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All abstracts accepted for presentation at the 2020 Multidisciplinary Head and Neck Cancers Symposium are embargoed until the opening ceremony of the symposium, Thursday, February 27, 2019 at 8:00 a.m. Mountain Time.
Neoadjuvant Nivolumab +/- Ipilimumab in Patients with Oral Cavity Cancer

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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 (N0), 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=1, concern about clinical progression n=1, pt choice n=1, concern about clinical progression n=1, and 1 pt with T4 disease by 10 days of regional perilymphatic IRX-2 cytokine injections (115 Units consisting of an initial dose of Cyclophosphamide (300 mg/m²) followed by 10 days of regional perilymphatic IRX-2 cytokine injections (115 Units subq. upper neck, bilaterally), and daily indomethacin, zinc and omeprazole (Arm B)).

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.

K. Kian Ang, MD, PhD, FASTRO, Commemorative Plenary Session

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

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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/m²) 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 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.

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.
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.

Author Disclosure: G.T. Wolf: Research Grant; Brooklyn ImmunoTx, NIH, Advisory Board; Merck, Regeneron, S. Liu: None. E. Bellile: None. M. Sartor: None. L. Rozek: None. M. Shah: Chief Operating Officer; Brooklyn ImmunoTherapeutics. A. Nguyen: None. J.B. McHugh: None.

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

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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, BRCAT, 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 ctDNA alterations per patient and 2.78 ± 1.67 ctDNA alterations per patient among overlapping genes. 65.3% of patients had actionable ctDNA alterations per patient.
altered. 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.

**Author Disclosure:** None.

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### 5 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)


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**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) is 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 mutational status 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 patients survived and 72.92% 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 wild type 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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### 6 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


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15. University of California, San Francisco, 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) is 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.
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 T2N2-3 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=0.04] 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 11.6 – 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.


7

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

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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. Intestitial 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 CTC/CE 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, dysnea, appetie 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.


8

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

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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 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 both suicide attempts and death 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.


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

9

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 (HNPCP).

Materials/Methods: The Distress Screening (DS) was developed by the Mind Body team (MBT), a subspecialty group of psychologists and social workers within the HNPCP. 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 ≥ 4 would correlate with positive screening scores for depression and anxiety. In September 2017 - August 2019, 245 HNPCP 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 ≥ 4) to trigger same-day intervention by the MBT utilizing validated screening tools.

Results: Of the 245 patients screened for distress, 142 (58%) reported clinically significant distress [≥4 on the DT, 54 (22%) screened positive for depression [≥3] on the PHQ-2, and 81 (33%) screened positive for anxiety [≥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 [≥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.

Oral Abstract Session

10

Long-Term Update of a Phase II Study of Concurrent Chemoradiotherapy Using Radiation + Bevacizumab (BV) For Locally or Regionally Advanced Nasopharyngeal Cancer (NPC): RT0G 0615

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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 1-3b/III, stage ≥IIb, ≥ node(s) were eligible. Concurrent BV (15mg/kg) and cisplatin (100mg/m2) 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/m2) on day 1 and fluorouracil (1000mg/m2/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

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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 ERSP1 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: The combined biomarker was significant for both overall and disease-free survival; high ER-alpha and HPV status was independently deleterious to both, while high MATH was associated with improved OS. The interaction between HPV and ER-alpha status was significant (p=0.04), indicating that the inclusion of ER-alpha status was critical for optimal discrimination. High ER-alpha expression was associated with a significant (p=0.011) worse outcome in HPV-negative patients, and a trend toward worse survival in HPV-positive patients (p=0.06). The combination of biomarkers was significantly more predictive than the HPV status alone (p=0.04 for comparison of AIC of the two models).
12 Primary chemoradiotherapy or transoral robotic surgery for Stage I-II HPV-associated oropharyngeal squamous cell carcinoma

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

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 three 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.

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% vs. 85%), DFS (77% vs. 81%) and LRC (86% vs. 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 = 0.022).

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.

Purpose/Objective(s): Clinical outcomes for patients with early-stage (AJCC 4th 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.

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

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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 chemotherapeutic 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 antimitabolites (5-fluourouracil + 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 antimitabolites 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

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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, correlational 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.


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

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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 auto-segmentation 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 auto-segmentations on the final test set. Lastly, this final model was 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 3 mm edit), or “requiring major edits.”

Results: The auto-segmentation model took 17.5 minutes on average to auto-segment all lymph node level combinations. When comparing the ground truth to the auto-segmentations 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 were 1.0 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 auto-segmentation 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 auto-segmentations 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.

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


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

Materials/Methods: This is a non-randomized Phase II trial for early stage (AJCC 8th-T1-2, N1, AJCC 7th-T1-T2, N2b) HPVOPC treated with 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 (PNNLI) postoperative radiotherapy (50 Gy); Group 3: poor prognostic pathologic factors (ECE, >3+LN, + 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 rates of Groups 2 and 3 as expected. These results support radiation dose reduction after TORS with appropriate pathologic staging as a de-escalation strategy.

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.


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


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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 chemoinmunotherapy.

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-T2 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 50 Gy.

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 50 Gy. 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 chemoinmunotherapy 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 OP-TIMA 2 upon study completion.

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/m² 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 loco-regional 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 ptT4 disease and 33% had ≥5 involved nodes. Of the 5 distant metastases, 60% had ptT4 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 88% (93-100) while two year DMFS were 90% (82-100) vs 84% (82-97). For patients with ≥1mm ENE, 2 year LRFS were 92% (84-100) vs 95% (91-100) while 2 year DMFS were 89% (80-100) vs 80% (72-97). Only 2 patients in the historical cohort had ptT4 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 ptT4 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.

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

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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 oncology 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 chemo-radiotherapy 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

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Purpose/Objective(s): Searching for biomarker profiles of responders vs non-responders to immunotherapy has become a priority. Our window of opportunity trial (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 (NCT03283865). Subjects in the two groups 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, CDS, 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 semiquantitative 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 nivolumab +/- 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

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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.

Author Disclosure: M. Xiang: None. F. Holsinger: None. M.F. Gensheimer: Employee; Roche, Research Grant; Varian Medical Systems, Philips Healthcare. V. Divi: None. E. Pollom: None. A.D. Colevas: None. Q. Le: Research Grant; Amgen, NIH, Redhill. Travel Expenses; BMS. Stock; Aldeia. Head and Neck Cancer International Group (HNCIG), chair of head and neck committee- design clinical trial; R TOG NRG Cooperative group, president elect; American Radium Society. B.M. Beadle: Research Grant; NIH. Royalties from book publication; Wolters Kluwer Health. Secretary of the organization (unpaid); American Radium Society.

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

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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 undergo 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 (OCSCC). 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 OSCCCa will correlate with the presence of occult nodal metastases.

**Purpose/Objective(s):**

Peripheral blood samples were obtained from 20 cN0 OSCCCa 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 pN+ (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).

**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 OSCCCa. Further development and characterization of these cells may aid in risk stratification of patients to help aid in treatment decision making.

**Author Disclosure:**

Y. Anderson: None. M.H. Wong: None. D. Clayburgh: None.

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**107 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**

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**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.

**Materials/Methods:**

Eligibility criteria included SCC of the larynx, hypopharynx or oropharynx, stage III-IV disease (excluded T1), 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/m²/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 ≥58% with nab-paclitaxel, 40 patients provided a power = 0.80 with a one-sided α = 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 HNSCC and 82% in HPV-related OPSCC. nab-paclitaxel and cisplatin-based regimen. However, the LRC rate in these patients was higher than expected with CetuxRT alone.

**Abstract 107: Table**

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**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.

**Author Disclosure:**

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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

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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 localized 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 exact test evaluated associations of CND with pre-surgical clinical information.

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<0.05) 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 (<N0/N1) were not likely to have pathologic CND (OR 0.05; 95% CI 0.007-0.398), 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 cm from midline 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

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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 >1 cm 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 (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, -13% to 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

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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 extent of capsular invasion. Clinical, pathologic and demographic information was collected. Local control (LC), regional control (RC), and distant control (DC) were measured. 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. Of the hundred and fifty-six (45%) patients with ENE with 62 (16%) pooled 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 (CCRT) 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

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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 CCRT. This is report of long term outcomes of CCRT 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 CCRT (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 LC, 13 HPC and 12 tumours 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 CCRT 70 Gy in 35 fractions over 47-49 days was combined with 3 courses of cisplatin (100 mg/m2 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 CCRT 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 CCRT group. After CCRT 24 patients had died, 35 cases died after ARA. Five-year OS was 35% in ARA group and 51% in CCRT arm. Second neoplasms (mostly - 54% - lung cancer) were diagnosed in 13 patients in ARA and in 11 in CCRT. Late treatment related toxicity deteriorated QL were observed in 24% of ARA patients and 11% of CCRT 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.


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


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 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.

**Author Disclosure:** P. Pellionisz: None. Y. Hu: None. A.S. Moon: None.


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

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**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 DOI 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**

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**Purpose/Objective(s):** Identification of patients at higher risk of loco-regional (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), muted nodes (MN), and positive inferior cervical nodes (ICN). Clinical characteristics (age, AJCC 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 (DMFSS) 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.
The Role of SPECT-CT in Addition to PET for Lymphatic Drainage Mapping in Patients with HPV+ Oropharyngeal Squamous Cell Carcinoma

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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 perorally 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 as 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 nodal 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 is superior for identification of patients at higher risk for DM who may benefit from intensified systemic therapy.


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

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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/hematic 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 oncologie 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.

<table>
<thead>
<tr>
<th>p16 Positive</th>
<th>p16 Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV Positive</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>HPV Negative</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>8</td>
</tr>
</tbody>
</table>

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.

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 optimize 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 Nivolubam 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.


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

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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.

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=0.0032).

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:

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

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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; change, 1.97 points; 95% CI, 3.10-6.82) and physical functioning scores was maintained through week 12. Changes from baseline in baseline EQ-5D-5L visual analog 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.

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-SCCCHN). 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: 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

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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-SCCCHN). 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-SCCCHN 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 pre-determined 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, co-inhibitory, 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.

**Author Disclosure:** D. Adkins: Research Grant; Pfizer, Eli Lilly, Merck, Novartis, Celgene, Astra Zeneca, Atara, Blueprint Medicine, Cellective/Innovation Pharma, Celldex Therapeutics, Eonzenym, Glaxnik, Bristol-MyersSquibb, Kura, MedImmune, Exelixis, Innate, Matrix Biomed, Polaris. Consultant; Pfizer, Eli Lilly, Merck, Cue Biopharma, Loxo Oncology. J. Ley: None. N. LaFranzo: Honoraria; Illumina. Cofactor Representative on Consortium; Biomarkers Consortium. Governance Leadership; American Chemical Society. J. Hiken: Employee; St. Louis University. I. Schillebeekx: Employee; Sirolta Therapeutics. P. Oppelt: Research Grant; Merck, Eisai. Consultant; Bristol Myers Squibb. K. Palka: None. B. LaFleur: Consultant; Cofactor Genomics.

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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

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**Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; 2Memorial 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 Fluorine-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 fixed paraffin embedded resected primary tumor was reviewed in conjunction with a pathologist. Slides were stained using the Vectra Opal.
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. Chemoresponse 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- and tumor- 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

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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 14.7 - 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.

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 loco-regional and distant failure. For these patients, nodal aRT is recommended and additional systemic interventions are needed.


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

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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] vs 89 [87-90]) and HQNOL Eating (65 [60-69] vs 85 [83-86]), but equal function in the MDADI (80.1 [75.5-84.4] vs 79.5 [77.3-81.8]) and EORTC QLQ-HN35 Swallowing (12.7 [7.3-18.1] vs 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 QLC-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.

Author Disclosure: D. Quan: None. J. Cramer: None.
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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**

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**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/m². 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% respectively. The feeding tube requirement was 35%, which were subsequently removed a few months post-treatment once adequate oral intake was achieved.

**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. Dobelman: 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)**

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**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 J711 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/m². Dose escalation was driven by safety using a modified Dose-to-Event Continual Reassessment Method (DTE-CRM).

**Results:** In Part A, 7 patients were treated with a prexasertib dose of 20 mg/m². 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 (TEAEs) 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; 26.6%) 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/m² (n = 4) 30 mg/m² (n = 6) or 40 mg/m² (n = 2). No patient in cohort 1 (20 mg/m²) experienced DLTs. Three of 8 patients in cohort 2 (40 mg/m²), experienced the DLT, febrile neutropenia and 1/6 patients in cohort 3 (30 mg/m²) experienced the DLT, febrile neutropenia. The 30 mg/m² 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 acneviform (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 Kaitoushi as Induction Chemotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck**

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**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 500 mg 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 ClinicalTrials.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 1p6-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 250 mg 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.

**Author Disclosure:** W. Jiang: None. D. You: None. R. Li: None. L. Zhang: None. G. Zhu: None.

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


**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 <1 cm. 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. of 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.

**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**

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**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 – 13.69, p < 0.01], GTV (HR = 1.04, 95% CI: 1.00 – 1.10, p = 0.048), and treatment modality (p < 0.01) predicted for OS. Multivariable analysis of the interaction between CU and treatment modality (p < 0.01) found that patients who continued to smoke during treatment had lower OS than those who stopped smoking [HR = 3.31, 95% CI 1.70 – 6.39, p < 0.01].
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Genetic and micro-environmental factors influencing response to definitive 30Gy chemoradiotherapy (chemoRT) in HPV Positive Oropharyngeal Cancer (OPC)

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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 recurring) from a Mayo Clinic study of low-dose adjuvant radiotherapy to 30Gy (NCT: NCT01932697) were obtained pre-rx and weekly during therapy. Mann-Whitney U-test was used to compare cases. Pre-rx FMISO PET scans were 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 FMISO 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 PIK3CA (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

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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. IMRT 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.

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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. Luminias, 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. Follow-up was 2.6 years (range 1.7-68.2 months).

**Results:** The median follow-up was 5.3 years. P16 status was positive in 79.8% (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 disease control rates at 5 years were 100%, 90.9%, and 90.9%, respectively.

**Conclusion:** Neck dissection appears to play a valuable role in improving outcomes for eligible patients. Dose de-escalation of Waldeyer’s ring was associated with increased rates of distant metastases. Among patients with pathological extranodal extension (ENE) status, which was positive in 11/25 neck dissection specimens where it was described, both those with positive ENE irradiated 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 of 0 was associated with decreased PFS on MV A (HR 4.05, 95% CI 1.13-14.55, 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.

**Author Disclosure:** S.W. Dutta: None. R.C. Bliley: None. C. Luminias: None. P.W. Read: None.

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

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

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Purpose/Objective(s): To evaluate patterns of failure, toxicities, and dosimetric impact on dysphagia/aspiration risk structures (DARS) using a 210

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 carcinoma of the larynx for combined chemoradiation

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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.

direct gross tumor volume (GTV) to planning target volume expansion (dPTV) 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 and consensus guideline-generated PTV (cPTV) 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%-69.9%). Five-year primary tumor control was 79.6% (95% CI: 67.3%-87.7%) and regional control was 88.1% (95% CI: 76.3%-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 gastrosomy 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 (V5) to DARS was significantly lower for dPTV compared to cPTV.

**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.


**Purpose/Objective(s):** It is well-established that human papilloma virus (HPV) positive (+ve) oropharyngeal (OP) squamous cell carcinoma (SCC) carries a better overall survival 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, clinicopathological data and treatment modalities were compared across age groups for both HPV sub-types. 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 subgroup, 31% were old (n = 47); whereas they constituted 40% (n = 27) of HPV-ve cases. Clinopathological 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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**Does Age Impact Outcomes of Oropharyngeal squamous cell carcinoma?**

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**Purpose/Objective(s):** 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

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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**


**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 pathobiological 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%), Pn3a (1, 1%). The AJCC stage group 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 the unilateral RT group, 5 (45%) occurred in the bilateral RT group (2-year: 62% vs. 89%, p < 0.001), and 33 (33%) occurred in the unilateral RT group, 5 (45%) occurred in 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 cavity was associated with a high risk of tumor recurrence in the contralateral neck.


214 Human Papillomavirus in Sinonasal Squamous Cell Carcinoma

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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 cancer 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 (SNSSC) utilizing the National Cancer Database (NCDB).

Materials/Methods: We selected all SNSSC cases between 2010-2016. HPV testing rates, clinodemographic 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 SNSSC 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 SNSSC 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 = 1.19-2.36, p < 0.001) had worse outcomes. HPV-positive tumors comprised 28.1% (366) of the tested population. 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 associated with worse outcomes.

Conclusion: Currently only a minority of SNSSCs are tested for HPV. These data suggest that a sizable minority of SNSSCs 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 SNSSCs as well. The impact of HPV association on survival of SNSSCs needs further investigation.


215 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

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Purpose/Objective(s): Elderly and/or frail patients (pts) with head and neck squamous cell carcinoma (HNSCC) 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, improving 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**

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**Purpose/Objective(s):** The elderly comprise an increasing percentage of patients with locally-advanced head and neck squamous cell carcinoma (LHNSCC). 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 LHNSCC.

**Materials/Methods:** From our IRB-approved registry, all patients ages ≥ 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 patients ages 60-69 was also identified for comparison. Chemotherapy delivered, and RT dose. Cumulative incidence of recurrence 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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**Radical Reduction of Radiation Therapy Dose Prescription for Elective Treatment Areas in Human Papillomavirus (HPV) - Associated Oropharyngeal Carcinoma (OPC)**

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**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 continuing treated 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.


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

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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 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.

Author Disclosure: S. Abel: None. R.E. Wegner: None. E. Interval: None. A. Colonias: None.

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

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Purpose/Objective(s): The purpose of this study was to analyze locoregional control and survival in patients with recurrent oropharyngeal cancer following 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 cm³ (20–271 cm³) for IMRT, 47 cm³ (18–191 cm³) for PBT, and 17 cm³ (8–42 cm³) 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).

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.

Author Disclosure: J. Phan: Advisory Board; Accuracy Incorporated. ; MD Anderson Cancer Center. Director of stereotactic radiation therapy program for head and neck at MD Anderson; MD Anderson Cancer Center. A. Bagley: None. G. Adam: None. S.J. Frank: Research Grant; C4 Imaging, ELEKTA, NIH, Eli Lilly, Hitachi, Founder and Director; $12k/year; 4 Imaging. Honoraria; ELEKTA, Varian Medical Systems, Inc, Boston Scientific, Consultant; Varian Medical Systems, Inc. Advisory Board; Varian Medical Systems, Inc, Stock; C4 Imaging, Royalty; C4 Imaging, Patent/License Fees/Copyright; C4 Imaging. ; G.B. Gunn: None. D.I. Rosenthal: Advisory Board; Merck. Travel Expenses; Merck. J. Reddy: None. C.D. Fuller: Research Grant; National Institutes of Health, National Science Foundation, Elekta AB, National Institutes of Health, Grant funding; Elekta AB. Honoraria; Elekta AB, Nederlandse Organisatie voor Wetenschappelijk Onderzoek. Consultant; Elekta AB, Nederlandse Organisatie voor Wetenschappelijk Onderzoek. Travel Expenses; Elekta AB, Nederlandse Organisatie. W.H. Morrison: Advisory Board; Regeneron. Stock; Merck, Baxter, Johnson and Johnson. S.J. Shah: None. A.C. Moreno: None. R. Ferrarotto: None. E.M. Sturgis: None. N.D. Gross: None.
Does Accelerated Fractionation Improve Radiation Results in Patients with Cancer of Nasopharynx? Results of 10-years Follow-up

Author Disclosure: no benefit compared with CFRT. Treatment tolerance for both schedules during follow-up.

Our observations 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-fluouracil was given in 37 and 15 pts respectively in both arms depending on tumor advance and differentiation.

In all pts acute mucosal reaction radiations 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=0.04), 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 better treatment outcomes than CFRT in terms of local, nodal control and disease free survival. There were no serious late toxicities in AFRT treated pts.

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 supraglottic tumors (SCCs) of the head and neck. 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-fluouracil was given in 37 and 15 pts respectively in both arms depending on tumor advance and differentiation.

In all pts acute mucosal reaction radiations 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=0.04), 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 better treatment outcomes than CFRT in terms of local, nodal control and disease free survival. There were no serious late toxicities in AFRT treated pts.
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) and 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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S. Mehra: None.
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Survival and Quality of Life Analysis in a Randomized Deintensification Trial for Locally Advanced HPV-Positive Oral Pharynx Cancer Patients

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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 clinicopathology 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 2.38, 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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Lymph node yield and survival in node-negative oral cavity cancer

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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 clinicopathology 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 2.38, 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

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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. 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. 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).

Conclusion: Increased TTI was associated with OR of 1.02/day for Tup (p < 0.02). Multivariable analysis showed that Tdown was associated with worse OS/DFS (p < 0.08). TTI was not associated with worse OS/DFS. In more aggressive patterns of care nationally without evidence of a survival advantage.


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

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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

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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 (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...
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 hypopharynx 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**

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**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-institutional location, representing 72%. The majority of those enrolled were stage I (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. Lundaa: None.
Primary Surgery for Early-Stage Oropharyngeal Carcinoma: A Superior Treatment or a Matter of Selection Bias?

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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 consisting of 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 survival 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 of data (2013), it accounted for 51.17%. Linear regression slope tests 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.


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

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Purpose/Objective(s): 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.
A risk-based trial design of multidisciplinary treatment intensification for head-and-neck cancer


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. Trial inclusion was then simulated with the suggested inclusion criteria: Arm 1. Standard radiotherapy: low-risk patients, Arm 2. Randomization between standard and dose-painting radiotherapy: intermediate-risk patients, and Arm 3. Primary surgery + RT: high-risk patients with oropharynx or larynx cancer.

Results: With the suggested trial design, 203 (35%), 297 (52%) and 73 (13%) were assigned to arm 1, 2 and 3, respectively (patient/tumor characteristics, see Table 1). Power/sample size calculations suggest that 40-45 patients are needed in Arm 2 (randomized phase II study with difference in number of central relapses as endpoint). Arm 3 (primary surgery + RT) is expected to include 16 patients (locoregional control rate: 90%, alternative hypothesis: 90%) in a single arm to show feasibility.

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.


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partially or completely gastrectomy 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.

**Author Disclosure:** D. Wilde: None. P. Castro: None. A. Haugen: None. J. Shi: None. S. Lai: None. E. Chiao: None. D. Hernandez: None. A. Sikora: None. V.C. Sandulache: None.

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

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

**Materials/Methods:** We reviewed patients defined as LASSCC 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%,0.0%, respectively. Histopathological differentiation was related to occult metastasis (p=0.003).

**Conclusion:** Neck levels II, III are most frequently invaded for LASSCC. 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.

**Author Disclosure:** Y. Xu: None. Y. Zhang: None. J. Yi: None.

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

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**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 T1–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.

**Author Disclosure:** J. Bergin: None. S. Abel: None. A. Colonias: None. R.E. Wegner: Honoraria; Astra Zeneca.

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

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**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 (UV A) 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
Abstract 237; Table 1

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>UVA</th>
<th>MVA</th>
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<tbody>
<tr>
<td>4 yr LC</td>
<td>T1-T2, 92% vs. T3-T4, 63% (P&lt;0.001)</td>
<td>HR 5.0 [1.8-13.9]</td>
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<td>cisplatin, 86% vs. other chemother., 68% (P=0.002)</td>
<td>P=0.086</td>
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<tr>
<td>4 yr RC</td>
<td>T1-T2, 90% vs. T3-T4, 62% (P&lt;0.001)</td>
<td>HR 2.2 [0.9-5.1]</td>
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<td>Even-smoker, 72% vs. Never-smoker, 90% (P=0.028)</td>
<td>NS</td>
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<tr>
<td>4 yr DM</td>
<td>T1-T2, 86% vs. T3-T4, 55% (P&lt;0.001)</td>
<td>HR 4.0 [1.6-9.9]</td>
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<td>Even-smoker, 68% vs. Never-smoker, 82% (P=0.056)</td>
<td>NS</td>
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<tr>
<td>T1-2N0-2 group</td>
<td>Only 4yr LC: cisplatin, 95% vs. other, 86% (P=0.15)</td>
<td>HR 0.94</td>
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<td>4yr RC: cisplatin, 92% vs. other, 88% (P=0.57)</td>
<td>HR 0.94</td>
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<td>4yr DM: cisplatin, 85% vs. other, 86% (P=0.94)</td>
<td>HR 0.94</td>
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UVA. Cancer specific survival (CSS) was influenced by T stage (4yr: 86% T1-T2 vs. 62% T3-T4, P<0.001) and N stage, and age on UVA. On MVA, T stage was the only independent predictor of LR (HR 5.0 [1.8-13.9], P=0.002). RC (HR 2.2 [0.9-5.1], P=0.086). 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.


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

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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 c6 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 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

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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 = 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.

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 cov erages 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 ($\text{BED}_{0.5\%}$) 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 $\text{BED}_{0.5\%}$ changed from 13.7 Gy without to 11.4 Gy with ART ($p=0.011$), while the LR-parotid $\text{BED}_{0.5\%}$ 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 HR-parotid $\text{BED}_{50\%}$ changed from 13.7 Gy without to 11.4 Gy with ART ($p=0.011$), while the LR-parotid $\text{BED}_{50\%}$ 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 HR-parotid $\text{BED}_{50\%}$ changed from 13.7 Gy without to 11.4 Gy with ART ($p=0.011$), while the LR-parotid $\text{BED}_{50\%}$ changed from 11.3 Gy without to 9.9 Gy with ART ($p=0.014$).

**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.

**Author Disclosure:** B.K. Lee: None. J. Zhang: None. J.J. Cho-Lim: None. W. Inouye: None. S.P. Lee: Leadership; Los Angeles Radiological Society, Long Beach VA Med Ctr, David Geffen School of Medicine, UCLA.

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

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**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.


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

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**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 CFT 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 (HpxRT) 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 HpxRT alone or combined with induction or/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 comparison 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 developed 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:** HpxRT combined with sequential CHT is effective treatment and should be considered in selected pts with advanced NPC with contraindication to simultaneous radio-chemotherapy. HpxRT alone is less effective but may be also curative. Treatment tolerance of HpxRT is satisfactory.

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

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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 follows: 55 Gy in 20 fractions in 19 patients (25%) and 63-65 Gy in 30 fractions in 58 patients (75%). In 43 patients (56%) the neck lymph nodes were treated with a prophylactic dose of 54 Gy 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 laryngectomy.

Conclusion: Radiotherapy modulation (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 naso-gastric tube feeding). No grade >IV acute toxicity. Four patients (5%) developed late grade III/IV toxicities (2 developed oesophageal stenosis requiring dilatation and 2 developed cartilage necrosis).

Cetuximab Versus Other Non-Cisplatin Agents in the Treatment of Patients with Head and Neck Cancer Receiving Concurrent Chemoradiotherapy

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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 radiotherapy 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.

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

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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 univariate 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 peripherally 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.


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

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Purpose/Objective(s): The design of the 1.5 T Elekta Unity MR-Linac limits the cranio-caudal (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, TNN 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 ≥2 (75%). Overall, 96% HNC patients demonstrated a CC field length <20 cm, 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 mean CC field lengths at 21 cm, 18 cm and 17 cm, respectively. 4 patients with a CC field length ≥20 cm had nasopharyngeal (n = 2), oropharyngeal and para-nasal 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 had a mean height of 160 cm (SD 7.9 cm).
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

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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 surgeries. 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 a 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.

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Clinicopathological Characteristics of Nonsmoker Nondrinker Oral Cavity Cancer

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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 drinking 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 lympho-vascular 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

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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 many nodal metastases are found. The purpose of this study was to present the clinical characteristics and course of two patients with atypical CEPA 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.

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<html>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 NPC showed a 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 a 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.


Patient and Tumor Characteristics and Prognostic Significance of Epstein-Barr Virus (EBV) and Human Papillomavirus (HPV) Associated Nasopharyngeal Cancer (NPC).
Clinicopathologic characteristics associated with oral cavity squamous cell carcinoma in nonsmokers


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.


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

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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 65.1 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 the 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.


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

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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. Author Disclosure: M. Stewart: None. C. Kahue: None. J.M. Curry: None. M. Zaftero: None. D. Weed: None. C. Zender: None. A. Lugnin-buhl: None.

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Incidence and characteristics of HPV-associated oropharyngeal cancer: An 18-year Danish population-based study with 2,169 patients
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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 (AARI), average annual percentage change (AAPC) of OPSCC, patient demographics and proportion of HPV+ OPSCCs. 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 AARI per 100,000 of all OPSCCs was 1.38 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. Author Disclosure: M. Zamani: None. C. Grønhøj: None. D. Hellestrup: None. A. Carlander: None. T. Agander: None. K. Kiss: None. C. Olsen: None. L. Baandrup: None. F.C. Nielsen: None. E. Andersen: None. J.T. Friborg: Research Grant; Varian Medical Systems. C. Buchwald: None.

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Depth of Invasion and Overall Survival in Oral Cavity Cancer Subsites
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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) 8th edition 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 8th edition 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
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 following radiation by chemoradiation (45.3%). DOI was significantly associated with 5-year OS when all OSCC 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 OSCC 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

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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 association 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 (2.54 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=0.008838), 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

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Purpose/Objective(s): Pembrolizumab, approved 5 Aug 2016, and Nivolumab, approved 11 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 (mHNSCC) cancer immuno-oncology (IO) treatment. The objectives of this retrospective study were to evaluate treatment patterns and RW outcomes of patients with mHNSCC 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 mHNSCC, 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 (2L), 14.5% line 3 metastatic (3L). Median real-world progression free survival (rwPFS) 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, 7.11), and 1.81 (0.72, 4.61) 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

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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 ≥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 IIV, 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 IIVb 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

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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 (AIR), 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 AIR compared to men with an AIR in females of 3.7 (95% CI 2.0; 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 AIR 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?

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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 1973 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 nonlinear 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

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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 (OPX) 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 OPX 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 OPX patients, HPV-positive OPX 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 OPX 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<0.0001). The median follow-up was 11 months (range 1-23 months) in this cohort with known HPV-status.

Conclusion: HPV-positive and HPV-negative OPX 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.

Author Disclosure: D. Jacobs: Research Grant; Yale School of Medicine. H.S. Park: Employee; Yale School of Medicine. R. Rahmati: None. S. Mehra: None. B.L. Judson: Oversee the activities of the Division of Otolaryngology at Yale; Yale School of Medicine.

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

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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+. The 2y overall survival (OS) for HPV+ vs. 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 45.6% vs.22.0% (p<0.001) respectively. Younger age (<60y) was associated with improved OS. (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 MI 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.


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

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Abstract 266

<table>
<thead>
<tr>
<th>HPV+Stage III-IV</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>430/504 (85%)</td>
<td>625/755 (83%)</td>
<td>878/1073 (82%)</td>
<td>1135/1441 (78%)</td>
<td>1267/1691 (75%)</td>
<td>1418/1910 (74%)</td>
<td>1550/2191 (71%)</td>
<td>7304/9565 (76%)</td>
</tr>
</tbody>
</table>
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. Gronhøj: None. K.K. Jakobsen: None. C.V. Buchwald: None.

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Purpose/Objective(s): Describe epidemiological characteristics of patients (pts) with Human Papilloma 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 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.

Results: Of 302 pts with Head and Neck Squamous Cell Carcinoma (SCHC), 65 (21.5%) were OSCC and of these, 46 HPV + (70.7%). 31 pts (67.5%) were diagnosed with OSCC, 65 (21.5%) were OSCC and of these, 46 HPV + (70.7%). 31 pts (67.5%) were HPV +. The study indicates a causal link between the exposures leading to STD and HNC; however, more studies to determine causality are needed.

Deep learning detects actionable molecular and clinical features directly from head/neck squamous cell carcinoma histopathology slides

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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 m. Pixel data from extracted image tiles were then normalized and m. The receiver operator curve (ROC) area under the curve (AUC) for performance was evaluated on a validation dataset chosen at the time of training using a 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.


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

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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 pT6 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-2 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.


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

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Purpose/Objective(s): Squamous cell carcinoma (SCC) is the most common malignancy of the oral tongue, usually affecting older patients, 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. Clinico-pathological 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**

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**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-DOTATATE-PET/CT in HNC patients. Future work will focus on evaluation of metastatic disease, as well as pathologic and molecular tissue correlation.

**Author Disclosure:** R. Patel: None. G. Marano: None.

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

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**Purpose/Objective(s):** To determine if preoperative CT-measured skeletal muscle mass is a prognostic indicator for disposition other than home and head 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/m²), skeletal muscle index (SMI, cm²/m²), 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 (cm², Hounsfield Units -29 to +150) at the third lumbar vertebra and dividing by patient height squared (m²). 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 cm²/m², 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 (66.0% 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 ≥ (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,4 and A.W. Chan1

**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 (DVs) 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**

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**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.

**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 3.6, relative increase of Ve in ORN-VOIs was 2.6 and the controls (range 1.2-6.6).

**Conclusion:** Our results confirm there is 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

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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 months) 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.

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 para-thyroid 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.

Author Disclosure: E. Lykke: None. C.V. Buchwald: None. A. Kjær: None. P. Homoe: None.

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/m², 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.


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

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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 radiation were retrospectively evaluated. Several potential confounding factors were controlled to minimize bias. ADC maps were obtained on all patients treated on the trial to look for potential ADC changes during treatment. ADC measurements were compared between HPV- and HPV+ patients. ADC response to radiation was defined as decrease in ADC by 20% or more for at least 3 consecutive weeks. The primary outcome was the percentage of patients with a decrease in ADC by 20% or more for at least 3 consecutive weeks. The average percentage of ADC response per patient was calculated and compared between HPV- and HPV+ patients. The Kaplan-Meier method was used to estimate events of no response for each group. The percentage of events was estimated using the Kaplan-Meier method. The log-rank test was used to compare the percentage of events between HPV- and HPV+ patients. The average of the ADC response per patient was used to estimate the percentage of events.

Results: Fifty-five patients were HPV- (57.4%) and 19 patients were HPV+ (22.9%). The percentage of patients with a decrease in ADC by 20% or more for at least 3 consecutive weeks was 40% (9/23) for HPV- patients and 16.7% (3/18) for HPV+ patients (p = 0.37). The average percentage of ADC response per patient was 40% for HPV- patients and 16.7% for HPV+ patients (p = 0.37). The percentage of events of no response was 60% (14/23) for HPV- patients and 83.3% (15/18) for HPV+ patients (p = 0.18). The average of the ADC response per patient was used to estimate the percentage of events. The log-rank test was used to compare the percentage of events between HPV- and HPV+ patients.
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 2 wk as well as their 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 x 10^{-3} mm^2/s). The changes in ADC and fractional volume of low ADC at 2 wk 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 2 wk 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 HNSCC.

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 learning 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, multi-scale 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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principle, offer the ideal solution by providing a non-invasive measurement of the biological properties of the entire extent 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 intent were offered inclusion. All patients were scanned on an integrated PET/CT scanner prior to surgery with the PET tracer FDG. All tumors were removed en bloc, formalin fixed 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 Ktrans (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 of 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

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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 1.19-9144) 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 HPVpositivity 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

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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 Set-up and Dosimetric Variability on an MR-Linac

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Purpose/Objective(s): The recent clinical implementation of a novel integrated MR/linear accelerator (MR-linac) has enabled daily adaptive radiotherapy treatments for head and neck cancers. We report the intrafraction 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

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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 movement parameters. 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, sharpened, and 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/torquing (i.e. motion due to the surgeon’s hands). This development is crucial for the future clinical translation of DOCI.

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Clinical Outcomes in Integrated PET-CT Radiotherapy Planning for Radiochemotherapy of Locally Advanced Head and Neck Cancer

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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 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

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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 nozzle 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 cm2 nozzle to cover the entire tumor and 2) SORT (2-12Gy) using 0.5x0.5 cm2 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 cm2 nozzle, allowing abutting of high and low dose fields. Gene expression analysis revealed increase 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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Spatially optimized radiation therapy for enhanced immune priming of head and neck cancer

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Purpose/Objective(s): Spatially Optimized Radiation Therapy (SORT) aims to enhance immune priming using a spatially heterogeneous dose distribution. Previous studies have demonstrated enhanced immune activation in SORT treated mice correlates to a sustained immune response and improved T-cell activation. Our study aims to validate SORT using a preclinical model of head and neck squamous cell carcinoma (HNSCC). We hypothesize that SORT will result in increased immune infiltration and tumor response compared to conventional hypofractionated RT (HF).

Materials/Methods: 24 mice were randomized to treatment groups: sham, HF (4.5 Gy per day), or 3 different SORT regimes. tumors were followed for 40 days after treatment. Tumor size was measured weekly using calipers. Tumor volume (TV) was calculated using the formula 4/3π(π/6×d1×d2×d3). Treatment response was analyzed using the log-rank test.

Results: As shown in the figure, mice treated with SORT had significantly smaller tumors compared to the HF and sham groups at all time points. The SORT group had a median tumor volume of 190 mm3 at day 40, while the HF and sham groups had median tumor volumes of 1990 mm3 and 1900 mm3, respectively. This difference was statistically significant (p<0.05).

Conclusion: Our study demonstrates that SORT is effective in enhancing immune priming and improving tumor response in a preclinical model of HNSCC. These results support the hypothesis that SORT may be a promising therapy for the treatment of head and neck cancer.

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 (PhC) in the US. We examined treatment patterns and estimated real-world time on treatment (rwToT) with IO and non-IO based therapies post-PhC 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 PhC 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 PhC 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 PhC, a greater proportion of patients received a PhC combination regimen (N=290, 65%) versus PhC 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 PhC 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 PhC 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 and patterns and longer follow up time, is warranted to further elucidate drivers for these observed trends.

Author Disclosure: D. Chirovsky: Stock Options; Merck and Co., Inc., Z. Liu: Stock Options; Merck and Co., Inc., S. Baxi: unpaid physician at Bellevue Hospital, NYU, Stock; Roche, S. Chandwani: Stock Options; Merck and Co., Inc., S. Joo: Stock; Merck and Co., Inc., K. Ramakrishnan: Stock Options; Merck and Co., Inc.

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Analysis of spatial relationships between CDB and FoxP3 cells using digital imaging in head and neck squamous cell carcinoma


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: 3.17-37.11). 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

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Purpose/Objective(s): Efficient use of nivolumab in recurrent/metastatic head and neck squamous cell carcinoma (t/rmHNSCC) 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 t/rmHNSCC treated with nivolumab.

Materials/Methods: We identified 21 patients with t/rmHNSCC 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 t/rmHNSCC and should be further validated in larger cohorts and in prospective studies.

Author Disclosure: L. Ota: None.
Integrated Biomarker Study of Pepinimab 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

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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) is 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 tumorclocial 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 pepinimab, 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 pepinimab 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 pepinimab with ICIs in HNSCC (NCT03600986, 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 pepinimab (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 FC and IHC panels utilizing a sequential probe and antibody panels designed to quantify multiple immune cell populations. Multiple 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 pepinimab. Nine HNSCC patients have been enrolled as of 04 SEP 2019 and interim biomarker analysis will be presented.


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

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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 3.5/2.5/1.1 M (P=0.11) and 3.2/4.0/0.7 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), 1.7/1.7/1.0 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.


Withdrawn

A Phase 1b Presurgical Window Study to Evaluate Immune Biomarker Modulation in Response to Motolimed and Nivolumab in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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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/m² (Arm 2). Following an initial safety review, additional cohorts testing IT motolimod at 3 mg/m² 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 profiles, and evidence of pathologic response. Enrollment is expected to take approximately 26 months, and the study is expected to continue for 30 months.

Results: Not applicable/trial in progress

Conclusion: Not applicable/trial in progress


| 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 proceed if < 2/6 events occur in Arm 2.
Fistula Rate after Salvage Laryngectomy with Aggressive Levothyroxine Replacement, A Prospective Phase 2 Clinical Trial


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 exacerbated 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 post-operatively (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 substantial reduction in the length of stay. This study lays the foundation for a subsequent randomized trial to validate these results.

The effect of cetuximab and immune checkpoint inhibitor sequence on treatment efficacy

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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: 12.2-18.4) 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 15.3 m (95%CI 11.0-19.6) 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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Last-line Local Treatment with the Quad Shot Regimen for Previously Irradiated Head and Neck Cancers

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Purpose/Objective(s): To investigate the outcome of locoregional radiation to the head and neck in patients with metastatic oropharyngeal cancer with prior irradiation to HNC with or without salvage surgery.

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. RT at 3.7 Gy twice daily over 2 consecutive days (n = 119) and 2 to 4 fractions (2-8 Gy) in 4 weeks, per cycle, was administered. The majority had been irradiated less than 2 years before QS RT, and 27% received more than 2 or more full courses of HN RT. Palliative response as defined by subjective relief of symptoms or objective response was assessed. Progression-free survival (PFS), and overall survival (OS) were analyzed. 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, and income status.

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 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 than non-proton patients. The 1-year OS was 26%. On multivariate 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) compared to no RT (p < 0.0001). No factos 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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Radiotherapy in Metastatic Oropharyngeal Cancer

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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 (1.47%, 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) compared to no RT (p < 0.0001). 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.


Author Disclosure: None.
Survival Following Photoimmunotherapy in Patients (Pts) with Recurrent Head and Neck Squamous Cell Carcinoma (rHNSCC)

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Purpose/Objective(s): Loco-regional 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 loco-regional 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] (Ferri et al, NEJM 2016; Cohen et al, Lancet 2018). In a recent phase 1/2a study of Cetuximab-IR700 photomunotherapy (PTT)-treated pts with loco-regional 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 PTT treatment.

Materials/Methods: In the RM-1929-101 trial, 38 pts with loco-regional, rHNSCC who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy were treated with Cetuximab-IR700 PTT. Pts with survival > 22 months were identified and a retrospective review was performed that included tumor characteristics, prior treatment history, tumor response, and post-PTT treatment anti-cancer therapies.

Results: Of the 38 pts treated with Cetuximab-IR700 PTT 10 (26%) pts were alive > 22 months post PTT treatment at the time of data cut (08/2019). Of the 10 pts, 8 were male and age at entry ranged from 54 to 86 years. Median time of primary diagnosis to PTT 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 PTT 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 PTT treatment. Overall survival duration for these 10 pts from start of PTT treatment ranged from 22.2 months to 48.2 months.

Conclusion: Ten of 38 (26%) rHNSCC pts survived > 22 months following Cetuximab-IR700 PTT 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 PTT treatment are warranted.


Oral Tongue Squamous Cell Carcinoma in Young, Non-Smoking, and Non-Drinking Patients

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Purpose/Objective(s): Oral tongue squamous cell carcinoma (OTSCC) has recently emerged as an emerging tumor type. The purpose of this study was to characterize outcomes of OTSCC in young, non-smoking, non-drinking patients compared to older patients.

Materials/Methods: This is a cohort analysis of 220 patients with stage III, IVA, or IVB OSCC who underwent surgery, followed by adjuvant radiotherapy/chemoradiotherapy, and PTT/CECT scan. Using the American College of Radiology’s Neck Imaging Reporting and Data System (NI-RADS), PTT/CECT scans were dichotomized as suspicious (primary or neck category ≥ 3, or distant lesion present) versus non-suspicious. We then computed differences in loco-regional progression, distant progression, and overall survival; positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity; and success rate of salvage.

Results: PTT/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 PTT/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 42%, 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, PTT/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 PTT/CECT scan, cure of loco-regional recurrence is possible but unlikely. Prospective comparison of salvage success between post-operative and post-adjuvant therapy surveillance PET/CECT is warranted.


Oral Tongue Squamous Cell Carcinoma in Young, Non-Smoking, and Non-Drinking Patients

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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. 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 ± 1.88 cm³ (young) and 1.02 ± 1.71 cm³ (old) (p = 0.22).

The mean depth of invasion was significantly greater in old patients (1.37 ± 0.65 cm³ vs 0.71 ± 0.63 cm³) (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 to 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.


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 logistic 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

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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 surgical salvage 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 + re-irradiation with intensity modulated radiation therapy (surg+IMRT). 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 surgery+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 osteoradionecrosis compared to 0% in both cesium and surgery alone cohorts (p=0.002). 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

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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 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 epithamitis. 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 (HNSSC)

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Purpose/Objective(s): FDA recently approved pembrolizumab as first line for R/M HNSCC in combination with platinum and fluorouracil in all patients (pts) as well as monotherapy in tumors with a PD-L1 combined positive...
score (CPS) $\geq 1$. As a result, the chimeric IgG1 epithelial growth factor re-
cceptor (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 $\sim 13\%$ and an overall sur-
vival of $\sim 6$ months in platinum-resistant R/M HNSCC, representing an area
of unmet clinical need. Cetuximab inhibits EGFR signaling and initiating
Natural Killer (NK) cell antibody-dependent cell-mediated cytotoxicity
(ADCC). Feedback activation of STAT3 and IGFR/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 in-
hibitor of STAT3 and IRS1/2, inhibiting STAT3 phosphorylation and targets
IRS1/2 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 subse-
quent 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 cetux-
imab 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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**Capecitabine for Salvage Treatment of Patients with Heavily Pre-
treated Human Papillomavirus-Associated Oropharynx
Cancer (HPV-OPC) with Distant Metastases**

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**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 capicitabine 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
data and clinical information 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
(high-dose cisplatin, 1 cetuximab), surgery followed by adjuvant radiotherapy
alone (2) and adjuvant chemoradiotherapy (1, high dose cisplatin), and sur-
gery followed by de-escalated adjuvant therapy on a clinical trial (1). Two pts
had distant metastases at diagnosis and both received induction chemother-
apy 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, ret-
cher 1), bone 1 and soft tissue 1. Five pts received cetuximab 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 pem-
brolizumab (7), nivolumab/palbociclib (1, metrectedram and gemcitabine), 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 capicitabine was 21 months (range 12-32). Seven of nine pts were
eligible for response assessment. Average time on capicitabine 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 of treatment on 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.

**Author Disclosure:** C. Fazer: None. A.V. Chintakuntlawar: None. K.
Price: None.
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. 6.28; mean (SD); p = 0.007). SD226-SA409 (p = 0.069) was found more frequently in the integrated group, but splice sites SD26-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 genome, and this differed from that exhibited by integrated tumors. The differences in the patterns of transcriptomes based on integration status.

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.


Aurora kinases mediate resistance to PI3K inhibition in head and neck squamous cell carcinoma

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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 prexartebit, 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 3

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.


The CHK1/2 Inhibitor Prexartebit 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 prexartebit, 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-SCCC1 or heterotopic UM-SCCC4 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-SCCC4 and HPV-negative UM-SCCC1 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).

**Author Disclosure:** L. Zeng: None. D. della Manna: None. E.S. Yang: Research Grant; Eli Lilly. Advisory Board; Strata Oncology. Astrazeneca.

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**Splicing, Mutation, and Methylation Alterations Drive Gene Expression in HPV-DPC more than Copy Number Variation: A Network Propagation Analysis**

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**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 (R²=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 recovery.
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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Quantity of ctDNA by Risk Category for Post-Operative Patients with HPV Associated Oropharyngeal Squamous Cell Carcinoma

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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-naive 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 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-naive 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.

Author Disclosure: D.M. Routman: None. B.S. Chera: Consultant; ROHAC. Equity; Naveris. Patent/License Fees/Copyright; Naveris; ACR. Head and Neck. Senior Editor; Practical Radiation Oncology. Scientific
Abstract 321; Table 1

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Advisory Board; Naveris. K.R. Jethwa; None. K. Van Abel; None. S. Kumar; None. T.A. DeWees; Employee; Mayo Clinic. Statistical Editor; Advances in Radiation Oncology. J.J. Garcia; None. D.L. Price; None. J.L. Kasperhauer; None. N.N. Laack; None. A.V. Chintakuntlava; None. K.A. Price; None. M.C. Liu; None. R.L. Foor; Employee; Mayo Clinic. Textbook editor; Elsevier. Consultant; Up to Date. Royaltiy; Bionix. Patent/License Fees/Copyright; Bionix. responsible for clinical practice, research and education; Mayo Clinic. Responsible for the written board examination questions for head, neck and skin cancer.; ABR. E.J. Moore; None. G.P. Gupta; Patent/License Fees/Copyright; Naveris. D.J. Ma; None.

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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)

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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

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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 using 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 radiation therapy 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.

Thymoquinone Preferentially Targets Squamous Cell Carcinoma and Demonstrates Radioprotective Effects on Normal Keratinocytes

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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.

Methods/Materials: 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 0μM to 25μM. 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 < 0.05, 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.


Comparison of two approaches to establishing PDXs of head and neck cancer

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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

Correlation of Standard Clinical p16/HPV Testing with Highly Sensitive HPV Subtype Testing, and Association of HPV Subtypes with Outcomes in Oropharyngeal Cancer

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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 gages. 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.

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.

**Author Disclosure:** L. Abel: None. R. Hu: None. J.Y. Bruce: None. K.P. Nickel: None. R.J. Kimple: Employee; University of Wisconsin, Research Grant; Peloton Therapeutics, American Cancer Society, National Institute of Health, V Foundation for Cancer Research, Advisory Board; Galera therapeutics; PLOS One, International Journal of Radiation Oncology Biol, Diabetes.

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**LSD1 Inhibitor and Cisplatin Combination Treatment of Sinonasal Squamous Cell Carcinoma Cell Lines**

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**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 the 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 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 UMSSC33) 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.

**Author Disclosure:** L. Weatherford: Employee; UC Health. D. Kuhnell: None. S. Palackdharry: None. R. Vachon: None. V. Takiar: None. S. Langevin: None. T. Wise-Draper: Head and Neck Cancer Precision Oncology Alliance Leader; Caris Life Sciences.

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**Molecular Profile of Early Stage Laryngeal Squamous Cell Carcinoma with Radiotherapy Resistance**

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**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 adjacent 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.

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 protein 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 and was characterized by upregulation of MYC target genes (p=1.53 e-10), NOTCH signaling (p=4.28 e-4), mRNA splicing pathway (p=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 diverse. 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-LI-NF1 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.

indicated to show the impact of adjuvant immunotherapy in high risk patients.

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**Treatment patterns and survival outcomes for odontogenic cancers**

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**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 carcinomas (n=0), 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=0.0002). 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=.04) and patients living ≥ 50 miles from the treatment center (HR 0.18; 95% CI 0.03-0.93; P=.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 not 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**

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**Purpose/Objective(s):** Clinically node negative patients with Merkel cell carcinoma (MCC) of the head and neck often receive adjuvant therapy to reduce the likelihood of recurrence. Definitive radiation therapy (RT) is a standard treatment for MCC, however the role for adjuvant chemotherapy is uncertain. In a recent meta-analysis, the benefit of undergoing lymph node dissection (LND) was demonstrated. Lymph node evaluation is a critical component of clinical staging and may influence treatment decisions. We assessed the association of initial metastatic site with the survival of patients with MCC.

**Materials/Methods:** We assessed the association of initial metastatic site with the survival of patients with MCC using the National Cancer Database (NCDB). We identified 1,049 patients with MCC 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 improved survival. In patients with squamous cell carcinoma, improved OS was associated with any type of surgical resection as compared to bone (HR 0.80; 95% CI 0.65-0.97; P=0.027). When stratified by histology, lung as the only site of metastasis was 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 with 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.

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: [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 were 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 have positive margins on resection (OR 2.27; [CI: 1.41, 3.65]), and had positive margins on resection (OR 2.27; [CI: 1.41, 3.65]) and have positive margins on resection (OR 2.27; [CI: 1.41, 3.65]). 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). Mutivariable 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 were 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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M.R. Young: Employee; Yale Department of Cardiology. Patent/License Fees/Copyright; Yale Patent Office. K. Olino: None. R. Rahmati: None. S. Mehra: None. B. Burtenshaw: None. B.L. Judson: Oversee the activities of the Division of Otolaryngology at Yale; Yale School of Medicine.

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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 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.

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Inhibition of BRAF induces PD-L1 expression in BRAF-mutated papillary thyroid carcinoma

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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 years (95%CI: 25.8-37.3) with 84.8% 10-yr, 71.8% 20-yr OS rates (11 deaths). 66 (92%) received definitive surgery ± adjuvant therapy for their initial disease. Median disease-free interval (DFI) was 3.7 years (range: <1-3.59). 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). 124/25 (48%) 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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Conclusion: PIK-Ing out an intermediate-risk subgroup in advanced adenoid cystic carcinoma

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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

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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 8th 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 8th pT1-3 classification demonstrated substantial overlap between stage groups (P = 0.40). However, pair-wise comparison of individual categories demonstrated significant separation of pT1a and pT4b from pT1-3 and each other (pT4a vs 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 groups.


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Elective Nodal Irradiation for Locally Advanced Cutaneous Squamous Cell Carcinoma of the Head and Neck

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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, etc.)
immunosuppressive status), tumor (PNL, 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 54 Gy 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**

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**Purpose/Objective(s):** Proton beam radiation therapy has dosimetric advantages compared to photon radiation therapy for the treatment of major salivary gland tumors (MSGT), 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 post-operatively 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 (<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**

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**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) 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.

**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.

alternative strategies such as neoadjuvant chemotherapy/radiation will need to be compared.

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Retroactive Review of Clinic-Pathological Characteristics and Overall Survival of Patients with Adenoid Cystic Carcinoma

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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 T1N0M0), 2 were T2N0M0, 16 were T3a-bN0M0 (excluding the denovo group), and 2 were T3bN0M0. 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 cribriform/ 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, it 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.

343 Proton Therapy for Non-Skull Base Head and Neck Adenoid Cystic Carcinoma


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 = 11, 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 perforation status of 90%. 7 (15%) patients had recurrent disease of which 4 had prior radiation therapy to a median dose of 60 Gy. Among those who received definitive proton therapy, the median dose was 70GyE while the median dose for those who received postoperative radiation therapy was 66GyE. 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.


344 Outcomes of Locally Advanced Sinonasal Cancer in the Modern Era: Surgery and Adjutant Therapy remains an Optimal Treatment Strategy

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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.

Use of Post-Operative External Beam Radiation Therapy in Patients with Differentiated Thyroid Cancer

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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 retrospective 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, or 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 42.2 months. 26 patients underwent surgery or lobe resection following radiation for persistent disease. 3 patients experienced failure in this setting. 8 patients developed distant metastatic disease following radiation therapy. Median time to distant metastasis was 37 months. 3 patients experienced death due to disease progression following radiation treatment. Median OS to death was 31 months. Median PFS to death was 20 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.

breast, or bone). Contrast this with our current edition, 

AJCC 8: T2 is defined as ≥t=2 cm, <4 cm; T3 as ≥t= 4 cm or minor 

to, 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 sys- 

tems. 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 

this patient had persistent disease at EOT.

Purpose/Objective(s): Anaplastic thyroid cancer is a rare tumor of the thyroid gland. It is characterized by rapid growth, local invasion, and metastasis. The overall survival rate is poor, with median survival ranging from 10 to 18 months.

Materials/Methods: We reviewed the records of patients with Anaplastic Thyroid Cancer who received treatment at our institution between 2010 and 2019. The patients were divided into two groups: surgery followed by radiation therapy (SRT) and radiation therapy alone (RT).

Results: A total of 30 patients with Anaplastic Thyroid Cancer were identified. The median age of the patients was 55 years (range, 20-80 years). The median follow-up time was 36 months (range, 6-120 months). The overall survival rate was 32% at 2 years and 15% at 5 years. The 5-year overall survival rate for the SRT group was 30%, compared to 10% for the RT group (P = 0.03). The median progression-free survival was 6 months in the SRT group and 3 months in the RT group (P = 0.01). The median overall survival was 3.2 months in the SRT group and 1.5 months in the RT group (P = 0.01).

Conclusion: Our study suggests that surgery followed by radiation therapy may offer improved survival outcomes in patients with Anaplastic Thyroid Cancer compared to radiation therapy alone. Further studies with larger patient populations are needed to confirm these findings.
A Phase II Prospective Trial of Photobiomodulation in Limiting Oral Mucositis in the Treatment of Locally Advanced Head and Neck Cancer Patients

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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 6600 cGy (±500 cGy) and 486 mg/m² of platinum-based chemotherapy. At baseline, all patients had grade 0 mucositis by WHO scale assessment. At 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 OMG (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.


Weekly Versus Tri-Weekly Paclitaxel and Carboplatin in Combination with Cetuximab in Recurrent/Metastatic Head and Neck Cancer Patients: a Toxicity Analysis

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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.


Can patient reported quality of life predict locoregional recurrence in oropharyngeal cancer?

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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.

**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<0.0001). PG was also associated with a reduction in 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 differ 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 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.

(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 compared the effect of 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**

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**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.

**Author Disclosure:** T.Q. Huang: None. R.K. Chin: None. A. Raldow: Consultant; Intelligent Automation, Inc.
Quality of Life Impact and Dosimetric Predictors of Radiation-Induced Fibrosis of the Neck in Patients Treated for Head and Neck Cancer

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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<0.00001) 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 correlations were identified in surg nerized 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.


Prevalence of Comorbidities and Effect on Survival in HPV-related Head and Neck Cancer Survivors and Matched Non-Cancer Controls in the United States

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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 comorbidity 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.


Late Oral Toxicity after Photon Radiotherapy for Oropharyngeal Cancer Patients with Tongue-lateralizing and Tongue-depressing Oral Stents

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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
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 (0.99) 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 improved in late treatment, 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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**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 rescans to optimize patients’ post treatment quality-of-life. Logistic regression models predicting patient-reported xerostomia.

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Dysphagia After Primary Tors vs Non-surgical Therapies for Low-to-Intermediate Risk Tonsil Cancer: A Prospective Registry Analysis

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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 biRT (n=60). Dysphagia grade (per DIGEST) and 19-item composite MDADI were compared between groups using Kruskall-Wallis test with post-hoc Dunn’s. Dysphagia grade (per DIGEST) and 19-item composite MDADI were compared between groups using chi-square test. MDADI scores were similar between groups both at baseline (TORS 42% (26-59); uniRT 24% (12-41); biRT 38% (26-52). Patient recovery outcomes between these treatment groups were compared using chi-square test and sidak correction. We tested the association between dysphagia prevalence (DIGEST grade) and FT placement (yes/no) using chi-square test.

Results: T-classification differed by treatment group (p<0.001) with T2 or T3 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 very commonly combined with uniRT (26/37, 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): TORS 42% (24-59); 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). 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). Rates of FT placement did not differ between groups (TORS 2/38, 5%, uniRT 3/37, 8%, biRT 12/60, 20%, p = .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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Chemosensory Outcomes in Nasopharyngeal Cancer Patients Treated with Proton Beam Therapy: A Prospective Longitudinal Study

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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 IIIB-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 76% but this wasn’t statistically significant (p = 0.309) were not found to be significant factors. The patients who required GT prior to or within 14 days of radiation (CCRT) with high-dose cisplatin (HDC). Malnutrition due to oropharyngeal squamous cell carcinoma (OPSCC) is concurrent chemo-radiation (CCRT) with high-dose cisplatin (HDC). Malnutrition due to 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

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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?

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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 toxicity treatment 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

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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 G2–3 acute event was mucositis (45%). The most common G2–3 late events were pharyngitis (17%) and dysphagia (16%), while G2–3 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

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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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<table>
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<tr>
<th></th>
<th>Acute</th>
<th>SD</th>
<th>Range</th>
<th>#pts</th>
<th>Late</th>
<th>SD</th>
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<th>#pts</th>
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<tbody>
<tr>
<td>Any</td>
<td>G2–3</td>
<td>83%</td>
<td>3%</td>
<td>77%–87%</td>
<td>1927</td>
<td>35%</td>
<td>14%</td>
<td>14%–54%</td>
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<tr>
<td>Toxic death</td>
<td></td>
<td>2%</td>
<td>2%</td>
<td>1%–7%</td>
<td>1230</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
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<tr>
<td>Mucositis</td>
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<td>45%</td>
<td>15%</td>
<td>16%–74%</td>
<td>2373</td>
<td>6%</td>
<td>6%</td>
<td>1%–15%</td>
</tr>
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<td>Dermatitis</td>
<td>G2–3</td>
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<td>14%</td>
<td>7%–42%</td>
<td>1300</td>
<td>3%</td>
<td>2%</td>
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<td>40%</td>
<td>24%</td>
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<td>2249</td>
<td>16%</td>
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<td>Xerostomia</td>
<td>G2–3</td>
<td>39%</td>
<td>21%</td>
<td>8%–52%</td>
<td>1041</td>
<td>38%</td>
<td>11%</td>
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<td>0%</td>
<td>-</td>
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<td>2%</td>
<td>3%</td>
<td>0%–6%</td>
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<td>G2–3</td>
<td>8%</td>
<td>3%</td>
<td>6%–12%</td>
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<td>3%</td>
<td>0%</td>
<td>-</td>
<td>208</td>
<td>17%</td>
<td>0%</td>
<td>-</td>
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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 impedance 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 (r²=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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Characterization of Pain Symptomatology in Head and Neck Cancer (HNC) Survivors

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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.

Author Disclosure: D. Lou: None. M. Dietrich: None. J. Deng: None. B. Murphy: None.

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Serious Illness Conversations with Head and Neck Cancer Patients

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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.

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

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1Fox Chase Cancer Center, Philadelphia, PA, 2Massachusetts 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

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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 intakeconsult duration 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 0.3-0.9, p = 0.03; and 2018/2019 vs 2016/2017 HR 0.5, CI 0.3-0.9, p = 0.01, respectively).
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.

Author Disclosure: S. Perni: None. A.W. Chan: None.

Abstract 373; Table 1  IAT by site.

<table>
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<th>Diagnosis</th>
<th>Median IAT (days)</th>
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</tr>
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<td>n/a</td>
</tr>
<tr>
<td>Lacrimal (n=11)</td>
<td>14</td>
<td>2-39</td>
</tr>
<tr>
<td>Nasal cavity/paranasal sinuses (n=36)</td>
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<td>0-102</td>
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<tr>
<td>Nasopharynx (n=16)</td>
<td>13</td>
<td>0-84</td>
</tr>
<tr>
<td>Oral cavity (n=3)</td>
<td>0</td>
<td>0-17</td>
</tr>
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<td>9.5</td>
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</tr>
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<td>Unknown primary (n=2)</td>
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<td>0-7</td>
</tr>
<tr>
<td>Skin (n=10)</td>
<td>5.5</td>
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</tr>
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</table>

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 NPC. Delineation and avoidance of the middle ear structures is prudent.

**Author Disclosure:** S. Seol: None. B. Lee: None. T. Sita: None. 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

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**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.

**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.

**Author Disclosure:** L. Mammen: None. J. Bott: None. K. Hans: None. E.M. Farhangi: None. K. Adil: None.
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 chemotherapy (47.6%); 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 when staging (stage 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%).

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 major 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

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Purpose/Objective(s): Quality of life (QOL) derangements and psycho-social 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 anxiety may increase. 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 lengths, 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

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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),
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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**Evaluating Oropharyngeal Cancer Patients’ Outcomes Across Different Treatment Modalities**

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**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 survival.

**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). Multi-variable 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.
Outcomes Following Proton Therapy for Squamous Cell Carcinoma of the Larynx

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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 chemoradiation therapy. The median follow-up time was 1.9 years. Of the 14 patients treated with chemoradiation therapy, 6 patients were treated with chemoradiation therapy. The cumulative incidence rate was estimated using the Kaplan-Meier method.

Results: Forty 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 I disease, 35.7% had stage II disease, and 35.7% had stage III 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, 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.

Mitigating Radiation Induced Xerostomia with Nigella Sativa Oil

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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 limited 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.
Radiation therapy alters pharyngeal mobility and strength during deglutition in patients with head and neck cancer

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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 pharyngoepithelial 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.


Some Weight Loss During Radiation Therapy for Head and Neck Cancer Portends Better Prognosis: Single Institution Review and Matched Pair Analysis

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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**

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**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?**

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**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:** 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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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.

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Quality of Life and Functional Outcomes after Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma

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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 palate 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

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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 = 8), 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.
Updated outcomes of split course accelerated hypofractionated radiotherapy for the treatment of head and neck cancers

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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 ≥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 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.

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.


A dosimetric comparison of proton versus photon irradiation for pediatric glomus tumor

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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 parasympathetic ganglia. 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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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.

395

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 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.

396

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. Holland1; 1Oregon Health and Science University, Portland, OR, 2Mayo 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 baroreflex 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.

Author Disclosure: H. Kim: None. K. Taparra: None. J.M. Holland: None.
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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,1 T. Hackman,3 J. Blumberg,4 T.J. Galloway,4 S. Patel,1 A. Zanation,1 C. Shen,1 D.N. Hayes,1 C. Hilliard,3 R. Mehra,3 K. McKinnon,8 H.H. Wang,1 M. Weisler,1 J. Bauman,3 S. Sheth,1 and B.S. Chera1; 1University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, 2University of North Carolina at Chapel Hill, Chapel Hill, NC, 3University of North Carolina Hospitals, Chapel Hill, NC, 4Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC, 5Fox Chase Cancer Center, Philadelphia, PA, 6University 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 (NCT02609501) enrolled 29 patients with LA-HNSCC (AICC 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 CTCAE v4 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 otopathy (69.0%), nephropathy (20.7%), and neuropathy (6.9%). Primary sites included base of tongue (10), tonsil (10), supraglottic larynx (3), hypopharynx (2), and soft tissue (2). By AJCC 8 (re-staged to describe 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.


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,1 N.E. Dunlap,5 C. Nangia,4 A. Lee,3 S.M. Gordon,1 P. Kovesoo,4 V. Bar-Ad,10 A.V. Peddada Jr,11 K.T. Colvett,12 D.M. Blakaj,13 M. Bonomi,13 C. Nangia,6 A. Lee,7 S.M. Gordon,8 P. Kovoor,9 V. Bar-Ad,10 F. Worden,14 J. Holmlund,15 J. Brill,16 M. Downs,17 S.T. Sonis,18 and J. Buatti1; 1University of Iowa Hospitals & Clinics, Iowa City, IA, 2Cancer Care Northwest, Spokane, WA, 3Northeast Cancer Centre, Health Sciences North, Sudbury, ON, Canada, 4Gibs Cancer Center, Spartanburg Medical Center, Spartanburg, SC, 5University of Louisville Hospital/James Graham Brown Cancer Center, Louisville, KY, 6UCIrvine Medical Center, Orange, CA, 7HOPE Jefferson Cancer Center of East Texas, Tyler, TX, 8East Carolina University, Greenville, NC, 9Texas Oncology, Plano West, Plano, TX, 10Thomas Jefferson University Hospital, Philadelphia, PA, 11Renown Regional Medical Center, Reno, NV, 12Mountain States Health Alliance, Johnson City, TN, 13James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH, 14University of Michigan, Ann Arbor, MI, 15Galera Therapeutics, Inc., Malvern, PA, 16Galera Therapeutics, Inc, Malvern, PA, 17Statistics Collaborative, Inc., Washington, DC, 18Primary 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.

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.

Materials/Methods: 223 patients (from 44 institutions) with locally-advanced oral cavity or oropharyngeal 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% tHBM 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.


Abstract LBA 2 Table

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<td>91%</td>
<td>88%</td>
<td>NS</td>
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<tr>
<td>PFS</td>
<td>82%</td>
<td>86%</td>
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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, T272-3del, D303G, D303V, D308G, S375*, R454*, R465*), also restored TRAIL induction of the immunosuppressive cytokines. Among these, caspase-8 D303G, restored HeLa and PEA-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.


LBA 4

Mobile Patient-Facing Application for Tracking Patient-Reported Outcomes in Head-and-Neck Cancer Survivors: a Pilot Usability and Feasibility Study

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Purpose: The mobile patient-facing application (PFA) was developed to address gaps in support for head-and-neck cancer survivors (HNCs) reporting symptoms via patient-reported outcomes (PROs). The PFA, called Symptom buddy, aimed to support HNCs in their daily lives by providing self-care, symptom tracking, and access to resources. The purpose of this study was to assess the usability and feasibility of the PFA.

Materials/Methods: This mixed-methods study involved a Pilot Usability and Feasibility Study (PUsFS) of the Symptom buddy PFA. A mixed-methods design with quantitative and qualitative data collection methods was used. Participants included HNC survivors who had completed a course of radiation therapy or surgery for HNC, and were engaged in follow-up care with a physician. The PFA was evaluated for usability and feasibility through an online survey and semi-structured interviews. Participants were recruited through clinical sites, social media, and email listservs. The study protocol was approved by the institutional review boards at Northwell Health.

Results: A total of 39 HNC survivors participated in the study. Participants reported high satisfaction with the PFA, with 86% reporting that the PFA was easy to use and 92% reporting that the PFA was helpful. The qualitative data revealed that participants found the PFA useful for tracking symptoms, accessing resources, and monitoring treatment progress. The PFA also provided psychological support and enhanced the patients’ self-efficacy. Feedback from participants was positive, with suggestions for improvement including adding more personalized cues and interventions.

Conclusion: The mobile patient-facing application for tracking patient-reported outcomes in head-and-neck cancer survivors was shown to be feasible and user-friendly. The PFA demonstrated potential for improving patient outcomes, satisfaction, and quality of life by providing a personalized and interactive platform for symptom tracking and support.

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 eligible 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.

Author Disclosure: W. Yarbrough: None. N. Issaeva: None.

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-κB 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.
etanexor) 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/kg x3x3s) or KPT-9274 (100 mg/kg BIDx5x3s) when combined with lenvatinib (50 mg/kg BIDx5x3s) 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**

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**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. Detailed loco-regional failure sites of 14 patients in relation to current SNI and RdENI policy is summarized in Table below.

**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.


### 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: RTG 3507 Foundation (KEYSTROKE)**

S. Wong, 1 P. Torres-Saavedra, 2 Q.T. Le, 3 C. Chung, 4 S. Jing, 5 M.S. Huq, 6 R. Jordan, 7 D.A. Clump II, 8 D.M. Blakaj, 9 M.W. Straza Jr, 10 R. Koyfman, 3 Department of Medical College of Wisconsin, Milwaukee, WI; 4 NRG Oncology Statistics and Data Management Center, Philadelphia, PA; 5 Stanford University, Stanford, CA; 6 H. Lee Moffitt Cancer Center, Tampa, FL; 7 Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA; 8 University Of Pittsburgh Medical Center, Pittsburgh, PA; 9 UCSF, San Francisco, CA; 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 therapy with policy of selective neck irradiation and reduced (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 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 < 7 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 × 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-OPp16 negative 86%; T1-2 57%, T3-4 43%; N0 86%, N2 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+ 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.

**Author Disclosure:** S. Wong: None. P. Torres-Saavedra: None. Q. Le: Research Grant; Amgen, NIH, Redhill. Travel Expenses; BMS. Stock; Aldeia, Head and Neck Cancer International Group (HNCIG). Chair of head and neck committee- design clinical trial; RTOG NRG Cooperative group. President elect; American Radium Society. C. Chung: None. S. Jing: Travel Expenses; UPMC. M. Huq: None. R. Jordan: None. D.A. Clump: None.
Comparative analysis of the cellular profile and architecture of metastatic and non-metastatic lymph nodes

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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.


Cohort Expansion Study of Neoadjuvant Immunoradiotherapy in Locoregionally Advanced HPV+ and HPV- Head and Neck Squamous Cell Carcinoma

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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 irPAC and rate of pathologic and radiographic down-staging after neoadjuvant therapy. A Simon two-stage optimal design was applied, 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.

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.


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