concurrent Chemoradiation with High-Dose Cisplatin?

B.W. Beard, O. Bhattasali, and S. Iganej; *Southern California Permanente Medical Group, Los Angeles, CA*

Purpose/Objective(s): The standard of care for patients with p16-positive oropharyngeal squamous cell carcinoma (OPSCC) is concurrent chemoradiation (CCRT) with high-dose cisplatin (HDC). Malnutrition due to treatment-related odynophagia and nausea is common with this regimen. Gastrostomy tubes (GT) are often used to improve nutrition, yet the optimal timing of GT placement is unclear. Some physicians recommend GT prophylactically (pGT) before or early in treatment in the absence of swallowing impairment. Others recommend expectant management (EM) with reactive GT (rGT) at the onset of swallowing impairment. We hypothesized that certain subsets of patients would benefit from pGT over EM.

Materials/Methods: Patients with p16-positive OPSCC were treated with CCRT to a dose of 70 Gy concurrent with triweekly HDC (100 mg/m2). Weights were recorded at initial consultation, weekly while on treatment, and at every follow-up. Patients requiring GT prior to or within 14 days of treatment start for dysphagia or weight loss were excluded. Patients were

in the pGT group if they had GT placed in the absence of swallowing impairment. Patients were in the EM group if they were managed without a GT through the first 14 days of treatment. Baseline characteristics and treatment toxicity data were compared between groups.

Results: From February 2006 through September 2016, 230 patients were treated with CCRT with HDC. Of these patients, 21 (9%) were excluded due to dysphagia or malnutrition requiring GT placement prior to or within 14 days of the start of treatment. Of those remaining, 103 (49%) received a pGT. Of the 106 EM patients, 28 (26%) required a rGT. Patients with pGT were more likely to receive all three cycles of HDC (85% versus 68%, $p = 0.007$). Patients with pGT had lower percent weight loss from start to end of treatment (median 10% versus 12%, $p = 0.001$) and lower percent weight loss within one year of treatment (median 16% versus 19%, $p = 0.007$). In the EM group, the only univariate predictor for rGT was AJCC 8th edition stage group with 15% of stage I, 33% of stage II, and 41% of stage III patients requiring rGT ($p = 0.04$). In a comparison of median weight loss from start to end of treatment, there was a benefit to pGT over EM for stage III patients (9% versus 15%, $p = 0.002$), but there was no benefit for stage I (9% versus 11%, $p = 0.07$) or stage II (10% versus 12%, $p = 0.42$) patients.

Conclusion: Compared to stage I and II patients, stage III patients receiving CCRT with HDC for p16-positive OPSCC derive greater benefit from pGT and are more likely to require rGT if managed expectantly. The benefit of pGT in stage III patients is likely due to greater tumor burden requiring larger treatment volumes and leading to more severe swallowing impairment compared to earlier stage disease. Stage should be considered in the nutritional assessment of patients, and patients with stage III disease may benefit from early nutritional intervention.

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Rates of Toxicity for Locally Advanced Head and Neck Cancer Patients Receiving Concurrent Chemoradiation in the Modern Era: A Review

J.A. Messer,[1,2] R. Zuhour,[1,2] A.S. Mohamed,[1] C.D. Fuller,[1] and L. van Dijk[1,3]; *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The University of Texas Medical Branch, Galveston, TX, [3]UMC Groningen, Groningen, Netherlands*

Purpose/Objective(s): In recent years, prospective, randomized controlled trials (RCTs) have established concurrent chemoradiation (CRT) as the standard of care for locally advanced head and neck cancers (LAHNC). The tradeoff for improved disease control with CRT is increased acute and late toxicities. Ongoing trials seek to either escalate dose, deescalate dose, or add induction chemotherapy. A useful reference is needed to clarify the current toxicity rates in LAHNC for patients undergoing CRT to be able to compare if future therapy regimens are more or less toxic, while also comparing disease control. The purpose of our study was to review modern prospective RCTs and summarize the rates of severe acute and late toxicity.

Materials/Methods: A literature search was done for prospective RCTs in LAHNC with at least one arm including chemoradiation and with toxicity data using PubMed from 2002-2019. Toxicity rates were compiled based on CTCAEv5.0 and divided into acute and late events. A weighted average based on the number of patients was calculated along with standard deviation (SD) and range.

Results: A total of 21 RCT were selected for this study. Cisplatin was the most common concurrent chemotherapy given in 13 (62%) of the studies followed by Cetuximab in 5 (24%). The radiation dose and fractionation were most commonly 70 Gy given at 2 Gy per fraction. One trial used 1.5 Gy BID fractionation. Two (10%) of the trials used induction chemotherapy with Cisplatin and 5-FU followed by CRT. Most of the trials included multiple tumor sites in their definition of LAHNC, while 3 (14%) trials specifically included larynx, and 1 (5%) trial included only oropharyngeal cancer. Any grade 3 or greater events were seen in 83% of patients in acute phase and 35% of patients in late phase. Toxic death occurred in 2% of patients in the acute phase, but none in the late phase. The most common G≥3 acute event was mucositis (45%). The most common G≥3 late events were pharyngitis (17%) and dysphagia (16%), while G≥2 xerostomia occurred in 38% of patients.

Conclusion: This review summarizes current rates of clinically meaningful acute and late toxicities in the chemoradiation era. This important reference can be used to counsel patients about expected rates of toxicity and to help prepare clinicians to anticipate and treat these side effects to help patients complete designated therapies. Future steps include comparing the objective toxicity rates and quality of life data at large cancer institutions.

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Characterization of Cardiac Function, Pulmonary Function and Body Composition Before and after Concurrent Chemoradiotherapy for Head and Neck Cancer

Z.A. Kohutek,[1] W. Bradham,[2] D.K. Smith,[3] D.A. Slosky,[2] and B. Murphy[4]; *[1]Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville, TN, [2]Department of Cardiology, Vanderbilt University Medical Center, Nashville, TN, [3]Department of Biostatistics, Department of Oral and Maxillofacial Surgery, Vanderbilt University Medical Center, Nashville, TN, [4]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN*

Purpose/Objective(s): Chemoradiotherapy (CRT) for head and neck cancer can result in profound physiologic changes including loss of weight and muscle mass akin to cancer cachexia. In animal models, cancer cachexia has been shown to be associated with a pro-inflammatory state during which there are fundamental changes in cardiopulmonary function, including diaphragmatic muscle weakness and cardiac atrophy. We hypothesized that CRT would similarly lead to decreased muscle mass with resultant increases in inflammation and cardiopulmonary dysfunction. In this study, we aimed to prospectively investigate changes in body composition, cardiac function and pulmonary function in a cohort of patients before and after CRT for head and neck cancer.

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		Acute	SD	Range	#pts	Late	SD	Range	#pts
Any	G≥3	83%	3%	77%-87%	1927	35%	14%	14%-54%	1575
Toxic death		2%	2%	1%-7%	1230	0%	0%	-	103
Mucositis	G≥3	45%	15%	16%-74%	2373	6%	6%	1%-15%	1298
Dermatitis	G≥3	22%	14%	7%-42%	1300	3%	2%	0%-7%	1447
Dysphagia	G≥3	40%	24%	4%-85%	2249	16%	12%	4%-36%	1527
Xerostomia	G2-3	39%	21%	8%-52%	1041	38%	11%	32%-54%	532
Osteonecrosis	G≥3	0%	0%	-	361	2%	3%	0%-6%	864
Pain	G≥3	8%	3%	6%-12%	416	2%	1%	1%-3%	815
Pharyngitis	G≥3	3%	0%	-	208	17%	0%	-	157

Materials/Methods: Fourteen patients with histologically-proven stage III/IV head and neck cancer undergoing definitive or adjuvant concurrent CRT were enrolled in a prospective clinical trial at our institution. Prior to and within two weeks of completing radiation therapy, patients underwent multiparametric testing including: 1) Body composition analysis using bioelectrical impedence analysis (BIA), 2) Cardiac magnetic resonance imaging (cMRI) to assess parameters such as left ventricular (LV) mass, left and right ventricular systolic and diastolic volumes, cardiac output, and ejection fraction, 3) Pulmonary function tests (PFTs) including spirometry and measurement of lung volumes, maximum voluntary ventilation, maximum expiratory pressure and maximal inspiratory pressure (MIP), and 4) Measurement of inflammatory markers including C-reactive protein (CRP).

Results: Patients developed a significant decrease in BIA-measured lean muscle mass after CRT (-4.09% ± 3.07%, $p<0.001$ by paired t-test). Serum CRP levels were markedly and significantly increased after CRT (491% ± 608%, $p=0.003$ by paired t-test). Changes were also seen on post-CRT cMRI, with patients demonstrating significantly reduced LV mass compared to pre-CRT measurements (97.4 ± 17.4 g vs. 89.3 ± 20.2 g, $p=0.017$ by paired t-test). Despite changes in LV mass, no significant changes were identified in measures of ventricular volumes, cardiac output or ejection fraction at this early timepoint. On PFTs, patient lean mass loss correlated strongly with decreases in MIP ($r^2=0.66$), a measure of respiratory muscle strength.

Conclusion: CRT for head and neck cancer can lead to acute inflammation, changes in body composition including reduced overall muscle and cardiac muscle mass, and impairment in pulmonary functioning. Future studies will be necessary to further characterize the nature of and potential long-term impact of these changes on patient physiology and quality of life.

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The Implementation of a Head and Neck Multidisciplinary Clinic and its Effects on Time to Treatment Initiation and Patient Satisfaction

R. Aulet,[1] J. Lebsack,[1] A. Patel,[1] B. Wampler,[1] J.J. Caudell,[2] A. Trotti,[3] J.A. Kish,[4] K. Otto,[1] L.B. Harrison,[2] and C.S. Chung[1]; *[1]Moffitt Cancer Center, Tampa, FL, [2]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, [3]Mofffitt Cancer Center and Research Institute, tampa, FL, [4]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Purpose/Objective(s): The treatment of head and neck cancer is complex and requires a multidisciplinary approach. We established a head and neck cancer multidisciplinary clinic at our institution to allow patients to see multiple physicians at a single clinic appointment. We examined the effects of this clinic on time to initiation of treatment and patient reported satisfaction.

Materials/Methods: A head and neck multidisciplinary clinic including radiation oncology, head and neck surgery, and medical oncology was started in 2015 at our institution. Charts of head and neck cancer patients seen in standard clinics and multidisciplinary clinics from September 1st, 2015 to December 31st, 2016 were reviewed. Data on, time to complete multidisciplinary evaluation, time to treatment initiation and patient satisfaction as measured by Press Ganey survey responses were collected. Statistical analyses were performed with the Wilcoxon rank-sum test.

Results: During the study period a total of 232 patients with newly diagnosed head and neck cancer were seen at our institution, 182 (78%) of which were seen in the multidisciplinary clinic. The median time from scheduling an appointment to completing radiation oncology and medical oncology evaluation was 7 days (0-33) in the multidisciplinary group and 13 days (0-35) in the standard group ($p=0.004$). The median time from initial appointment to initiation of treatment with radiation therapy +/- chemotherapy was 22 days (3-84) for the multidisciplinary group compared with 29 days (15-53) for the standard group ($p = 0.021$). Press Ganey surveys were returned by 101 patients in the multidisciplinary group and 35 patients in the control group, with an overall outpatient score of 92.75% vs 86.93%, respectively.

Conclusion: For patients with newly diagnosed head and neck cancer, implementation of a multidisciplinary head and neck clinic resulted in a statistically significant decrease in time to treatment initiation and time to multidisciplinary evaluation completion. Patients also reported increased overall satisfaction when initially seen in the multidisciplinary clinic. This lends further support for the utilization of multidisciplinary teams in treating these complex patients.

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Characterization of Pain Symptomatology in Head and Neck Cancer (HNC) Survivors

D. Lou,[1] M. Dietrich,[2] J. Deng,[3] and B. Murphy[4]; *[1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University, Nashville, TN, [3]Vanderbilt University School of Nursing, Nashville, TN, [4]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN*

Purpose/Objective(s): HNC and its treatment causes an array of acute and chronic pain syndromes which are poorly characterized. This impedes development of novel preventive and treatment strategies. We present prospective data characterizing HNC related pain from baseline through 12 months post treatment including diverse pain syndromes such as painful mouth ulcers, dental sensitivity, mucosal sensitivity (peripheral sensitization), and widespread pain (central sensitization).

Materials/Methods: HNC patients participating in R01DE024982 completed the Vanderbilt Head and Neck Symptom Survey 2.0 - General Symptom Survey which includes 14 pain items (scale 0 (none) to 10 (severe)). Surveys were completed at baseline, end of treatment (EOT), and 3, 6, 9, and 12 months post-treatment.

Results: Of the 117 patients enrolled (mean age 59 years, 72% male), 66.1% received multimodal treatment. Average pain was moderate to severe (>4) in 39% of patients at baseline, 57.9% EOT, 9.7% 12 months. Pain medication use was 56% at baseline, 76% at EOT, and 40% at 12 months. If on medications, pain relief declined from 78% at EOT to 35% at 12 months. Specific pain syndromes demonstrated differing trajectories. Painful mouth sores peaked at EOT (50% with pain >4) and resolved quickly over time. Moderate to severe dental sensitivity prevalence (16% patients) was stable over time. Mucosal sensitivity to spicy, acidic or hot foods, and dryness in the air peaked at EOT and decreased slowly over time, remaining moderate to severe at 12 months for >25% of patients. Moderate to severe widespread pain in joints and muscles was reported by 20% of patients at 12 months post treatment.

Conclusion: Mucosal sensitivity and widespread pain, which are neuropathic in origin, tended to persist over time and can be resistant to medical therapy as substantiated by our results. Findings suggest that a deeper understanding of pain mechanisms affecting HNC survivors is needed to ensure effective therapeutic regimens. Furthermore, validated questionnaires must be carefully designed and used in routine clinical assessment to fully capture symptom burden in this patient population.

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Serious Illness Conversations with Head and Neck Cancer Patients

F. Buen,[1] E.J. Martin,[2] K. Buen,[3] N. Wenger,[4] and A. Walling[4]; *[1]Ronald Reagan-UCLA Medical Center, Dept of Head and Neck Surgery, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA, [3]University California Los Angeles School of Nursing, Los Angeles, CA, [4]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA*

Purpose/Objective(s): Head and neck cancer is associated with significant morbidity and mortality, yet little is known about the frequency and content of discussions addressing patients' values, goals of care, and treatment preferences.
Materials/Methods: Using an institutional cancer registry, we conducted a retrospective analysis of 70 decedents who underwent surgical treatment for squamous cell carcinoma of the head and neck. An independent reviewer re-abstracted 20% of the records and for abstracted data pertaining to documented values, goals of care, and/or treatment preferences our inter-rater reliability was greater than 93%.
Results: The mean age at diagnosis was 66 years and 69% were male. The most common disease subsite was the oral cavity (64%), followed by oropharynx (20%) and larynx (10%). Sixty-three percent of patients had stage 4 disease at the time of initial diagnosis and 49% had known distant metastases at the time of death. An enduring advance directive, a completed Physician Order for Life Sustaining Treatment form, and a documented discussion about the patients' values, goals, and treatment preferences were identified in 27%, 4%, and 49% of the medical records, respectively. Half of the documented goals of care discussions occurred in the inpatient setting; over half were held in the last month of life and one-fourth were held in the last week of life. These conversations involved specialist palliative care providers (47%), hematologist/oncologists (41%), hospitalists (32%), head and neck surgeons (21%), radiation oncologists (19%), and intensivists (18%). Of the patients with a known location of death, 58% died in the hospital. Of the patients that underwent cardiopulmonary resuscitation (CPR) and 80% percent died during CPR. Twenty-one percentof patients were enrolled in hospice prior to death.
Conclusion: In this retrospective analysis, serious illness communication was documented in a minority of patients who died of head and neck cancer and these discussions occurred late in the trajectory of illness. The continuity relationships of teams treating head and neck cancer patients (e.g., head and neck surgeons, radiation/oncologists, and hematologist/oncologists, palliative care specialists) situate these clinicians in the best position to engage patients in discussions about their goals, values, and treatment preferences. These data suggest that there are multiple opportunities to have these discussions earlier in the disease course.
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A Pilot Study of a Comprehensive Palliative Care Intervention to Improve Symptoms and Coping During Curative-Intent Chemoradiation in Patients with Head and Neck Cancer

J. Bauman,[1] J. Panick,[1] T.J. Galloway,[1] J.A. Ridge,[1] M. McShane,[1] M. Chwistek,[1] M. Collins,[1] L. Kinczewski,[1] K. Murphy,[1] M. Welsh,[1] M. Farren,[1] M. Clark,[1] J. Kelly,[1] K. Schuster,[1] L. Stokes,[1] S. Amrhein,[1] F. Bender,[1] B. Egleston,[1] A. El-jawahri,[2] and C. Fang[1]; [1]*Fox Chase Cancer Center, Philadelphia, PA,* [2]*Massachusetts General Hospital, Boston, MA*

Purpose/Objective(s): Patients receiving curative chemoradiation treatment (CRT) for head and neck cancer (HNC) undergo some of the most intensive treatments in oncology, resulting in immense physical and psychological symptoms. Integrated palliative care (PC) improves symptoms and coping in patients with advanced cancer, but has not been evaluated in patients with curable solid tumors. Thus, we are conducting the first pilot study of a collaborative palliative and oncology care intervention among patients receiving CRT to assess feasibility and acceptability.
Materials/Methods: Eligible participants include newly diagnosed HNC patients starting curative-intent CRT. The intervention entails weekly in-person PC visits integrated with standard oncology care during CRT, followed by four weekly phone calls after CRT ends. The PC visits are conducted primarily by a PC nurse, with a supervising MD or NP available. Visits focus on coping and on managing prominent symptoms during CRT. PC clinicians also receive a weekly patient-reported symptom assessment. Additionally, at baseline, week five, and one, three, and six months after CRT ends, patients complete questionnaires evaluating symptoms, mood, coping, and quality of life. Acceptability of the intervention is assessed at one month post CRT. The primary outcome is feasibility, defined as a >50% enrollment rate with >70% of participants attending at least half of the PC visits. Planned accrual is 20 patients.
Results: We have enrolled 90% (19/21) of eligible patients to date. 14/19 (74%) have p16+ disease. Fourteen have completed CRT and are evaluable for feasibility and acceptability thus far. These participants attended 98% (94/96) of all possible PC visits and completed 99% (95/96) of weekly symptom assessments. PC clinicians spent an average of 35.5 minutes (SD 15.1) per visit with participants. At four weeks post CRT, all 14 (100%) found the intervention "very helpful" and would "definitely recommend" it to others undergoing CRT.
Conclusion: Our novel PC intervention to improve symptoms and coping during CRT for HNC is both feasible and acceptable with a high enrollment rate, excellent intervention compliance, and high patient satisfaction. This is the first study to integrate PC systematically into the care of the HNC population, the first study to integrate PC into outpatient curative treatment, and the first study to use a PC nurse as the cornerstone of a PC intervention. The success of this pilot study clearly establishes the significant perceived need for better supportive care during intensive curative-intent treatment. Future studies will evaluate the effects of the PC intervention on patient-reported outcomes and health care utilization.
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Time to Insurance Approval and Treatment for Proton Beam Therapy for Head and Neck Cancers

S. Perni, P.M. Busse, A.W. Chan, R.J. Connolly, and H.A. Shih; *Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Purpose/Objective(s): Proton beam therapy (PBT) can have dosimetric advantages in treatment of head and neck cancer (HNC), allowing for both dose escalation and reduction of dose to normal tissues which may improve control and reduce toxicity. Despite this, insurance barriers have delayed access. We aim to characterize insurance approval time (IAT) and treatment delays for HNC patients receiving PBT.
Materials/Methods: Given limited treatment slots, an internal review process called "proton rounds" (PR) was implemented to allocate PBT based on greatest clinical benefit. We performed a retrospective chart review of PR patients with intakes submitted January 2016 to January 2019 who received PBT. IAT was calculated, as was PR intake/consult date to RT start. Patients were ≥ 18 years with malignant HNC and did not have induction chemotherapy or surgery delaying RT start after PR intake/consult. Statistical analyses were performed using JMP® (Version 14, SAS Institute Inc., Cary, NC).
Results: 102 patients were identified. Median age was 57 (range 18−89) years, with 59% male and 80% white. 31% received prior RT.

Median IAT was 10 days (Range 0-158), with 34% >14 days. Median time to RT was 50 (Range 6-190) days. **Table 1** shows IAT by site. Median IAT for publicly insured (Medicaid/Medicare/state, 34%) was 5 (CI 2-10) days versus 13 (CI 8-13) days for privately insured (66%, p=<0.0001). Median IAT days were: 5.5 (range 0-102) in 2016, 11.5 (range 1-45) in 2017, and 14 (range 1-158) in 2018 (p=0.009).

In multivariate analyses including age, sex, race, diagnosis, year of treatment, and public insurance, only public insurance predicted shorter IAT (HR 1.3, CI 0.8-2.2, p=0.003). Insurance approval >2 weeks and year of treatment were significant predictors of longer time to RT in both univariate and multivariate analyses including age, sex, race, and diagnosis (HR 0.6, CI 0.3-1.0, p=0.03; and 2018/2019 vs 2016/2017 HR 0.5, CI 0.3-0.9, p=0.01, respectively).

Abstract 373; Table 1 IAT by site.

Diagnosis	Median IAT (days)	Range (days)
Ear (n=1)	8	n/a
Lacrimal (n=11)	14	2-39
Nasal cavity/paranasal sinuses (n=36)	10	0-102
Nasopharynx (n=16)	13	0-84
Oral cavity (n=3)	0	0-17
Orbit/Eye (n=10)	9.5	5-52
Oropharynx (n=7)	10	2-14
Salivary (n=6)	20.5	1-158
Unknown primary (n=2)	3.5	0-7
Skin (n=10)	5.5	0-24

Conclusion: Over a three-year period, despite internal selection for greatest clinical benefit, a third of patients had IAT of at least two weeks, with median of ten days. IAT significantly predicted time to RT, while private insurance predicted for longer IAT. Both IAT and time to radiation increased yearly. Treatment delays for head and neck patients portend poorer outcomes, and this work suggests that there are increasing private insurance barriers to timely treatment initiation of proton radiation. Consensus guidelines and advocacy for proton beam therapy are called for to improve access to timely treatment.

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Improvement in Time-to-Treatment Initiation and Use of Ancillary Services for Patients Seen in a Head and Neck Multidisciplinary Clinic at a Safety Net Hospital

N.S. Khakoo,[1] S. Dooley,[2] H. Perlow,[1] E. Nicolli,[3] D. Kwon,[4] M.A. Samuels,[5] M. Mora,[1] L.M. Freedman,[4] and S. Samuels[6]; *[1]University of Miami Miller School of Medicine, Miami, FL, [2]University of Miami/Jackson Memorial Hospital/Sylvester C. Cancer Center, Miami, FL, [3]Department of Otolaryngology, University of Miami / Sylvester Comprehensive Cancer Center, Miami, FL, [4]University of Miami, Miami, FL, [5]Department of Radiation Oncology. University of Miami / Sylvester Comprehensive Cancer Center, Miami, FL, [6]Department of Radiation Oncology, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL*

Purpose/Objective(s): A Head and Neck (H&N) Multidisciplinary Clinic (MDC) was implemented in 2017 at a safety net hospital to improve the coordination of care for H&N cancer patients. Patients evaluated in MDC were seen by an ENT surgeon, radiation oncologist, medical oncologist, and speech pathologist at the initial visit compared to non-MDC patients who visited these services separately. In this study, we hypothesized that patients treated in MDC have improvement not only in the utilization of ancillary services but also in the time-to-treatment initiation (TTI), an important metric in H&N cancer care.

Materials/Methods: We retrospectively reviewed demographics, ancillary service consultations, and treatment information for 48 consecutively treated patients prior to MDC (non-MDC) from 9/2013 to 2/2016 and 34 consecutively treated MDC patients from 10/2017 to 12/2018 with biopsy-proven, primary H&N cancers treated with radiotherapy (RT). TTI was defined as the time between the date of diagnosis and the initiation of primary treatment with RT or surgery. Analysis of consultations for nutrition, speech pathology, and dental care before the start of treatment was included. Kaplan-Meier analysis and univariable regressions were conducted to estimate hazard ratios, odds ratios and p-values.

Results: On Kaplan-Meier analysis, for patients receiving primary RT, MDC patients (n=24) had a decreased TTI compared to non-MDC patients (n=30) with median TTI for MDC patients 1.33 months versus 2.05 months for non-MDC patients (HR 0.49 (95%CI, 0.28-0.86; p=0.0127). We found no significant difference in TTI for patients receiving primary surgery with median TTI for MDC patients (n=10) 0.82 months versus 1.08 months for non-MDC patients (n=18) (HR 0.96 (95% CI, 0.43 to 2.14; p=0.913). MDC was also associated with increased nutrition consultation compared to non-MDC (OR 0.26, 95%CI, 0.09 - 0.79, p=0.0177), although dental consultation showed no significant difference between the two groups.

Conclusion: MDC patients who had primary RT showed statistical improvement in TTI. This improvement was not seen in MDC patients who had primary surgery and adjuvant RT; however, the cohort of surgical patients was small. The utilization of ancillary services such as nutrition was significantly increased amongst MDC patients compared to non-MDC patients. Speech pathology was also more accessible for MDC patients. The MDC-associated improvement of early initiation of treatment as well as increased use of ancillary services may translate into improvements in treatment outcomes. Future analysis on local recurrence, survival, and quality of life in MDC patients vs. non-MDC patients is needed.

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Conductive Hearing Loss after Chemoradiation for Nasopharyngeal Carcinoma: A Prospective Longitudinal Study

S. Patel,[1] S.I. Goldberg,[2] E.A. Weyman,[1] P.M. Busse,[1] and A.W. Chan[1]; *[1]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA*

Purpose/Objective(s): Hearing loss (HL) after treatment for nasopharyngeal cancer (NPC) is common. Prospective data assessing predictors of ototoxicity are lacking. The purposes of this study were to assess patient-reported and objective hearing function and to determine dosimetric predictors of hearing loss after chemoradiation for NPC.

Materials/Methods: A prospective phase II clinical trial was conducted at our institution. Adult patients with biopsy-proven stage IIB-IVB nasopharyngeal carcinoma were treated with proton and concurrent/adjuvant cisplatin. Pure tone audiometry for air (AC) and bone conduction (BC) was performed before RT and 12-24 months following completion of CRT. The threshold for both AC and BC was measured at 0.25 to 4 kHz. For each frequency, increase in BC threshold indicated sensorineural HL (SNHL) and increase in air-bone gap indicated conductive HL (CHL). DVHs were obtained for the middle ear, Eustachian tube, mastoids, vestibulocochlear nerve, and cochlea. Patient-reported hearing function was assessed prior to and 12-24 months after RT using EORTC QLQ H&N35 questionnaire.

Results: Overall, 52% developed early and late onset CHL in at least one ear. Among the 16 ears demonstrating early-onset CHL on audiometry, 9 ears had a clinically significant rise in air-bone gap at .25 kHz, 7 ears at .50 kHz, 5 ears at 1 kHz, 4 ears at 2 kHz, and 4 ears at 4 kHz. Among the 17 ears that sustained or developed late-onset CHL on audiometry, 6 ears had a clinically significant rise in air-bone gap at .25 kHz, 7 ears at .5 kHz, 6 ears at 1 kHz, 1 ear at 2 kHz, and 5 ears at 4 kHz). Patient-reported hearing loss, described as any decline in serviceable hearing that is noticeable with activities of daily living, at 24 months was recorded. Of the 11 patients with evidence of early-onset CHL, 8 (73%) reported subjective hearing decline on quality-of-life questionnaire. Of the 10 patients who had no abnormalities on audiometry studies at 12 and 24 months, 2 (20%) reported subjective hearing decline. Among the patients with early-onset CHL, 15 of total 55 EORTC domains had a worsening score on the four-point Likert scale. On the other hand, only 7 of 50 domains among the patients with no changes on audiometry had worsening score in hearing-related domains. On multivariate analysis, middle ear Dmean remained the only significant predictor for late-onset CHL following CRT (adjusted HR 1.03, 95% CI 1.03-1.07, $p=0.005$). On multivariate analysis, accounting for placement of typanostomy tube, advanced T-stage, or serous otitis,

middle ear Dmean ≥ 26Gy(RBE) was associated with a 9-fold increase in risk of developing CHL compared to those with middle ear Dmean < 26Gy(RBE) (adjusted HR 9.01, 95% CI 1.90-42.84, $p=0.005$).

Conclusion: Dmean ≥ 26Gy(RBE) to middle ear predicts conductive hearing loss after for NPC. Delineation and avoidance of the middle ear structures is prudent.

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Hippocampal dosimetry and hippocampus sparing volumetric modulated arc therapy in patients with loco-regionally advanced oropharyngeal cancer

S.W. Seol, B. Lee, T. Sita, T.J. Kruser, S. Sachdev, M.S. Gentile, and B.B. Mittal; *Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL*

Purpose/Objective(s): The hippocampus (HC) is a highly radiosensitive organ. Recent animal studies have shown that the radiation dose as low as 2 Gy can significantly impair the generation and maturation of the neuronal stem/progenitor cells and compromise the HC-dependent learning and memory. In this study, we aimed to evaluate the incidental radiation dose to the hippocampus in HPV-positive oropharyngeal cancer (OPC) patients who were treated with intensity modulated radiation therapy (IMRT). We also investigated the feasibility of IMRT plan optimization for HC sparing without compromising the target coverage and the dose constraints applied to the initial plan.

Materials/Methods: We retrospectively evaluated the volumetric modulated arc therapy (VMAT) plans of 10 patients who were treated between 2014 and 2018 for biopsy-proven HPV-positive loco-regionally advanced OPC (LA-OPC). Initial VMAT plans had been generated without dose-volume constraints to the HC. We included only the patients who had undergone MRI of the brain previously, for any clinical indications. CT and T1-weighted MRI fusions were rigidly registered for all 10 patients in Phillips Pinnacle 3 treatment planning software (Fitchburg, WI). Two CNS specialized radiation oncologists delineated the HC on the fused images using the RTOG HC atlas. A range of dose-volume statistics was calculated. The VMAT plan optimization was performed to decrease the HC dose to 1-2Gy without compromising the dose distributions on the targets and surrounding organs at risk (OARs).

Results: The total prescribed dose to the planning target volume was 69.69 -70Gy (D95%) in 2-2.12Gy daily fractions in 9 out of 10 patients and 66Gy in 2Gy daily fractions in 1 patient who was treated postoperatively. Eight patients received radiation therapy to the bilateral neck whereas 2 patients to the unilateral neck. The mean dose to the HC ipsilateral to the primary lesion was 3.18±0.88 Gy, HC contralateral to the primary lesion was 2.72±0.82 Gy, combined HC was 2.89±0.70 Gy and the D40% of combined HC was 3.03±0.77 Gy. When the IMRT plan optimization with VMAT was performed, the doses to the hippocampus were significantly lowered. The mean dose to the combined HC was 1.74±0.47 Gy ($p<0.05$) and the D40% of combined HC was 1.78±0.49 Gy ($p<0.05$) with the re-plan.

Conclusion: This is the first study to examine the incidental radiation exposure of the HC in LA-OPC patients undergoing IMRT and the feasibility of HC sparing plan optimization. We conclude that the incidental dose to the HC with VAMT in LA-OPC is a significant amount that can persistently compromise the HC microenvironment, and it is feasible to reduce the HC dose with IMRT plan optimization. Given that HPV-related OPC patients are usually in their working-age and have long life expectancy, dose reduction to HC regions by taking HC into surrounding OARs should be considered.

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Unplanned Hospital Encounters in Head & Neck Cancer Patients Treated with Radiotherapy

L. Mammen, J. Bott, K. Hans, E.M. Farhangi, and K. Adil; *Albany Medical College, Albany, NY*

Background: Radiotherapy is an effective treatment method for cancer of the head and neck (H&N), but it is often associated with significant toxicities and morbidity. Unplanned hospital encounters (UHE) such as emergency department visits and hospitalizations are common during treatment. These UHE result in substantial fiscal burden as well as compromised disease and quality of life outcomes due to treatment interruption.

Purpose/Objective(s): The purpose of this study is to examine the effect of patient anticipatory intervention services (AIS) on UHE of patients receiving radiotherapy for H&N cancer.

Materials/Methods: A total of 30 patients were included in the study and divided into 2 cohorts. All the patients were developed and retrospectively analyzed using administrative data. The first cohort included 12 patients treated mostly between January and March 2019. At the end of March 2019, AIS were implemented to reduce UHE. These AIS included an early referral system, nutritional assessment, social work, speech language pathology, and smoking cessation therapy. The second cohort included 18 patients treated mostly between April and June 2019 after these AIS were implemented. UHE during treatment and within the 30-day post-treatment period were determined. Reasons for UHE were sub-categorized into nutrition, infection, wound complication, or PEG-tube related. Any reason that was outside of these classifications were categorized as other. Categorized data was analyzed using Incidence Rates (IR) and the Fisher Exact Probability Test.

Results: From the first cohort, 8 (IR 67%) H&N cancer patients receiving radiotherapy had an UHE. Of these patients, 4 (IR 33%) were nutrition related, 2 (IR 17%) were infection related, 2 (IR 17%) were related to other issues. From the second cohort, 5 (IR 28%) H&N cancer patients receiving radiotherapy had an UHE. Of these patients, 2 (IR 11%) were nutrition related, 1 (IR 6%) was wound related, 1 (IR 6%) was PEG-tube related, and 1 (6%) was due to other issues. No significant difference was found between the two cohorts for total UHE (P 0.06), nutrition related (P 0.18), infection related (P 0.15), wound related (P 1.0), PEG-tube related (P 1.0), and related to other issues (P 0.54). Patients were 24-80 years old, 21 male: 9 female, 18 oropharynx cancer: 4 larynx cancer: 2 nasopharynx cancer: 6 other head & neck cancer, 3 stage 0: 7 stage I: 9 stage II: 7 stage III: 4 stage IV, 26 with prescribed dose greater than 6000cGy, 10 with concurrent chemotherapy.

Conclusion: The high rate of UHE emphasizes the need to offer AIS that enable patients to complete their radiological intervention uninterrupted. Despite lack of statistical significance in this study, these AIS appear to trend toward reduction in nutrition related, infection related, and total UHE.

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Factors affecting long-term dependency of radiologically inserted gastrostomy (RIG) feeding in patients with head and neck cancer

J. Tee,[1] M.S. Iqbal,[1] K. Scollen,[2] I. Bowe,[3] N. Lynch,[3] L. Gradwell-Nelson,[4] W. Philip,[4] K. Carlson,[4] D. Miller,[4] J. Adams,[5] M. Kennedy,[5] D. Goff,[2] J. O'Hara,[4] H. Fox,[4] L. Warner,[4] D. Hamilton,[4] J. Kovarik,[1] M. Cunnell,[1] and C.G. Kelly[1]; *[1]Northern Centre for Cancer Care, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom, [2]Speech and Language Therapy, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom, [3]Head and Neck Nutrition, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom,*

[4]Otolaryngology, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom, [5]Maxillofacial Surgery, The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, United Kingdom

Purpose/Objective(s): Gastrostomy dependent feeding during head and neck cancer (HNC) treatment is common however its long-term dependence can be problematic. We investigated the impact of various factors affecting long-term dependence of RIG feed in HNC patients.

Materials/Methods: During August 2017 − December 2018, data was collected till June 2019 on all 92 consecutive patients with HNC who underwent RIG insertion. Long-term dependency was defined as continuation of RIG feed for the duration of ≥9 months. T test/ANOVA was performed using SPSS for comparison of groups for normal distribution data and chi-square test for categorical data.

Results: Mean age was 62.9 years (SD 9.6). 71.7% were males and 28.3% were females. Most patients were with stage IVa (TNM 7th edition) 67%, followed by 16.5% with stage III, 8.8% with stage II, 5.5% with stage IVb and 2.2% with stage I. Most common subsite was oropharynx 51.1% followed by larynx 19.6%, oral cavity 17.4%, hypopharynx 5.4% and others 6.5%. Treatment intention was as follows: radical chemoradiotherapy (CRT) 46.7%, adjuvant (chemo)radiotherapy 21.7%, radical radiotherapy (RT) 20.7% & palliative RT 10.9%. 52.8% received concurrent chemotherapy (40.4% received cisplatin & 12.4% received cetuximab). 53.3% had their RIG prophylactically, 46.7% reactively. Median duration of RIG used was 8 months (range: 0 − 48 months). 21.6% had complications with their RIGs which included infection, leakage or blockage (6.5% required re-insertion). 58.1% patients required hospital admission. At the time of analysis, swallow was fully recovered in 28%, partially in 32% while in remaining 40%, there was no swallow recovery. 84.8% patients were alive at the end of data collection date. Analysis of variables affecting duration of RIG use, <9 months (n=59) vs ≥9 months (n=33), showed no statistically significant difference in stage (stage I-II, III vs IV; p 0.38), disease site (p 0.21), smoking status (p 0.75), or addition of chemotherapy (p 0.47). Younger patients (≤60 years) had longer median duration of RIG use as compared to older patients (11.6 months vs 8.5 months, p=0.04). 65% of adjuvant patients were RIG dependent for ≥9 months compared to 26.8% of patients treated with primary RT ± chemotherapy. There was a trend of less long-term dependence when RIGs were inserted prophylactically rather than reactively (28.9% vs 47.6%) however this difference was not statistically significant (p 0.11).

Conclusion: Gastrostomy assisted nutrition is widely used in HNC. A minority of patients become long-term dependent on this form of nutrition and a few patients remain dependent indefinitely or until death. Adjuvant and younger HNC patients are at main risk of developing long-term dependence but we found no other causative factors including stage, disease site or addition of chemotherapy. Prophylactic RIG insertion appears to shorten period of RIG use and should be encouraged.

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Quality of Life Assessment in Head and Neck Cancer Patients: Preliminary Survey Results

T.L. Arnell,[1] R. Aulet,[2] M. Sajisevi,[2] S. Lane,[2] J. Dulin,[2] H.M. Gagne,[3] and M.M. Barry[4]; [1]Larner College of Medicine at the University of Vermont, Burliington, VT, [2]University of Vermont, Burlington, VT, [3]Division of Radiation Oncology, University of Vermont Cancer Center, Burlington, VT, [4]Division of Hematology Oncology, University of Vermont, Burlington, VT

Purpose/Objective(s): Quality of life (QOL) derangements and psychosocial distress are common in head and neck cancer (HNC) patients undergoing treatment and in the first year of survivorship, however there is no data suggesting the most effective interventions in this population. We hypothesize that patients would benefit from a more rigorous approach to identifying and addressing their needs related to these domains. The objectives of this study were to 1) determine the incidence rates of depression and anxiety and evaluate QOL both before and at various time points following completion of treatment in HNC patients, and 2) measure patient interest in several proposed interventions.

Materials/Methods: This ongoing study enrolls Stage III and IV HNC patients undergoing definitive treatment with surgery, radiation, and/or chemotherapy at a single health network. QOL, anxiety, and depression were assessed using validated survey instruments, including the EORTC QLQ C-30 and the supplemental head and neck section EORTC QLQ-H&N35, the GAD-7, and the PHQ-9. Each of these surveys were administered at set intervals before, during and after therapy. We report preliminary data from patients who have completed their treatment.

Results: Seven patients who completed definitive therapy were identified. Compared with pre-treatment levels, patients had worse scores in multiple QOL measures at two-weeks post-treatment, including global QOL, fatigue, appetite loss, swallowing, taste, mouth opening, dry mouth, sticky saliva, social eating and contact, and sexuality. Physical, role and social functioning scores all decreased at two weeks post-treatment. Percentage of patients with at least "mild" anxiety decreased from 57.1% pre-treatment to 42.9% at two weeks post-treatment, while percentage of patients with at least "mild" depression increased from 42.9% to 85.7%. At pre-treatment visits, two out of seven patients indicated interest in the following interventions: group counseling, support group, and physical therapy/rehab. One patient who initially expressed no desire in any intervention reported interest in acupuncture, Reike, and massage therapy at two weeks post-treatment.

Conclusion: Preliminary results indicate that HNC patients suffer substantial derangements in multiple QOL measures at two weeks post-treatment. Incidence of depression may increase following treatment while incidence of anxiety may decrease. Patients expressed interest in several interventions, including group counseling, support group, and physical therapy. In addition, patients' interest in these interventions can change over the course of treatment. Data collected from future follow-up visits will help better characterize patient needs as time from completion of therapy lengthens, enabling the development of an evidence-based program to support HNC patients from diagnosis through survivorship.

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BMI trends of overweight/obese head and neck cancer patients who received definitive non-operative treatment

B.A. Harr,[1] J. Bodmann,[2] C.A. Reddy,[1] M. Fox,[3] J. Ferrini,[4] D. Ives,[2] L. Schwartzman,[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, [4]Cleveland Clinic, Independence, OH, United States

Purpose/Objective(s): Head and neck cancer (HNC) radiation treatment has improved significantly in the past decade with patients living longer with fewer long-term toxicities. Many patients have near normal swallowing and eating habits post-treatment. In this study, we explore BMI trends and the relationship between acute weight loss during definitive non-operative treatment and overall weight loss.

Materials/Methods: A random sample of HNC patients were identified from an IRB approved database who were treated using IMRT with and without chemotherapy between 2008 and 2017. Patient and treatment characteristics as well as BMI were coded at specific time intervals (pre-treatment or baseline, 3 months post-treatment completion [MPTC], and 24 MPTC). The CDC's BMI classifications of normal (18.5-25),

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BMI Classification change	Baseline to 3 MPTC (n=145)	3 to 24 MPTC (n=114)	Baseline to 24 MPTC (n=118)
Decrease	106 (73.1%)	2 (1.8%)	46 (39%)
No change	39 (26.9)	64 (56.1)	64 (54.2)
Increase	0 (0)	48 (42.1)	8 (6.8)

overweight (25-30), obese class 1 (30-35), obese class 2 (35-40), and obese class 3 (>40) were used to further classify BMI at each time point.

Results: 205 patients were analyzed; 56 (27.3%) were excluded from further analysis due to a normal BMI at baseline. The remaining were classified as overweight (85, 57%) or obese (64, 43%); obesity was further categorized as class 1 (39, 26.2%), class 2 (17, 11.4%), and class 3 (8, 5.4%). All received definitive non-operative therapy and had no evidence of disease at 24 MPTC. 78% were male, 65% received concurrent chemotherapy, and a majority of patients had an oropharynx primary (53%). Weight loss stabilized at 3 MPTC with a mean BMI percent decrease of 14.4; 56 (38.6%) patients achieved a normal BMI. However, only a fraction of this weight loss was sustained at 24 MPTC. On average, patients lost 6.03% BMI with only 25 (21.1%) having a normal BMI classification. The table below further illustrates BMI classification trends across time.

Conclusion: In the era of IMRT, HNC patients have fewer eating and swallowing late and long-term toxicities from definitive non-operative therapy. While patients still acutely lose weight during treatment, some patients are more likely to regain weight overtime potentially increasing their risk for chronic conditions. Targeted interventions to promote sustained weight loss should be considered post-treatment completion.

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Immediate dental implants in fibula free flaps to reconstruct the mandible: A pilot study of the short-term effects on radiotherapy for patients with head and neck cancer

D. Gelblum,[1] M.L. Sandoval,[2] E. Matros,[3] J.A. Nelson,[3] R.J. Allen,[3] and E.B. Rosen[4]; *[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, [2]New York Medical College, Valhalla, NY, [3]Memorial Sloan Kettering, New York, NY, [4]Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): The current pilot study aims to report short-term experience with post-operative radiation therapy delivery in patients in fibula free flaps reconstruction with immediate dental implants as compared to a historical cohort of patients with fibula free flap reconstructions without dental implants.

Materials/Methods: A retrospective review of patients who underwent segmental mandibulectomy for cancer treatment, reconstruction with fibula free flaps, and adjuvant radiotherapy with (n=10) and without immediate dental implants (n=10) at a tertiary cancer center from 2015 to 2018 was performed (IRB #17-271). Incidence of post-operative complications, time to initiation of radiation therapy, development of acute toxicity, and patient reported outcome data were recorded. The radiation plans were evaluated to identify the mean and maximum doses received by the mandible and oral cavity as well as the locations of radiation global hot spots.

Results: A retrospective review of patients who underwent segmental mandibulectomy for cancer treatment, reconstruction with fibula free flaps, and adjuvant radiotherapy with (n=10) and without immediate dental implants (n=10) at a tertiary cancer center from 2015 to 2018 was performed (IRB #17-271). Incidence of post-operative complications, time to initiation of radiation therapy, development of acute toxicity, and patient reported outcome data were recorded. The radiation plans were evaluated to identify the mean and maximum doses received by the mandible and oral cavity as well as the locations of radiation global hot spots.

Conclusion: The current study suggests that the presence of dental implants does not increase the risk of complications during post-operative radiation treatment. Implants do not alter radiation dosimetry and do appear to positively impact patient quality of life. Although longer follow-up is needed, based on this preliminary experience, cancer patients should be offered this type of reconstruction.

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Evaluating Oropharyngeal Cancer Patients' Outcomes Across Different Treatment Modalities

R. Naithani,[1] B. Elgohari,[2] H. Elhalawani,[2] A.S. Mohamed,[2] and C.D. Fuller[3]; *[1]Campbell University School of Medicine, Lillington, NC, [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [3]University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): Oropharyngeal cancers of the head and neck affect all ethnicities and age groups and account for significant mortality and therapy-related side-effects with over 50,000 new cases diagnosed each year in the United States alone. Despite the great amount of data, the current risk prediction algorithm is built on non-spatial information and heavily relies on cancer staging. Our data reveals heterogeneity in response to different therapy outcomes that can be detrimental to treatment. Specifically, in head and neck cancers, proximity of tumor to organs-at-risk increases radiation dose exposure which leads to toxicities. We hypothesized that with the following measures, significant treatment toxicity factors will be identified and thus improve survivorship.

Materials/Methods: We collected retrospective data on 147 randomized patients based on an approved IRB protocol that supports patient-specific outcomes based on demographics, toxicity, and complex imaging post-treatment. Approximately 90% were Caucasian males in age range of 43 to 86 years old with 57% being HPV positive and at stage 3 cancer diagnosis; 61% received concurrent chemotherapy and radiation. After obtaining EPIC consent, we extracted diagnostic CT contrast and exported the images to Velocity software so that primary tumor and nodal disease could be contoured. The data was collected by medical students and revised by a Radiation Oncologist for accuracy. A topological map with tumor and organs-at-risk approximated dose distribution and dose-volume intensity. We used survival curves to detect significant factors and then hazard ratios further refined and identified the most significant of those factors that contribute to overall survival, local tumor control, and distant metastasis.

Results: Kaplan-meier survival curves demonstrated HPV status ($P<0.0001$), requirement of feeding tube during treatment ($P<0.0001$), being Caucasian ($P=0.0053$), and Tumor stage ($P=0.0118$) were significant. Loco-regional control was also significantly affected by Caucasian race ($P=0.0244$), HPV status ($P=0.0126$), T stage ($P=0.0283$), and feeding tube requirement ($P=0.0001$). Aspiration rate post-treatment was also significantly associated with distant metastasis ($P=0.0055$). Multivariable statistics (Cox model) demonstrated that feeding tube placement ($p=0.0005$) and HPV status ($0=0.00372$) during treatment significantly affected survival endpoints.

Conclusion: The most significant survival endpoints during treatment regimen were requirement of feeding tube and HPV status. There was a higher risk of mortality when patients required feeding tube but a higher risk of survival when they were HPV positive. Requirement of feeding tube also worsened loco-regional disease control. Further studies will expand the database and introspect the time length of the need for a feeding tube and its impact on mortality.

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Outcomes following Proton Therapy for Squamous Cell Carcinoma of the Larynx

N. Ausat,[1] D.I. Rosenthal,[2] G.B. Gunn,[3] R. Ye,[4] A.S. Garden,[1] W.H. Morrison,[5] C.D. Fuller,[1] J. Phan,[5] J.P. Reddy,[1] A.C. Moreno,[5] H. Bahig,[6] E.M. Sturgis,[7] B.S. Glisson,[8] and S.J. Frank[1]; *[1]University of Texas MD Anderson Cancer Center, Houston, TX, [2]The University of Texas MD Anderson Cancer Center Institution *, Houston, TX, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]Department of Biostatistics, 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]Centre Hospitalier de l'Universite de Montreal (CHUM), Montreal, QC, Canada, [7]MD Anderson Cancer Center, Houston, TX, [8]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose/Objective(s): To assess the outcomes and toxicities for squamous cell carcinoma (SCC) of the larynx treated with proton therapy.

Materials/Methods: Twenty-two laryngeal cancer patients on two prospective trials were treated between February 2012 and July 2018. Eight patients were excluded from analysis due to the following reasons: prior history of radiation to the head and neck (n=3); disease recurrence (n=3); not treated with proton radiation (n=1); and non-SCC histology (adenoid cystic carcinoma) (n=1). Patients were treated with a total dose ranging from 60Gy to 70Gy (RBE) over 28 to 35 fractions, with the dose per fraction ranging from 2.00 to 2.25Gy (RBE). The distribution of time-to-event endpoints, overall survival, local-regional control, disease free survival, and cumulative incidence rate were estimated using the Kaplan-Meier method.

Results: Fourteen patients met the inclusion criteria. The mean age at diagnosis was 69 years with a median of 70 years. 85.7% of patients were male and 14.3% were female. Using AJCC 8th edition staging 28.6% had Stage IV disease, 35.7% had Stage II disease, and 35.7% had Stage I disease. 64.2% of patients had a history of smoking, and 28.6% had a gastrostomy tube inserted during treatment. Six of the 14 patients were treated with chemoradiation therapy. The median follow-up time was 1.9 years, with a range of 0.4 to 4.7 years. There were a total of 73 acute toxicities reported: 54.8% were grade 1, 32.9% were grade 2, and 12.3% were grade 3 toxicities. These reported acute toxicities included aspiration, dehydration, dysgeusia, dysphagia, fatigue, nausea, oral mucositis, oral pain, pharyngeal mucositis, and radiation dermatitis. The cumulative incidence rate for chronic grade 3 toxicities at both 1 and 2 years was 8.3%. Seven patients experienced a maximum toxicity of grade 3 which were aspiration, dysphagia, fatigue, nausea, oral mucositis, pain, and radiation dermatitis. There were no grade 4 or 5 toxicities reported during treatment and follow-up. Overall survival (OS), local-regional control (LRC), and disease free survival (DFS) at 2 years were 92.3%, 91.7%, and 84.6%. Of the three deaths reported, two were for unrelated or unknown causes and one involved a local recurrence. There were no regional or distant recurrences reported.

Conclusion: Proton therapy for SCC of the larynx demonstrates a high rate of overall survival, local-regional control, and disease-free survival with a low toxicity profile.

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Mitigating Radiation Induced Xerostomia with Nigella Sativa Oil

Y.M. Alhiyari,[1] K. Kwan,[2] B. Cameron,[3] and M. St. John[4]; *[1]Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [2]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [3]University of Southern California, Los Angeles, CA, [4]Ronald Reagan-UCLA Medical Center, Dept of Head and Neck Surgery, Los Angeles, CA*

Purpose/Objective(s): Xerostomia, dry mouth, is one of the most common complications during and after radiotherapy for head and neck cancers due to terminal damage to the salivary glands. Xerostomia often contributes to both minor and serious health problems, which severely decrease quality of life for patients. Current methods of management and preventative measures of xerostomia have shown little success and effectiveness. Like all tissues, salivary glands are maintained by a small group of cells, stem/progenitor cells, with the capacity to repopulate and differentiate into the needed cell types upon tissue injury. The objective of this study is to determine if protecting salivary gland stem/progenitor cells from radiation damage will mitigate the development of xerostomia by allowing for tissue repair after radiation induced damage.

Materials/Methods: Nigella Sativa Oil (NSO), contains the active ingredient Thymoquinone (TQ), which in previous studies has been shown to function as a radioprotector with very limited biological toxicity. To identify the optimal treatment regimen, oral gavage of NSO was utilized on 20 C3H/HeJ male mice. Five groups were as follows: no radiation, no NSO "control group"; 15 gy radiation to the head only; NSO (2.5 ul/g) 3 days before radiation; NSO 30 minutes before radiation and 15 days after; NSO 3 days before radiation and 15 days after. Prior to sacrifice, salivary production was measured via pilocarpine stimulation. Mice were sacrificed 15 days after initial radiation treatment. Immunohistochemistry (IHC) was performed for inflammatory markers (Cox-2, Nf-kB, and TNF-α) and Kr5+ duct progenitor cells. Once the ideal treatment regimen was identified, pilocarpine stimulation and IHC were performed at 3 days and 60 day timepoints.

Results: NSO showed a dose-dependent response. Mice who received the highest dosage of NSO expressed less oral inflammation, more Kr5+ cells, and more salivary production compared to all other groups.

Conclusion: Preliminary data suggests that administering NSO orally had a radioprotective effect and potentially, this could be further explored in patients. Future work includes utilizing TQ, the active ingredient in NSO, through a localized delivery instead of a systemic approach.

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Radiation therapy alters pharyngeal mobility and strength during deglutition in patients with head and neck cancer

K. Crawford,[1] M. Armaneous,[2] R. Leonard,[3] K. Linnemeyer,[4] A. Vahabzadeh-Hagh,[1] R.K. Orosco,[5] and L. Blumenfeld[4]; *[1]University of California San Diego, San Diego, CA, [2]Touro University Nevada College of Osteopathic Medicine, Henderson, NV, [3]University of California Davis, Davis, CA, [4]UC San Diego, Moores Cancer Center, La Jolla, CA, [5]University of California, San Diego, La Jolla, CA*

Purpose/Objective(s): Radiation therapy in the setting of head and neck cancer can cause significant damage to tongue, pharyngeal and laryngeal mobility and strength. The aspiration rate following chemoradiation for HNSCC nears 68%, and patients routinely become temporarily or permanently dependent on gastrostomy tube feeding. The functional mechanisms by which radiation affects deglutition remain poorly characterized. In this study, we applied quantitative analysis to determine if the mobility and strength of pharyngeal structures including the pharyngeal constrictors, hyoid, and larynx were impaired in patients who had undergone radiation therapy as compared to age-matched healthy patients.

Materials/Methods: Patients with head and neck malignancies who had undergone both radiation and post-treatment quantitative video fluoroscopic swallow study (VFSS) analysis were identified in accordance with IRB approval. Retrospective chart review was performed applying the Mann-Whitney U test to assess differences between swallow metrics in treated and age-matched normal patients.

Results: Twenty-nine patients met inclusion criteria; of these, 23 were male and 6 were female. Of the primary sites, nineteen were oropharyngeal, four were oral cavity, four were laryngeal, one was thyroid cancer, and one primary site was unknown. The mobility and strength of pharyngeal structures were found to be statistically significantly different between healthy patients and post-radiation therapy patients in the following swallow metrics: pharyngeal constriction ratio ($p = 0.005$), hyopharyngeal transit time ($p < 0.001$), total pharyngeal transit time ($p < 0.001$), hyolaryngeal elevation ($p < 0.001$), hyoid motion ($p < 0.001$), maximal pharyngoesopheageal sphincter opening ($p < 0.001$). No difference was observed in oral cavity transit time ($p = 0.212$).

Conclusion: Radiation therapy significantly alters mobility and strength of pharyngeal, hyoid and laryngeal structures during deglutition in patients with head and neck cancer.

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Treatment Related Risk Factors for Percutaneous Endoscopic Gastrostomy (PEG) Tube Placement in Locally Advanced Head and Neck Squamous Cell Carcinoma (LA-HNSCC)

H.J. No,[1] M.M. Tam,[2] and P. Wu[3]; *[1]Flushing Hospital Medical Center, Flushing, NY, [2]NYU Langone Health, Department of Radiation Oncology, New York, NY, [3]Holy Name Medical Center, Teaneck, NJ*

Purpose/Objective(s): Definitive treatment for LA-HNSCC varies by anatomic subsite and may include surgery, chemotherapy, and/or radiation therapy (RT). LA-HNSCC patients treated with RT are typically at risk for PEG placement due to symptomatic dehydration or malnutrition as a direct result of therapy. However, it is unclear whether therapies preceding or concurrent with RT are associated with PEG tube placement. Therefore our objective was to assess treatment-related risk factors leading to reactive PEG tube placement in patients undergoing RT.

Materials/Methods: 2840 consecutive patients with HNSCC treated with curative-intent with RT at a single institution from 2003 to 2013 were screened. Amongst those, 215 were selected for inclusion in The Cancer Imaging Atlas (TCIA) due to the availability of CT imaging before and after RT. All patient demographics, pathology, and complete surgical, systemic, and radiation courses were queried from the database. PEG tube placement was performed per clinician judgment during treatment and was not offered prophylactically. Fisher's exact test and logistic regression were used to identify associations with clinical variables and reactive placement of a PEG tube.

Results: Among the 215 patients who were categorized in the TCIA database, 206 exhibited LA-HNSCC. Of these, 176 (85%) were male with a median age of 57 years (range 24-91) and median BMI of 28 (range 17-49). There were 148 Oropharynx (72%) cases, 24 (12%) Larynx, 12 (6%) Hypopharynx, 7 (3%) Oral Cavity, 6 (3%) Nasopharynx, 6 (3%) Cancer of Unknown Primary, and 3 (1%) Facial Sinus cases. All patients received RT, 112 (54%) received concurrent chemoradiation. Prior to RT, 73 (35%) had induction chemotherapy, 19 (9%) had surgery, and 5 (2%) had both. PEG tubes were reactively placed in 109 patients (53%). Patients requiring PEG tube placement, versus those who did not, were treated more often with concurrent chemoradiation (67% vs 51%, $p=0.04$), received radiation doses of 70Gy or greater (79% vs 58%, $p<0.01$), and had no prior surgery or chemotherapy (62% vs 42%, $p=0.01$). Additionally, reactive PEG tube placement was seen less often in patients who received induction chemotherapy (26% vs. 46%, $p=0.01$). There were no significant associations of PEG use by anatomic subsite, stage, or previous surgery.

Conclusion: Patients with LA-HNSCC treated with concurrent chemoradiation and doses of 70Gy or greater are at elevated risk for reactive PEG tube placement. Patients treated with prior surgery and/or induction chemotherapy do not appear to be at higher risk for reactive PEG tube placement.

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Some Weight Loss During Radiation Therapy for Head and Neck Cancer Portends Better Prognosis: Single Institution Review and Matched Pair Analysis

H.R. Han,[1] G.M. Hermann,[2] S.J. Ma,[2] A.J. Iovoli,[1] K.E. Wooten,[2] H. Arshad,[2] V. Gupta,[3] R. Mcspadden,[2] M. Kuriakose,[2] W.L. Hicks,[2] J.M. Chan,[2] M.E. Platek,[4] and A.K. Singh[2]; *[1]Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, [3]Roswell Park Cancer Institute, Buffalo, NY, [4]Buffalo State College, Buffalo, NY*

Purpose/Objective(s): One frequent consequence of definitive or post-operative radiation therapy (RT) for head and neck cancer (HNC) is weight loss (WL). HNC patients reportedly lose about 9% of their body weight during treatment, regardless of pretreatment WL and nutritional support. We investigated whether significant WL during RT has association with overall survival (OS).

Materials/Methods: We retrospectively reviewed weight during RT in 857 HNC patients treated at Roswell Park Comprehensive Cancer Center with definitive or post-operative RT between 2003 and 2017. Patients were categorized into quartiles of WL, with patients with weight gain categorized as zero or lowest weight loss quartile. Kaplan-Meier analysis was used to estimate overall survival (OS) between quartiles of weight loss. Logistic regression analysis was performed to identify predictive factors or weight loss.

Results: Patients with least or no weight loss are associated with worst OS whereas patients with most weight loss are associated with best OS. On univariate analysis, complete or partial treatment response ($p<0.0001$), induction cisplatin chemotherapy ($p=0.0123$), artificial nutrition support ($p=0.0301$), diabetes mellitus ($p=0.0188$), stroke ($p=0.0265$), and

admission for altered mental status (p=0.0398) were associated with increased weight loss.

Conclusion: Surprisingly, this study reports that patients with the least weight loss actually have worse OS. Matched pair analysis is ongoing.

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Carotid Sparing Conformal Radiotherapy for Early Larynx Cancer

N.S. Kalman,[1] J. Laher,[2] and B. Zholendz[2]; [1]*Miami Cancer Intitute, Miami, FL,* [2]*Miami Cancer Institute, Miami, FL*

Purpose/Objective(s): Parallel opposed lateral (POL) portals have been adopted as the mainstay radiation therapy technique for early-stage carcinoma of the glottis. Although the use of POL has been associated with excellent control rates and tolerability, the partial inclusion of carotid arteries (CAs) in the high dose regions of the fields has been shown to lead to an increased long-term risk of carotid stenosis and hemorrhagic stroke. Many researchers have proposed the utilization of three-dimension conformal therapy (3DCRT) or Intensity-modulated radiation therapy (IMRT) as viable carotid-sparing techniques via reductions to the mean and maximum doses received by the carotid arteries during a course of therapy. This study seeks to examine whether there are any significant dosimetric advantages of utilizing IMRT or 3DCRT techniques over POL fields for the purposes of carotid artery sparing and whether these advantages, if any, are cost-effective for clinical implementation.

Materials/Methods: Using anonymized patient scans for five cases, clinical target volumes (CTVs) and planning target volumes (PTVs) for radiotherapy were generated. Prescription dose was 63 Gy in 28 fractions. POL fields, 3DCRT with four or five coplanar fields, and IMRT plans were generated to meet standard coverage goals for CTV and PTV. Carotid arteries were contoured in all cases. Mean dose to the carotid arteries were compared between treatment modalities, as were estimated treatment charges

Results: Mean carotid dose was lower with 3DCRT and IMRT plans relative to POL field plans. Expected treatment charges were lower with 3DCRT and POL fields relative to IMRT plans.

Conclusion: Reductions in mean carotid artery dose can be achieved with both 3DCRT and IMRT plans. Use of 3DCRT plans may offer similar reduction in the risk of carotid artery stenosis with lower estimated charges than with IMRT.

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Does Integration of Advanced Practice Provider in Radiation Oncology Influence UCC Visit Rate of Head and Neck Cancer Patients Treated with Definitive Radiation Therapy?

Y. Wu,[1] S. Kitpanit,[2,3] A. Lee,[3] K. Schwed,[1] and N. Lee[1]; [1]*Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand,* [3]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Purpose/Objective(s): Acute toxicities as a result of definitive radiation therapy (RT) +/- chemotherapy in head and neck cancer are severe and significant supportive care is needed for these patients. In order to complete the prescribed curative intent combined modality treatment, urgent care center (UCC) visits are common during treatment and may be needed even up to 8 weeks after the conclusion of all therapies resulting in substantial financial burden. Advanced Practice Practitioner (APP), whether a Nurse Practitioner or a Physician Assistant, who is integrated into the radiation oncology practice can be extremely valuable for these patients. They independently provide expert symptom management to ensure that head and neck cancer patients' urgent needs are met both during treatments and even for weeks post treatments. The purpose of this study is to evaluate the added benefit of APPs to a busy radiation oncology practice by evaluating whether these interventions decrease patient UCC visit rate.

Materials/Methods: Medical records of head and neck cancer patients undergoing definitive radiation therapy from July 1, 2016 to June 30, 2017 and July 1, 2018 to June 30, 2019 at a single institution treated by one head and neck radiation oncologist were reviewed. The first period was without APP integration and the latter period was with the APP integrated into the service. UCC visit was defined as a visit taking place between the first radiation treatment until 8 weeks after treatment completion. UCC visit rate was defined as the number of UCC visits per patient per year undergoing definitive radiation therapy. This rate was obtained and compared for the two aforementioned treatment periods.

Results: Before integration of the APP role, 59 patients were undergoing definitive radiation therapy from July 1, 2016 to June 30, 2017 and the UCC visit rate was 100%. In comparison, 60 patients were undergoing definitive radiation therapy from July 1, 2018 to June 30, 2019 and the UCC visit rate was 76.7%.

Conclusion: Successful integration of the Advanced Practice Provider in the head and neck radiation oncology practice addresses urgent needs that occur during treatments and provide close follow-up to patients within weeks after radiation therapy. Our data has shown that the intervention of APP has decreased UCC visit rate through close outpatient monitoring. Data collection is ongoing as to the causes and high risk timeframe of head and neck cancer patients' UCC visits which will guide the individualized APP follow-up plan and further decrease UCC visit rate of head and neck cancer patients undergoing definitive radiation therapy.

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Quality of Life and pain evolvement after TORS for OPSCC

S.I. Scott,[1] A.K.Ø. Madsen,[1] H. Kehlet,[2] and C.V. Buchwald[3]; [1]*Department of Otorhinolaryngology, Head & Neck Surgery and Audiology at Copenhagen University Hospital, Rigshospitalet, Denmark, Copenhagen, Denmark,* [2]*Section for Surgical Pathophysiology at Copenhagen University Hospital, Rigshospitalet, Denmark, Copenhagen, Denmark,* [3]*Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Purpose/Objective(s): The aim of this ongoing study was to examine Quality of Life (QoL) and pain in the first three months after trans-oral robotic surgery (TORS). Results will be available in November 2019. With the rising incidence of Human Papilloma Virus (HPV) induced oropharyngeal squamous cell carcinoma (OPSCC) this cancer has become the most frequently diagnosed head and neck cancer world-wide. Currently there are two main treatment options: radiotherapy (with or without chemotherapy) and TORS. TORS is still a relatively new treatment modality (approved by the FDA in 2000) and more research into outcomes, particularly functional and QoL outcomes is needed. We hypothesize that the QoL assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Head and Neck-35 (QLQ-H&N35) and QoL Questionnaire core 30 (QLQ-30) will decline less than the minimal clinically important difference when comparing baseline scores with scores at 3-months follow-up. The questionnaires were used together as they complement each other.

Materials/Methods: This was a prospective observational study. TNM stage (according to UICC 7) was limited to: T-stage <3, N-stage <2 without signs of extra-capsular extension and M-stage 0. Patients with significant trismus were excluded. Our primary endpoints were changes in EORTC QLQ-H&N35 and QLQ-30 from baseline to 3-months follow-up. Secondary endpoint was pain evolvement from baseline until the participants no longer needed regular analgesia. Pain intensity was recorded twice a day during activity and rest using a visual analog scale (VAS). Changes in EORTC QLQ-H&N35 as well as QLQ-30 were compared using paired t-test for each of the subscales (e.g. pain, swallowing and fatigue). Pain evolvement was explored analyzing bi-daily visual analog scale scores during activity and at rest.
Results: Thirty-one consecutive patients were enrolled in the study from April 2017 to September 2018. Patient demographics: male to female ratio was 22:9. TNM-stage: 14 T1, 16 T2, 15 N0 and 15 N1. Five patients were advised to have adjuvant radiotherapy (with or without concomitant chemotherapy) -due to extracapsular extension, peri-nodal spread and one non-radical T-site resection (upstaged to T4 at time of surgery). One patient declined.
Conclusion: If accepted the final results will be presented as a poster at the Multidisciplinary Head & Neck Cancer Symposium in 2020.
Author Disclosure: **S.I. Scott**: Research Grant; Candys Foundation. **A.K. Madsen**: None. **H. Kehlet**: None. **C. Buchwald**: None.

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Quality of Life and Functional Outcomes after Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma

S.I. Scott,[1] A.K.Ø. Madsen,[1] N. Rubek,[1] I. Wessel,[1] B. Charabi,[1] H. Kehlet,[2] and C.V. Buchwald[1]; [1]*Department of Otorhinolaryngology, Head & Neck Surgery and Audiology at Copenhagen University Hospital, Rigshospitalet, Denmark, Copenhagen, Denmark,* [2]*Section for Surgical Pathophysiology at Copenhagen University Hospital, Rigshospitalet, Denmark, Copenhagen, Denmark*

Purpose/Objective(s): The aim of this ongoing study is to investigate swallowing-related QoL and functional outcomes before and one year after TORS for OPSCC. Results will be available in November 2019. We hypothesized that swallowing-related QoL and swallowing function would initially decline after TORS and then return to a marginally sub-normal level one year after treatment, while saliva flow rates would be largely unaffected. Oropharyngeal squamous cell carcinoma (OPSCC) is the most frequently diagnosed head & neck cancer with an increasing proportion of HPV positive cancers. HPV-positive OPSCC is associated with a good prognosis and a 5-year survival of 80% which means that treatment options are not only scrutinized with regards to oncological but also functional and QoL outcomes. Historically OPSCC has predominantly been treated with radiotherapy. However with the FDA approval of the da Vinci surgical robot in 2000 transoral robotic surgery (TORS) with neck dissection has been introduced in many centers as an alternative to radiotherapy. Both treatment modalities can cause dysphagia, which has been associated with a worsened quality of life (QoL). As TORS is still a relatively new treatment option few studies on QoL and practically no studies on functional outcomes have been performed. However, it has been hypothesized from observational studies that TORS can be gentler in terms of both, calling for detailed functional outcome studies.
Materials/Methods: A prospective observational study. TNM stage (according to UICC 7) was limited to: T-stage <3, N-stage <2 without signs of extra capsular extension and M-stage 0. Patient with significant trismus were excluded. MD Anderson Dysphagia Index (MDADI) questionnaire, modified barium swallowing study and saliva flow rate tests were completed at baseline and 3- and 12-months follow-up. MDADI, MBSS and saliva flow rate results were compared separately at each time-point using repeated measures ANOVA. The trends between the different outcome measures were also examined.
Results: From April 2017-September 2018, a total of 31 patients (22 men, 9 women) with OPSCC were enrolled. Tumor location: 22 palatine tonsil carcinomas, 6 tongue base and 3 soft palate carcinomas. After final pathology five patients were advised to have adjuvant radiotherapy due to extracapsular extension, perinodal spread and one non-radical T-site resection (upstaged to T4 at time of surgery). One patient declined adjuvant radiotherapy.
Conclusion: To the best of our knowledge this is the first study examining swallowing function (MBSS) and saliva flow rates before and after TORS. Final results will be presented at the 2020 Multidisciplinary Head and Neck Cancer Symposium.
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Patient Reported Outcomes, Oral Health, Taste and Dietary Impact During and Following Head and Neck Cancer Therapy

J. Epstein,[1] D. Villines,[2] G. Epstein,[3] and G. Smutzer[4]; [1]*Cedars Sinai Medical Center, Los Angeles, CA, United States,* [2]*Advocate Healthcare, Chicago, IL,* [3]*Private Practice, Los Angeles, CA,* [4]*Temple University, Philadelphia, PA*

Purpose/Objective(s): Patient reported impact of oral function and toxicity associated with head and neck cancer (HNC) and cancer therapy are presented along with clinical oral findings in diet and body weight changes during and following cancer therapy.
Materials/Methods: Patients with HNC were evaluated during and following radiation therapy with/without chemotherapy. Oral intake and oral conditions affecting taste and diet were assessed. Patients completed the Vanderbilt Head and Neck Symptom Survey (VHNSS) for symptom report. Clinical examination, including taste and smell function, were assessed in comparison with patient reports as recorded in the VHNSS. Ten patients were evaluated 4-6 weeks after starting HNC treatment and following treatment. Data collected during treatment were defined as in the acute treatment group (N = 6), and following treatment in the post-treatment group (N = 8). WIRB approved informed consent was completed by all patients.
Results: Weight decreased of 5% during treatment and 12% at follow-up. Most patients reported that appetite declined and was reported as poor/very poor by 16.7% in the acute group, and by 50% of the post-treatment group. Prior to treatment, eating was rated as very pleasant/ pleasant by all patients. However, 66% of patients reported unpleasant/ very unpleasant eating in the acute group and 28.6% in the post-treatment group. A decrease in taste function was reported by 50% of acute patients, and 62.5% of post patients. Decreased food intake and altered food choice were reported as severe in 50% of patients. Dry mouth was reported by 50.0% of the post-treatment group but was not reported in the acute group. The spicy perception of capsaicin was reported to have severe impact for 80% of acute and 70% of post-treatment patients. Bitter taste affected oral diet either often or all the time in 33% of acute and in 83% of post patients. The following taste impacts were experienced by 50-60% during treatment but reduced to between 0-28% in post treatment: bland, umami (savory), sweet, metallic and fat taste.
Conclusion: Oral complications including mucositis and saliva affect taste change throughout cancer treatment and in the first two years of survivorship. While prior studies are based primarily on patient report, this report evaluates clinical oral functions including taste and smell testing, saliva production in addition to patient report. This study provides a basis for management of oral status and diet for the HNC patient. The primary taste quality most affected was umami. Results from this study show a decreased chemosensory response during both HNC treatment and patient follow-up indicating the importance of nutrition in sustaining patient health following HNC treatment.

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Updated outcomes of split course accelerated hypofractionated radiotherapy for the treatment of head and neck cancers

C. Domb,[1] T. Smile,[2] C.A. Reddy,[2] N.P. Joshi,[2] N.M. Woody,[2] D. Chute,[3] B.B. Burkey,[4] J. Ku,[4] E. Lamarre,[4] R.R. Lorenz,[4] B. Prendes,[4] J. Scharpf,[4] J.L. Geiger,[5] D.J. Adelstein,[5] S. Koyfman,[2] and C.W. Fleming[2];
[1]Cleveland Clinic, Department of Radiation Oncology, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Department of Otolaryngology, Head and Neck Institute, Cleveland Clinic, Cleveland, OH, [5]Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Purpose/Objective(s): Head and neck cancers are prone to locoregional recurrence (LRR) and merit intensive locoregional therapy, often involving 6 to 7 weeks of radiotherapy (RT). Many patients are unable to tolerate such extended courses of RT. Split course accelerated hypofractionated RT (SCAHRT) offers the potential for durable control with the ability to reduce treatment intensity based on patient tolerance. In this study we aim to update our experience using this technique.

Materials/Methods: We retrospectively reviewed patients from an IRB-approved single institution database of patients treated for primary head and neck cancer between 1999 and 2019. Patients were included if they received an initial course of RT delivering 20 to 40 Gray (Gy) and were considered for a split course treatment. For patients who underwent a second course of RT, competing risks regression was used to assess for factors associated with LRR. Overall survival (OS) was estimated with Kaplan-Meier methods.

Results: 98 patients were included with a median follow up of 5.2 months. Median age was 72.5 years. 62% were male and 31% were active smokers. ECOG performance status was 0 for 13%, 1 for 56%, and $\geq$2 for 31%. The most common primary tumor sites were larynx (25%), hypopharynx (18%), oral cavity (16%), and oropharynx (15%). 81% had stage IV disease and 27% had distant metastases at time of RT. 18% had recurrent disease and 9% had previously undergone RT to the head and neck. 81% of tumors were squamous cell carcinoma, of which 20% were HPV associated. 18% were treated post-operatively and 6% received concurrent chemotherapy. 75% of patients underwent a second course of radiotherapy. The most common fractionation was 30 Gy in 10 fractions for both first and second courses. Intensity modulated RT was utilized in 48% of first courses and 51% of second. Median interval between courses was 36 days. In those undergoing a second course of RT, median OS was 9.7 months, with 43.6% alive at 12 months and 24.8% at 24 months; cumulative incidence of LRR at 6, 12, and 24 months were 17.0%, 23.1%, and 29.4%, respectively. No factors were significantly associated with LRR. 21.9% experienced distant progression. Among the entire cohort, rates of acute grade $\geq$3 dysphagia, mucositis, dermatitis, and xerostomia were 22%, 6%, 1%, and 0%, respectively. Feeding tube and tracheostomy rates within 90 days of treatment were 46% and 14%, respectively. 74 patients had died at last follow up, of which 38% were due to head and neck cancer, 15% due to comorbidities, and 43% due to unknown causes.

Conclusion: Despite favorable disease control after SCAHRT, this population of elderly and poor performance status patients remained at significant risk of death from both cancer-related and other causes. SCAHRT offers an attractive treatment paradigm to tailor intensity based on tolerance, while still maintaining efficacy in those unfit for standard full course RT.

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A dosimetric comparison of proton versus photon irradiation for pediatric glomus tumor

G. Vidal,[1] J. Arntzen,[1] and C. Henson[2]; *[1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]University of Oklahoma Health Science Center, Stephenson Cancer Center, Department of Radiation Oncology, Oklahoma City, OK*

Purpose/Objective(s): We seek to compare dose parameters using proton and photon beam planning for pediatric skull base paraganglioma. We specifically seek to compare normal tissue doses. When treating these tumors with radiotherapy, the goal is to achieve local control with the least amount of toxicity to surrounding tissues. This goal is even more important in pediatric populations due to the much greater risk of secondary malignancies compared to older adult patients, as well as longer time over which to develop and deal with late treatment sequelae.

Materials/Methods: For this sixteen-year old patient, magnetic resonance imaging (MRI) of the head and neck region demonstrated a cystic mass near the left jugular foramen measuring 3.6 cm x 2.2 cm x 4.3 cm mass. The mass was noted to occupy the left superior parapharyngeal space. Computed tomography (CT) of the neck with and without contrast was ordered soon after and confirmed the cystic and necrotic mass. Contrast enhancement allowed for better visualization revealing a 3.1 cm x 2.3 cm x 4.6 (AP x W x CC) thick-walled lesion extending from the jugular foramen to C1-C2 level. Anterior and medial displacement of the left internal carotid artery was also noted along with significant compression of the left internal jugular vein. Both a proton and a photon arc plan were generated. Due to the patient's young age, as well as superior dosimetric profile, the decision was made to treat the patient with the protons. The patient was treated with a dose of 5000 CGE in 25 fractions.

Results: The table below compares mean and maximum doses to various normal tissues of interest. Most notable are the lower doses to ipsilateral (left) cochlea, right-sided structures, and expanded cord with the proton plan. The mean oral cavity dose was also significantly lower.

Conclusion: Dosimetric superiority of protons in the skull base region is largely due to the absence of dose deposition distal to the target, or "exit dose". This phenomenon is explained by the distinctive Bragg Peak that protons have which allows for a rapid fall-off of the irradiation dose beyond the target. Contralateral structures were significantly spared with the proton plan. As previously established, proton beam therapy remains the therapy of choice for pediatric patients given their long term survival

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	Proton mean (CGE)	Proton max (CGE)	Photon mean (cGy)	Photon max (cGy)
brain	132.1	5045.8	86	5179.5
oral tongue	209.6	2704.3	676.8	2195.4
expanded cord	48.1	1841.5	669	2748.1
brainstem	193.2	2259.6	388.4	2426
L parotid	1660.8	4826.7	1846.7	4827.7
R parotid	1.3	8.7	386.3	854.7
L orbit	8.7	54	69.9	173.7
R orbit	3.8	8	134.1	435.1
L lens	6	11.9	66.4	173.7
R lens	5	6.9	124.6	219.3
L cochlea	2272.9	3062.4	2401.9	4753.83.8
R cochlea	3.8	6.7	129.6	161.4

and concerns for secondary malignancy, as well as lower doses to most if not all normal structures of interest.

Author Disclosure: **G. Vidal**: None. **J. Arntzen**: None. **C. Henson**: None.

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Prone Treatment Position as a Novel Option for Head and Neck Cancer Patients with Unmanageable Secretions

C. Henson; *University of Oklahoma Health Science Center, Stephenson Cancer Center, Department of Radiation Oncology, Oklahoma City, OK*

Purpose/Objective(s): A prone treatment setup is used by some institutions for treatment of breast, rectal, and anal cancer, for enhanced normal tissue sparing, specifically lower doses to heart, lung, and bowel. However, many have reported that a supine orientation demonstrates better setup reproducibility. Radiotherapy for head and neck cancers (HNC) is typically delivered with the patient in supine position due to reproducibility and comfort, with a thermoplastic mass for head and shoulder immobilization. It is not uncommon, however, to have a patient who cannot tolerate this position because of pooling of secretions, which can lead to aspiration, anxiety, and subsequent issues during setup and treatment, and at times, patient noncompliance with treatment — all of which can lead to adverse patient outcomes. In the past, we have occasionally had to treat such patients under daily anesthesia for airway management. With one such patient recently, we opted instead to perform awake prone setup and treatment, rather than daily general anesthesia, hypothesizing that with modern image guidance with 6D X-ray and rigid immobilization, reproducibility would be of similar robustness to supine treatment, and that the patient would be less bothered by secretions and better able to tolerate treatment.

Materials/Methods: We report on the treatment of a patient with inoperable locally advanced squamous cell carcinoma of the maxillary sinus. Due to significant sinus congestion as a result of his tumor, he was unable to tolerate a supine position at the time of simulation. We opted instead for a prone position, with a thermoplastic mask placed over the back of his head and his shoulders, and we utilized 6D X-ray image-guidance for verification of treatment setup, as well as weekly cone beam computed tomography (CBCT).

Results: The prone treatment position was well-tolerated by the patient, who then did not require anesthesia for management of secretions/airway. Accuracy of setup was confirmed with daily 6D X-ray image guidance, and weekly CBCT, and was deemed to be acceptable by the treating physician within the 3-5 mm acceptable PTV margin for head and neck intensity-modulated radiotherapy.

Conclusion: We successfully demonstrated feasibility of a prone treatment position for patients with HNC who are unable to tolerate a supine position due to unmanageable secretions. This theoretically would decrease the risk of aspiration pneumonia, anxiety, noncompliance, and intra-fractional breaks, and avoids the risks and costs of daily general anesthesia. Current NRG head and neck protocols stipulate that patients should be planned and treated supine. Reconsideration should be given to this policy.

Author Disclosure: **C. Henson**: None.

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Baroreceptor Reflex Failure after Curative Chemoradiation for Oropharyngeal Cancer: A Potential Use of an Established Therapy

H. Kim,[1] K. Taparra,[2] and J.M. Holland[1]; *[1]Oregon Health and Science University, Portland, OR, [2]Mayo Clinic School of Medicine, Mayo Clinic, Rochester, MN*

Purpose/Objective(s): Baroreceptor failure is a rarely described late effect after head and neck radiation (H&N RT) characterized by labile blood pressure. The combination of pentoxifylline and Vitamin E has been used to treat other late effects of H&N RT including soft tissue fibrosis and osteoradionecrosis. We describe its successful use in helping a patient with signs and symptoms of baroreceptor failure.

Materials/Methods: Our patient is a 68 year old man with history of chemoradiation (70 Gy IMRT with weekly cisplatin) for T1N2b squamous cell carcinoma. Thirteen years after his therapy, he first noted signs and symptoms of baroreceptor reflex failure with labile hypertension (systolic BP>200) and associated epistaxis. These episodes were poorly controlled with antihypertensive medications. We initiated pentoxifylline 400 mg and Vitamin E 400 IU twice-a-day as therapy directed at baroreceptor fibrosis.

Results: By three months of therapy, the patient had clinical improvement with no further episodes of epistaxis. The patient has continued on this regimen for 17 months with persistent benefit. Quantitatively, his blood pressure has lowered and stabilized. Pretreatment average systolic pressure was 186 mmHg (range 165-218) and diastolic pressure was 109 mmHg (range 94-127). After initiation of therapy, there has been a gradual improvement with average systolic pressure 149 mmHg (range 104-180) and diastolic pressure of 91 mmHg (range 63-110). Blood pressure lability has also improved as reflected in decreased variation of blood pressure measurements on single days. Pretreatment systolic numbers varied 88 mmHg (130-218) and diastolic numbers varied 58 mmHg (69-127). Our most recent single day measurements show systolic variability of 57 mmHg (92-149) and diastolic variability of 25 mmHg (59-84). He has tolerated this regimen with no ill effects.

Conclusion:

1. Baroreceptor failure is a late effect of curative H&N chemoradiation seen many years after therapy.
2. We report clinical improvement in symptoms and quantitative improvement in blood pressure using a regimen of pentoxifylline and Vitamin E.

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2020 Multidisciplinary Head and Neck Cancers Symposium Late-Breaking Abstracts

ORAL ABSTRACT SESSION

LBA 1

Progression-free survival, overall survival and immunophenotyping outcomes for patients with stage III-IV head and neck cancer and cisplatin contraindication treated with definitive radiotherapy plus pembrolizumab

J. Weiss,[1] B. Vincent,[1] A. Deal,[2] J. Grilley-Olson,[3] S. Patel,[3] T. Hackman,[3] J. Blumberg,[4] T.J. Galloway,[5] S. Patel,[3] A. Zanation,[3] C. Shen,[6] D.N. Hayes,[7] C. Hilliard,[8] R. Mehra,[9] K. McKinnon,[8] H.H. Wang,[8] M. Weissler,[3] J. Bauman,[5] S. Sheth,[1] and B.S. Chera[6]; *[1]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina Hospitals, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC, [5]Fox Chase Cancer Center, Philadelphia, PA, [6]Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC, [7]University of Tennesee, Germantown, TN, [8]Lineberger Comprehensive Cancer Center, Chapel Hill, NC, [9]University of Maryland, Baltimore, MD, United States*

Purpose/Objective(s): Although cisplatin plus radiotherapy is a standard definitive treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC), contraindications to cisplatin are common. Radiation elicits and promotes tumor-directed immune-stimulation, which may potentiate anti-PD-1 therapy. For the first time, we report the efficacy of combined pembrolizumab and radiotherapy (XRT) in LA-HNSCC.

Materials/Methods: This single arm, multi-institution, phase II study (NCT02609503) enrolled 29 patients with LA-HNSCC (AJCC v7 stage III-IV) who were platinum ineligible. Patients received XRT concurrently with 3 cycles of pembrolizumab 200mg q3 weeks followed by 3 adjuvant cycles. The primary endpoint was a PFS of at least 16 months. Toxicity was measured using CTCAEv4 and PRO-CTCAE. Quality of life was measured with FACT-HN. PFS and OS were measured using Kaplan-Meier method. Correlative studies included PDL1, mononuclear cell (PMBC) peripheral blood flow cytometry and Luminex cytokine profiling.

Results: Reasons for cisplatin ineligibility included otopathology (69.0%), nephropathy (20.7%), and neuropathy (6.9%). Primary sites included base of tongue (10), tonsil (10), supraglottic larynx (3), hypopharynx (2), unknown (2), oral tongue (1) and uvula (1). By AJCC 8 (re-staged to describe combined anatomic and biologic risk), 72.4% of patients had stage III or IV disease. One year PFS and OS rates were 76% (95% CI 56-88) and 86% (67-95). The primary PFS endpoint has exceeded the hypothesized 16 months; with a median followup of 21 months its median has not been reached. For p16+ oropharynx, (n = 17) 1 year PFS was 88% (61-97) and OS 94% (65-99) while in others (n = 12) it was 58% (27-80) and 75% (41-91). Median OS has not been reached. Toxicities were typical of XRT; however high rates of grade 3/4 lymphopenia (58.6%) were observed. Evaluation by flow cytometry revealed a relative decline in CD4 cells and B cells, but not CD8 cells. Upon treatment, frequencies of transitional B cells and tissue-like memory B cells increased while resting memory B cells decreased. Patients with progression had greater percentages of baseline naïve B cells and fewer marginal zone B cells. PDL1 did not distinguish patients with or without progression. No significant changes were seen in Luminex cytokine profile through therapy and there were no differences between patients with or without progression.

Conclusion: Concurrent pembrolizumab and radiotherapy has demonstrated promising PFS and OS in LA-HNSCC, regardless of p16 status or anatomic location, with a favorable toxicity profile and deserves evaluation in a randomized trial. The observed changes in B-cell markers deserve further study both as potential biomarkers of treatment response and as therapeutic targets.

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LBA 2

Tumor Outcomes of Phase IIb, Randomized, Double-Blind Trial of GC4419 Versus Placebo to Reduce Severe Oral Mucositis Due to Concurrent Radiotherapy and Cisplatin For Head and Neck Cancer

C.M. Anderson,[1] C.M. Lee,[2] D. Saunders,[3] A.E. Curtis,[4] N.E. Dunlap,[5] C. Nangia,[6] A. Lee,[7] S.M. Gordon,[8] P. Kovoor,[9] V. Bar-Ad,[10] A.V. Peddada Jr,[11] K.T. Colvett,[12] D.M. Blakaj,[13] M. Bonomi,[13] F. Worden,[14] J. Holmlund,[15] J. Brill,[16] M. Downs,[17] S.T. Sonis,[18] and J. Buatti[1]; *[1]University of Iowa Hospitals & Clinics, Iowa City, IA, [2]Cancer Care Northwest, Spokane, WA, [3]Northeast Cancer Centre, Health Sciences North, Sudbury, ON, Canada, [4]Gibbs Cancer Center, Spartanburg Medical Center, Spartanburg, SC, [5]University of Louisville Hospital/James Graham Brown Cancer Center, Louisville, KY, [6]UC/Irvine Medical Center, Orange, CA, [7]HOPE Cancer Center of East Texas, Tyler, TX, [8]East Carolina University, Greenville, NC, [9]Texas Oncology, Plano West, Plano, TX, [10]Thomas Jefferson University Hospital, Philadelphia, PA, [11]Renown Regional Medical Center, Reno, NV, [12]Mountain States Health Alliance, Johnson City, TN, [13]James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH, [14]University of Michigan, Ann Arbor, MI, [15]Galera Therapeutics, Inc., Malvern, PA, [16]Galera Therapeutics, Inc, Malvern, PA, [17]Statistics Collaborative, Inc., Washington, DC, [18]Primary Endpoint Solutions, Watertown, MA*

Purpose/Objective(s): 90mg of GC4419, a superoxide dismutase mimetic, significantly reduced the duration, incidence, and severity of severe OM (SOM, WHO Grade 3-4) in a Phase 2b, multi-institutional, randomized, double-blind trial of patients receiving concurrent cisplatin and radiotherapy for head and neck cancer. Here we report the final results for 1-year and 2-year tumor outcomes of this 3-arm trial.

Materials/Methods: 223 patients (from 44 institutions) with locally-advanced oral cavity or oropharynx cancer planned to be treated with definitive or post-op intensity-modulated (IM)RT (60-72 Gy [≥50 Gy to ≥ 2 oral sites]) plus cisplatin (weekly or q3wk) were randomized to receive 30 mg (n=73) or 90 mg (n=76) of GC4419, or placebo (n=74) over 60-minutes IV, prior to each IMRT fraction. The primary endpoint was duration of SOM tested for each active dose level vs placebo (ITT population, 2-sided alpha 0.05). The secondary endpoints included SOM incidence and severity (i.e., specific incidence of WHO Grade 4 OM), safety, and Kaplan-Meier estimates of OS, PFS, LRC, and DMFS. Pairwise comparisons of Kaplan-Meier estimates (each active arm separately vs placebo) were made.

Results: Baseline patient and tumor characteristics (86% male; 77% oropharyngeal; 87% Stage IV [AJCC 7th ed]; 72% tumor HPV +; 29% never-smokers; median [range] pack yrs prior smokers 25 [0.1-140], current smokers 37.5 [3-100]), and treatment delivery (62% weekly cisplatin) were balanced. Efficacy and Safety results were previously reported (JCO 2019, PMID: 31618127) showing GC4419 90mg, compared with placebo, produced a significant, clinically meaningful reduction of SOM duration, incidence and severity, with acceptable safety. At a median follow-up for the entire cohort of 25.5 months (range: 0.2 to 31.9 months), Kaplan-Meier estimates of 1-year and 2-year OS, PFS, LRC and DMFS were statistically identical (Table 1).

Conclusion: GC4419 does not compromise tumor control outcomes when used concurrently with curative-intent cisplatin and radiotherapy for head and neck squamous cell carcinoma. A Phase 3 trial ("ROMAN," NCT 03689712) is enrolling.

Author Disclosure: **C.M. Anderson**: Employee; University of Iowa Hospitals & Clinics, University of Iowa College of Nursing. Travel Expenses; Elekta. Enrolling patients on industry-sponsored clinical trial, discussing research related to trial drug with the company; Galera Therapeutics,Inc. Involved in lobbying congress, representing regional CRNA interests at the national A. **C.M. Lee**: None. **D. Saunders**: Research Grant; Health Sciences North. Honoraria; Amgen, Pfizer. Consultant; Dermtreat. Travel Expenses; Galera Therapeutics/Alira Health. **A.E. Curtis**: Travel Expenses; Galera Therapeutics. **N.E. Dunlap**: Honoraria; Osler Institute. Speaker's Bureau; AstraZeneca. Advisory Board; Galera Therapeutics. **C. Nangia**: None. **A. Lee**: None. **S.M. Gordon**: Research Grant; Vigilant Biosciences. **P. Kovoor**: Stock; Gridalis, Saans Health; Saans Health, Baylor Plano. **V. Bar-Ad**: None. **A.V. Peddada**: None. **K.T. Colvett**: None. **D.M. Blakaj**: None. **M. Bonomi**: None. **F. Worden**: Research Grant; Lilly, Galera Therapeutics, Pfizer, Genetech. Consultant; Fusion. **J. Holmlund**: Independent Contractor; Galera Therapeutics. Consultant; Baxalta, Prometheus Labs. Stock Options; Galera Therapeutics. ad-hoc reviewer; Aspire IRB. **J. Brill**: Employee; Incyte, Array Biopharmaceuticals. Stock Options; Galera Therapeutics, Incyte, Array. **M. Downs**: Consultant; Statistics Collaborative, Inc. Travel Expenses; The Medicines Company, Seattle Genetics. **S.T. Sonis**: Partner; Primary Endpoint Solutions. Stock; Inform Genomics. Partnership; Immunity Health. volunteer advisor; Immunity Health. research leadership; Primary Endpoint Solutions, Biomodels. **J. Buatti**: Review chapters Up to Date; Up to Date.

Abstract LBA 2 Table

	Placebo (n=74)	30mg (n=73)	90mg (n=76)	p-value
1-year				
OS	93%	91%	88%	NS
PFS	82%	86%	80%	NS
LRC	95%	95%	91%	NS
DMFS	92%	92%	95%	NS
2-year				NS
OS	87%	85%	86%	NS
PFS	77%	76%	77%	NS
LRC	91%	89%	91%	NS
DMFS	90%	89%	91%	NS

RESEARCH FEATURE

LBA 3

HNSCC-associated CASP8 mutations promote resistance to apoptosis and mediate induction of immunosuppressive cytokines

Z. Cui, H. Tal, J. Grandis, and D.E. Johnson; *UCSF, San Francisco, CA*

Purpose/Objective(s): The CASP8 gene, encoding caspase-8 protease, is mutated in 10% of the head and neck squamous cell carcinoma (HNSCC) tumors analyzed by The Cancer Genome Atlas (TCGA). To determine the potential impact of HNSCC-associated caspase-8 mutations on anti-tumor immunity and the development of HNSCC, we investigated the functional capacity of caspase-8 mutants to mediate death ligand induction of apoptosis and cytokine production.

Materials/Methods: In this study, the endogenous CASP8 gene in HeLa cells was knocked out using CRISPR-Cas9 technology. The HeLa-CASP8 KO cells were then engineered for doxycycline-inducible expression of WT or 21 HNSCC-associated caspase-8 mutants (MT). The engineered cells were then stimulated with death ligands TRAIL, and analyzed for induction of apoptosis using MTT assays or annexin V staining. Induction of immunosuppressive cytokines was assessed by qPCR and ELISA assays. Those were further evaluated in the engineered HNSCC cell line PE/CA-PJ49-CASP8 KO cells.

Results: HeLa-CASP8 KO cells engineered to express WT caspase-8 underwent rapid apoptosis following TRAIL treatment. By contrast, 16 of the 21 caspase-8 MTs expressing cells failed to undergo apoptotic cell death. Interestingly, 5 mutations (L7V, G11E, G11R, S99F, Y178del) occurring in the death effector domains (DEDs) domains of caspase-8, retain partial abilities to mediate TRAIL-induced apoptosis. TRAIL treatment of parental HeLa cells, but not HeLa-CASP8 KO cells, led to upregulation of the immunosuppressive cytokines IL-6, IL-8, and CXCL1. Exogenous expression of WT caspase-8 in the KO cells restored TRAIL induction of the cytokines. Further, exogenous expression of caspase-8 proteins with mutations in the catalytic domain (R248, TT272-3del, D303G, D303V, D308G, S375*, R435*, R465*), also restored TRAIL induction of the immunosuppressive cytokines. Among these, caspase-8 D303G, restored HeLa and PE/CA-PJ49 CASP8 KO cells with prominent TRAIL induction of cytokines at both mRNA and protein levels. Moreover, cells expression MT proteins capable of TRAIL induction of the cytokines, were characterized by increased phospho-p65 following TRAIL treatment, suggesting a role for NF-kB in mediating cytokine induction by the MT proteins.

Conclusion: Our findings demonstrate that HNSCC-associated caspase-8 mutations have lost the capacity, or exhibit reduced capacity, to mediate TRAIL-induced apoptosis. Hence, HNSCC cells harboring these mutations are likely more resistant to killing by immune cells which utilize death receptor-mediated apoptosis to kill target cells. Notably, MTs in the catalytic domains of caspase-8 protein retained the capacity to mediate TRAIL induction of immunosuppressive cytokines. These mutations are likely to enhance the immunosuppressive tumor microenvironment, further contributing to HNSCC development.

Author Disclosure: **Z. Cui**: None. **H. Tal**: None. **J. Grandis**: None. **D.E. Johnson**: None.

LATE-BREAKING POSTERS

LBA 4

Mobile Patient-Facing Application for Tracking Patient-Reported Outcomes in Head-and-Neck Cancer Survivors: a Pilot Usability and Feasibility Study

S. Teckie,[1,2] J. Solomon,[3] K. Kadapa,[3] K. Sanchez,[3] D. Frank,[3] D. Kamdar,[3] L. Pereira,[3] D. Kraus,[1,4] L. Potters,[2] and M. Diefenbach[5]; *[1]Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, [2]Northwell Health, Lake Success, NY, [3]Northwell Health, New Hyde Park, NY, [4]Northwell Health, New York City, NY, [5]Northwell Health, Manhasset, NY*

Purpose/Objective(s): Survivors of head-and-neck cancers (HNC) grapple with long-term effects of treatment that impact their quality of life. Patient-reported outcome (PRO) measurement has been shown to improve clinical management and disease outcomes. We created a mobile application, LogPAL, where HNC survivors can track their symptoms, access educational tips, and find support services. The purpose of this pilot study was to test the usability and feasibility of LogPAL for PRO measurement among HNC survivors repeatedly over an eight week period. We hypothesized that the engaging application design would lead to successful data collection.

Materials/Methods: From Jan-Oct 2019, we conducted an IRB-approved, prospective pilot study at one multi-site cancer institute. Symptom questions were created using the PRO-CTCAE customized for HNC. We independently created all app and educational content. Eligible patients were recruited from surgical clinics and had completed curative treatment for HNC in the preceding 24 months. Participants were prompted to rate the severity of their symptoms in the app twice a week for 8 total weeks. While tracking symptoms, patients had the option of accessing self-care tips. All information logged by the patient in the app was collected for data analysis.

Results: 38 patients signed consent and enrolled in the study. 33 were eligble for analysis. Mean age was 58 yrs (range 24-91) and 71% were male. Median time post-treatment at time of study enrollment was 10 months (range, 0-23 months). Patients had 16 opportunities to track their symptoms over the 8 week study. 88% of tracking sessions were completed fully (463/528). In addition, 60 unscheduled tracking sessions were completed. The app was opened by patients a total of 693 times, and patients repeatedly (i.e., 3,445 times) checked their progress throughout the study. Overall, 33 patients interacted with the app 6,137 times, over the course of the eight weeks. At the end of the study, 15 patients re-consented and completed the System Usability Scale (SUS) including additional satisfaction questions. From the SUS, 89% thought LogPAL was "easy to use," and 94% felt that "most people could learn to use LogPAL very quickly;" 81% reported that LogPAL was useful, 75% did not feel there were too many questions, and 56% accessed the Tips feature while tracking their symptoms. In addition, 78% of users found the Tips useful. 75% would recommend LogPAL to other cancer survivors (25% were neutral.)

Conclusion: In this prospective feasibility pilot study of a patient-facing mobile application for HNC survivors who completed their treatment on average 10 months prior to enrolling, we found extremely high engagement rates and usability scores and successfully collected PRO-CTCAE outcomes data. Future directions include expanding use of the application to a larger set of patients as part of clinical practice for PRO measurement.

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LBA 5

Predictive Genetic Biomarkers of Survival in HPV-associated HNSCC

W. Yarbrough and N. Issaeva; *UNC School of Medicine, Chapel Hill, NC*

Purpose/Objective(s): Identify prognostic genetic biomarkers for HPV+ HNSCC and determine if they are involved in HPV carcinogenesis.

Materials/Methods: Data analysis from TCGA and cancer cell biology experimentation to determine effects of TRAF3 or CYLD loss on HPV gene expression and replication.

Results: In head and neck squamous cell carcinoma (HNSCC) HPV positivity indicates improved response to therapy and better survival. Using TCGA data, we recently found that HPV+ HNSCC patients whose tumors harbored inactivating mutations or deletions in two functionally related genes, TRAF3 and CYLD, had improved survival. Further analysis of the entire TCGA cohort revealed that the survival benefit associated with HPV could be ascribed to the subset of patients whose tumors had TRAF3 or CYLD gene defects. On the other hand, patients whose tumors were wild-type for these defects had survival similar to those with HPV-negative HNSCC. TRAF3 or CYLD inactivation was associated with activation of NF-kB and absence of HPV genome integration. Using CRISPR/Cas9, we inactivated TRAF3 and CYLD in human cancer cells. This model revealed novel TRAF3 and CYLD-dependent regulation of HPV replication and HPV gene expression.

Conclusion: TRAF3 and CYLD mutations are uncommon in uterine cervical cancer, and their association with HPV integration status, HPV gene expression, and HPV replication suggests a new model of HPV carcinogenesis occurs in the head and neck. HPV+ HNSCC patients are frequently treated with high dose radiation with concomitant cisplatin. After this aggressive therapy, ~25% of these patients develop recurrent disease. For those who are cured, concurrent chemoradiation has long-term deleterious side effects. Pre-treatment segregation of HPV+ HNSCC patients into subsets with good and poor prognosis would not only enable studies to de-escalate therapy and decrease treatment morbidity, but also identify patients appropriate for new or intensive therapy. We are currently analyzing a second HPV+ HNSCC cohort to validate TRAF3 and CYLD as prognostic genetic biomarkers.

Author Disclosure: **W. Yarbrough**: None. **N. Issaeva**: None.

LBA 6

Novel combinations to overcome lenvatinib therapy resistance in thyroid cancer models in vitro and in vivo

A. Sukari,[1] and A. Azmi[2]; *[1]Karmanos Cancer Institute Detroit, MI, [2]Wayne State University, Detroit, MI*

Purpose/Objective(s): Evaluated the lenvatinib resistance mechanism in thyroid cancer cell lines grown in long term culture conditions.

Materials/Methods: The human MTC cell line TT and 8505 were cultured in a mixture of Dulbecco's Modified Eagle Medium (DMEM) with 10% FBS and pencillin and streptomycin. For development of lenvnatinib resistant cell lines 8505C and TT cells were exposed to lenvatinib over 22 weeks. Resistant and sensitive cells were seeded at a density of 5 x 10^3 cells per well in 96-well micro-titer culture plates. Cell Apoptosis was detected. ICR SCID mice were inoculated with 8505C cells in the flank. Once tumors were established, they were trocared in 36 different mice (for the 6 group study). Once palpable tumors were observed, mice were randomly divided into 6 different groups (n=6). Group 1 received vehicle; Group 2 lenvatinib 50 mg/kg twice a day 5 days a week for 3 weeks; Group 3 KPT-330 (selinexor 10 mg/kg orally twice a week for 3 weeks; Group 4 selinexor 10mg/kg orally twice a week for 3 weeks + lenvatinib 50 mg/kg twice a day 5 days a week for 3 weeks ; Group 5 KPT-9274 at 100 mg/kg twice a day orally 5 days a week for 3 weeks and Group 6 KPT-9274 at 100 mg/kg twice a day orally 5 days a week for 3 weeks + lenvatinib 50 mg/kg twice a day 5 days a week for 3 weeks. Mice tumor were measured every three days. Tumor volume was calculated using the formula (lenghtx-width^2)/2 At the end of the treatment the mice were humanely sacrificed and tumors were harvested.

Results: Long-term exposure to lenvatinib caused phenotypic changes in 8505 and TT thyroid cancer cell lines. Consistent with morphology change, EMT markers such as ZEB1, Vimentin and Snail were up-regulated in 8505 Res and TT Res compared to parent cell lines. We also observed the activation of pro-survival signaling, RhoGTPase effector signaling, and activation of nuclear export pathways. RNA-seq analysis showed that prolonged lenvatinib treatment caused alterations in pathways related angiogenesis, apoptosis, cell cycle and inflammatory pathways. Moreover, several oncogenes such as CEACAM (Carcinoembryonic Antigen Related Cell Adhesion Molecule) and NUPR1 (Nuclear protein 1) were also up regulated. The impact of nuclear exporter protein exportin 1 (XPO1) and Rho GTPase effector p21 activated kinase 4 (PAK4) inhibition in the presence or absence of lenvatinib was also evaluated. Targeted XPO1 by specific inhibitor of nuclear export compounds (selinexor or

eltanexor) could sensitize the 8505C and TT cells to lenvatinib. Similar synergy was observed with PAK4 inhibitor (KPT-9274).

Conclusion: Selinexor given at sub-optimal doses (10 mg/kgx2x3wks) or KPT-9274 (100 mg/kg BIDx5x3wks) when combined with lenvatinib (50 mg/kg BIDx5x3wks) showed superior anti-tumor activity in 8505 subcutaneous xenograft. These studies bring forward a novel combination for lenvatinib resistant thyroid cancers that warrant further clinical investigations.

Author Disclosure: **A. Sukari**: Research Grant; Eisai. Speaker's Bureau; Eisai. **A. Azmi**: None.

LBA 7

Clinical outcomes according to HPV status in oropharynx cancer patients following upfront definitive radiation therapy with policy of selective neck irradiation and reduced elective neck irradiation dose

S.G. Park,[1] Y.C. Ahn,[2] D. OH,[2] J.M. Noh,[2] M.J. Ahn,[3] H.A. Jung,[3] Y.H. Ko,[4] and H.S. Jeong[5]; *[1]Deptartment of Radiation Oncology, Keimyung University Dongsan Medical Center, Daegu, Korea, Republic of (South), [2]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South), [3]Department of Medicine (Division of Hematology-Oncology), Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South), [4]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South), [5]Department of Otorhinolaryngology-Head and Neck Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South)*

Purpose/Objective(s): Upfront definitive radiation therapy (RT) with selective neck irradiation (SNI) and reduced dose elective neck irradiation (RdENI) has long been our treatment strategy in treating oropharynx cancer (OPC) patients at authors' institute. This study is to investigate impact of human papillomavirus (HPV) status to clinical outcomes along our strategy.

Materials/Methods: From 2008 to 2017, 150 consecutive OPC patients, whose HPV status evaluation was done by DNA microarray test, underwent definitive RT using helical Tomotherapy. Same RT dose schedule was applied to all patients, regardless of HPV status, and majority (92.0%) received concurrent systemic therapy, based on disease extent and patients' condition. Through adaptive re-plan with SNI and RdENI policy, planned doses were 68.4 Gy/30 fractions to gross tumor volume (GTV), 60 Gy/30 fractions to high-risk clinical target volume (HR-CTV), and 36 Gy/18 fractions to low-risk clinical target volume (LR-CTV), respectively. Clinically uninvolved contralateral and low necks (2 levels away) were not included in target volume.

Results: HPV status were HPV (+) in 115 patients (76.7%), and HPV (-) in 35 (23.3%), respectively. Grade ≥3 treatment-related acute toxicities developed in 37 patients (24.7%): oral mucositis in 30 (20.0%); weight loss in 8 (5.3%); and dermatitis in 5 (3.3%), respectively. No grade ≥3 hematologic acute side effect occurred. After median 29 months' follow-up, treatment failure developed in 27 patients (18.0%): distant metastasis in 14 (9.3%); regional relapse in 11 (7.3%); and local failure in 7 (4.7%), respectively. 3-year rates of loco-regional recurrence-free survival (LRRFS) progression-free survival (PFS), and overall survival of all were 89.9%, 78.1%, and 88.1%, respectively. HPV (-) patients showed significantly worse 3-year rates of LRRFS (78.6% vs. 93.3%, p=0.013) and PFS (63.4% vs. 82.9%, p=0.006), respectively. Detail loco-regional failure sites of 14 patients in relation to current SNI and RdENI policy is summarized in Table below.

Abstract LBA 7 Table

Failure site	HPV (+) (N=115)	HPV (-) (N=35)	Total (N=150)
Within GTV	5 (4.3%)	6 (17.1%)	11 (7.3%)
Within HR-CTV	-	1 (2.9%)	1 (0.7%)
Within LR-CTV	1 (0.9%)	-	1 (0.7%)
Outside target	1 (0.9%)	-	1 (0.7%)
Total	7 (6.1%)	7 (20.0%)	14 (9.3%)

Conclusion: We achieved favorable clinical outcomes and HPV (-) patients showed inferior LRRFS and DFS at 3 years. Based on very few regional failures attributable to current SNI and RdENI policy, current policy is believed to serve as baseline for future refinement of de-intensification strategy for HPV-associated OPC patients.

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LBA 8

Safety of reRT with SBRT plus concurrent and adjuvant pembrolizumab in patients with recurrent or new second primary head and neck squamous cell cancer in a previously irradiated field: RTOG 3507 Foundation (KEYSTROKE)

S. Wong,[1] P. Torres-Saavedra,[2] Q.T. Le,[3] C. Chung,[4] S. Jang,[5] M.S. Huq,[6] R. Jordan,[7] D.A. Clump II,[8] D.M. Blakaj,[9] M.W. Straza Jr,[1] and S. Koyfman[10]; *[1]Medical College of Wisconsin, Milwaukee, WI, [2]NRG Oncology Statistics and Data Management Center, Philadelphia, PA, [3]Stanford University, Stanford, CA, [4]H. Lee Moffitt Cancer Center, Tampa, FL, [5]Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, [6]University Of Pittsburgh Medical Center, Pittsburgh, PA, [7]UCSF, San Francisco, CA, [8]UPMC Hillman Cancer Center, Department of Radiation Oncology, Pittsburgh, PA, [9]James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH, [10]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Purpose/Objective(s): Pembrolizumab (P), a PD-1 inhibitor, is approved for first-line treatment of recurrent (R)/metastatic head and neck squamous cell carcinoma (HNSCC). A phase II trial with lead-in component was designed to evaluate the safety and efficacy of stereotactic body radiation (SBRT) re-irradiation (reRT) plus concurrent and adjuvant P in patients with R/new second primary (NSP) HNSCC. Safety data for seven patients on the lead-in study are reported.

Materials/Methods: Eligible patients had previously irradiated R/NSP HNSCC, disease limited to a single or adjacent site treatable in a single contiguous target volume, prior RT (>30 Gy) with overlap of at least 25% of current PTV with previous treated area, maximum GTV < seven cm, and Zubrod performance status (PS) 0-1. Intravenous P (200 mg) was delivered every three weeks starting two weeks prior to SBRT (40 Gy, 8 Gy x 5 fractions over two weeks). The primary endpoint was dose-limiting toxicity (DLT), defined as grade 4+ non-immune-related adverse event (AE; NCI CTCAE v5) related to protocol treatment or grade 3+ immune-related AE related to P up to four weeks following completion of SBRT; 0-2 DLTs in six evaluable patients was considered acceptable.

Results: Seven patients were enrolled between November 2018 and October 2019. Median follow-up from registration is 2.3 months (min-max 2.2-3.6). Median follow-up from end of RT is 1.3 months (min-max 1.0-2.7). Characteristics of the seven enrolled patients were: Median (min-max) age 68 (52-80); 100% male; 100% Caucasian; 14% PS 0, 86% PS 1; 57% recurrent, 43% NSP; p16 positive oropharynx (OP) 14%, non-OP/p16 negative 86%; T1-2 57%, T3-4 43%; N0 86%, N2b 14%. All seven patients completed SBRT and were evaluable, having received four+ doses of P to date; 1 patient discontinued P after 4 doses due to progression. No DLTs were observed. No grade 4-5 AEs were observed. No grade ≥ 3 AEs were considered related to P or protocol treatment.

Conclusion: ReRT with SBRT plus concurrent P seems safe and feasible to administer for patients with HNSCC in a previously irradiated field. Clinical trial information: NCT03546582.

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None. **D.M. Blakaj**: None. **M.W. Straza**: None. **S. Koyfman**: Research Grant; Merck.

LBA 9

Comparative analysis of the cellular profile and architecture of metastatic and non-metastatic lymph nodes

J.R. Booth,[1] G. Guo,[2] C. Myint,[1] N. Patel,[2] R. Bollag,[2] W. Albergotti,[2] M. Groves,[2] J.K. Byrd,[2] and Y. Cui[2]; *[1]School of Medicine, Augusta University, Augusta, GA, [2]Georgia Cancer Center, Augusta University, Augusta, GA*

Purpose/Objective(s): Lymph nodes (LN) serve a crucial role in host defense against cancer. Oral cancer commonly metastasizes to the LN, which is a marker for poor prognosis. The mechanisms behind tumor metastasis in oral squamous cell carcinoma (OSCC) remain elusive despite the study of cellular and molecular tumor characteristics. We hypothesize that tumor-draining LN develop alterations in their infrastructure and inflammatory cell populations prior to establishment of tumor cells. We examined the LN microenvironment of patients both with and without LN metastasis. For those patients with metastasis, we compared LN with involvement to those without involvement.

Materials/Methods: De-identified formalin-fixed paraffin-embedded human lymph nodes from OSCC tumor patients both with and without lymph node metastases were evaluated. Hematoxylin/eosin (H&E) staining was used for analysis of histology. Human Multiplex Immunohistochemistry staining was used to examine the immune and stromal cell composition with computer-assisted image analysis.

Results: We examined the immune and stromal cell populations of LNs in patients without metastasis and in the positive and negative LN of patients with metastasis. H&E staining from non-metastatic patients shows well-organized B cell germinal centers, while the same regions in metastatic patients show abnormal organization. The immune cell profile and stromal architecture differ between all three populations. T cells (CD3+) and B cells (CD20+) were low in pre-metastatic LN compared to non-metastatic LN. T cells and B cells were the lowest in tumor and metastatic tissue. Immunosuppressive macrophage cells (CD163+) doubled in tumor tissue and tripled in tissue surrounding tumor compared to LN.

Conclusion: Lymph node architecture is altered in oral squamous cell carcinoma prior to metastatic establishment of malignant cells, suggesting that soluble factors secreted by the primary tumor may enable regional spread. Full characterization of the interaction between cancer and the nodal microenvironment may lead to the development of therapies that prevent or counteract tumor spread.

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LBA 10

Genetic Variation in HPV+ Head and Neck Squamous Cell Carcinoma

A. Miller,[1] T. Zhang,[2] Y.M. Alhiyari,[3] A.Y. Han,[3] R. Sun,[2] and M. St. John[3]; *[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, [2]University of California Los Angeles, Los Angeles, CA, [3]Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Purpose/Objective(s): HPV+ Head and Neck Squamous Cell Carcinoma (HNSCC) comprises 70% of the cancer of the oral cavity. The sudden increase in HPV+ HNSCC is in stark contrast to the decrease in HPV related cervical cancers. Understanding the pathophysiology of HPV cancer disease progression will aid in rapid detection, prevention, and treatment. The oral cavity is a unique space with a variety of squamous tissues that can all be exposed to HPV. Within the oral cavity it is unknown which tissue types are more susceptible to developing HPV related cancers, and/or what strains or variants of HPV may be more virulent. It is well established that E6 and E7 gene segments are particularly important for HPV to potentially cause malignancy, targeting p53 and Rb tumor suppressors respectively, ultimately leading to genome instability and enhanced proliferation. However, we hypothesize specific mutations in HPV DNA E6/E7 regions may correlate with different infectivity of oral infection, development of HNSCC, severity of disease, and ultimately treatment outcomes. The purpose of this study is to screen patient cancer tissues collected from the head and neck for HPV, subtype, and E6/E7 mutation frequency.

Materials/Methods: Consented patient tissues, blood and saliva were collected. DNA extraction and amplification was performed to test all samples for HPV infection. Tissues that were HPV+ and contained the E6/E7 regions were deep sequenced. Mutational changes in E6/E7 were compared intra-patient across different tissue types, as well as, across different patients. Our patient data was compared with current known E6/E7 mutations and blasted against the TCGA database of head and neck cancer patients.

Results: Preliminary data identified known and novel mutations within the E6/E7 region. Additionally, tissue and swab samples from the same patient source showed different mutations present when compared to tissue samples. Additional analysis could demonstrate correlations between specific gene variants and severity of disease, as well as, poor treatment outcomes.

Conclusion: Identifying and understanding mutations and progression of mutation subtypes in the E6/E7 region can help identify individuals or groups with an increased risk of developing HPV-associated HNSCC. Furthermore, these methods could be utilized as novel screening tools and therapeutic targets for severe disease. This data could be used to design minimally invasive, highly sensitive, affordable, and portable screening tools to detect cancers at an early stage and to identify subpopulations of HPV-positive individuals who are at increased risk of developing treatment refractory or recurrent HNSCC.

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LBA 11

Cohort Expansion Study of Neoadjvuant Immunoradiotherapy in Locoregionally Advanced HPV+ and HPV- Head and Neck Squamous Cell Carcinoma

R.B. Bell,[1] R. Leidner,[1] K.H. Young,[1,2] B. Curti,[1] M. Couey,[1] A. Patel,[1] A. Watters,[1] H. Xiao,[1] G. Morris,[1] L. Rushforth,[1] M. Gough,[1] and M.R. Crittenden[1,2]; *[1]Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR, [2]The Oregon Clinic, Radiation Oncology, Portland, OR*

Purpose/Objective(s): We recently reported the results of a phase Ib clinical trial in which 10 patients with previously untreated stage I-III (AJCC 8th Ed) p16+ head and neck squamous cell carcinoma (HNSCC) underwent neoadjuvant immunoradiotherapy (NIRT) with nivolumab 240mg IV q2 weeks x3 prior to surgery (NCT03247712). Stereotactic body radiation (SBRT) to gross tumor volume was delivered between doses 1 & 2 of nivolumab in one of two dose finding cohorts: Cohort A (40Gy, 8Gy X5, M-F); and Cohort B (24Gy, 8Gy X3, M-W-F). The pathologic complete response rate (pCR) was 90% and all patients were successfully down-staged prior to surgery. Here we aim to test the hypothesis that nivolumab contributed to the exceptional local response to radiation by modulating the tumor microenvironment via blockade of upregulated PD-L1.

Materials/Methods: Following assessment of dose limiting toxicity in the safety portion of the trial, we opened two expansion cohorts that evaluated NIRT at the lower radiation dose (24Gy, 8Gy X3) with and without immunotherapy: Cohort C consisted of patients with stage I-III HPV+ HNSCC who were treated with SBRT alone; Patients in Cohort D had stage III-IV HPV-*negative* HNSCC and were treated with nivolumab and SBRT as in Cohort B. Surgery in all cohorts was performed five weeks post-SBRT, followed by adjuvant nivolumab 480mg IV q 4 weeks X3 starting four weeks after surgery. The primary endpoints were pathological response by irPRC and rate of pathologic and radiographic down-staging after neoadjuvant therapy. A Simon two-stage optimal design was applied,

assuming that a decrement in T or N stage by week 6 in > 10% of cases would be clinically significant (alpha = .05 level of significance with a power of 90% to detect a difference when the true rate of down-staging ≥ 33%).

Results: Between April 8, 2019 and December 17, 2019, 11 patients with previously untreated, loco-regionally advanced HNSCC involving the oral cavity (N = 2), oropharynx (N = 7), and larynx (N = 2) were enrolled into Cohort C (N = 6) or D (N = 5). Neoadjuvant treatment was well tolerated and there were no grade 3 or 4 adverse events. To date, 8/11 patients completed surgery and had evaluable pathologic reports. Of these, all patients were successfully down-staged and one patient with HPV-negative cancer required adjuvant radiation per protocol. Although the pCR rate was higher in Cohorts A and B than in the expansion cohorts evaluated to date, resection specimens were characterized by major pathologic responses (<10% viable tumor cells) in the majority of patients, as well as robust inflammatory infiltrates into the regression bed, plasma cells and cholesterol clefts.

Conclusion: NIRT prior to surgery for loco-regionally advanced HNSCC results in significant rates of major pathologic response and pathologic downstaging regardless of HPV status.

1. Leidner RS, Bell RB, Young K, et al. Cancer Res 2019;79(13 Suppl):Abstract nr CT182.

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