2024 Multidisciplinary Head and Neck Cancers Symposium (February 29 - March 2, 2024)

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TRAVEL GRANT WINNERS

Congratulations to the 2024 Multidisciplinary Head and Neck Cancers Symposium travel grant winners, awarded based on the high quality of their submitted abstracts.

Samuel Regan, MD, University of Michigan
"FDG-PET-based Selective De-escalation of Radiotherapy for HPV-Related Oropharynx Cancer: Results from a Phase II Trial"

Pooja Karukonda, MD, Duke University Medical Center
"Patient-Reported Outcomes and Financial Toxicity in Head and Neck Cancer (PaRTNer): Longitudinal Assessment of Financial Toxicity and Coping Mechanisms"

2024 Multidisciplinary Head and Neck Cancers Symposium (February 29 - March 2, 2024)

Oral Scientific Sessions

1

Pembrolizumab with or Without Lenvatinib As First-line Therapy for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC): Phase 3 LEAP-010 Study

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Purpose/Objective(s): The PD-1 inhibitor pembrolizumab (pembro) is approved as first-line monotherapy for patients (pts) with PD-L1-expressing R/M HNSCC (PD-L1 combined positivity score [CPS] ≥1). A phase 1b/2 study of pembro plus the multikinase inhibitor lenvatinib (len) showed promising antitumor activity and manageable toxicity in pts with HNSCC. In LEAP-010, a phase 3, randomized, placebo-controlled, double-blind study, we hypothesized that first-line len + pembro would improve efficacy compared with placebo + pembro, and have a manageable safety profile, in pts with PD-L1 CPS ≥1 R/M HNSCC (NCT04199104).

Materials/Methods: Eligible pts had R/M HNSCC incurable by local therapy, PD-L1 CPS ≥1 by central laboratory assessment, known HPV status, and ECOG PS 0 or 1. Pts were randomized 1:1 to len 20 mg or placebo orally once daily plus pembro 200 mg IV Q3W for ≤35 cycles given until intolerable toxicity, progression, or withdrawal. Primary end points were ORR and PFS per RECIST 1.1 by BICR and OS; secondary end points were DOR per RECIST 1.1 by BICR and safety. Per the prespecified analysis plan, ORR and PFS are reported from the first interim analysis (IA1) and OS and DOR are reported from IA2. Data cutoff dates were July 6, 2022 for IA1 and May 30, 2023 for IA2.

Results: 511 pts were randomized to len + pembro (n = 256) or placebo + pembro (n = 255). Median follow-up (ie, time from randomization to data cutoff) was 11.5 months (mo; range, 0.0-27.6) for IA1 and 21.3 mo (range, 9.0-38.4) for IA2. At IA1, median PFS was 6.2 mo (95% CI: 5.1-7.2) for len + pembro vs 2.8 mo (95% CI: 2.0-4.0) for placebo + pembro (HR: 0.64, 95% CI: 0.50-0.81; P=0.0001040). At IA1 and among the 351 pts with ≥6-mo follow-up, ORR was 46.1% (95% CI: 38.6-53.7) for len + pembro vs 25.4% (95% CI: 19.1-32.6) for placebo + pembro (difference 20.2, 95% CI 10.5-29.6, P=0.0000251). At IA2, median DOR was 10.1 mo (range, 1.3-30.9) for len + pembro vs NR (1.2-32.2) for placebo + pembro. At IA2, the median OS was 15.0 mo (95% CI: 13.2-17.0) for len + pembro vs 17.9 mo (95% CI: 13.8-21.6) for placebo + pembro (HR = 1.15, 95% CI: 0.91-1.45; P=0.882), with respective 24-month OS of 35.7% (95% CI: 29.0-42.4) and 40.0% (95% CI: 32.8-47.1). At IA2, 156 (61.4%) pts on len + pembro had grade ≥3 treatment-related adverse events (TRAEs) vs 45 (17.8%) on placebo + pembro, 28% vs 8% pts discontinued any treatment due to TRAEs, and 7 vs 3 pts had treatment-related deaths, respectively.

Conclusion: In pts with PD-L1 CPS ≥1 R/M HNSCC, first-line len + pembro significantly improved PFS and ORR, but not OS, compared with pembro alone. The safety profile was consistent with previously reported data; more TRAEs were found in pts receiving len + pembro. Further research is needed to identify effective treatment options for these pts.

2

Pembrolizumab and Cabozantinib in Recurrent Metastatic Head and Neck Squamous Cell Carcinoma (RMHNSCC): 2-year Long Term Survival Update with Biomarker Analysis

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Purpose/Objective(s): Anti-programmed cell death protein 1 (PD-1) therapy is a standard of care in recurrent metastatic head and neck squamous cell carcinoma (RMHNSCC). Vascular endothelial growth factor receptor tyrosine kinase inhibitors have immunomodulatory properties and may improve clinical outcomes in combination with anti-PD-1 therapy. Pembrolizumab and cabozantinib were well tolerated and showed promising clinical activity in patients with RMHNSCC in our reported phase 2 trial. Baseline CD8+ T cell infiltration correlated with overall response rate (ORR) (p=0.0512). We report 2-year follow-up results focusing on long-term efficacy and safety of this combination as well as further biomarker analyses.

Materials/Methods: This open label, single arm, multicenter, phase 2 study screened 50 patients with RMHNSCC, of whom 36 received pembrolizumab and cabozantinib. The primary endpoint was (ORR) as well as safety and tolerability. Secondary endpoints included PFS, OS, and correlative studies of tissue and blood. We report the 2-yr long term efficacy and safety of this regimen. Multiplex immunohistochemistry staining for CD3, CD8, CD20, and CD103+ cells, as well as hypoxia gene expression signature were evaluated and correlated with ORR, PFS and OS.

Results: With a median follow-up of 22.4 months (95%CI 19.2-31.8), 14 pts (38.9%) remain alive with 7 pts (19.4%) having no disease progression and 1 pt (2.8%) with no evidence of disease. One pt continues on treatment. Median PFS was 12.8 mos., with 1-yr PFS of 53.2% (95% CI 38.8-72.9%) and 2-yr PFS of 32.6 % (95% CI 18.8-56.3%). Median OS was 27.7 mos, with 1-yr OS of 73.8% (95% CI 60.4-90.1%) and 2-yr OS of 54.7% (95% CI 38.9-76.8%). Median duration of response is 12.6 mos, with 2-yr rate of 38.5% (95% CI 30.8-81.8%). Most common grade 3-4 treatment-related adverse events (TRAEs) included AST increase and oral mucositis (5.6%); ALT, bilirubin, GGT, and lipase increase (2.8% each); and hyponatremia (2.8%). TRAEs persisting beyond 12 months from enrollment include hypothyroidism (5.6%) and increased AST and ALT (5.6%). The higher median number of tumor-infiltrating CD103+ cells correlated with improved OS (HR=0.15, p=0.007).

Conclusion: Long-term results of our phase II pembrolizumab and cabozantinib study in RMHNSCC demonstrate encouraging 2-yr PFS and OS and maintaining manageable safety profiles. Our findings support further investigation of this combinatorial regimen in a confirmatory randomized trial. Evaluation of CD103 + cells as a predictive biomarker deserves further validation.

3

Final Analysis of the Phase 4 KEYNOTE-B10 Study: First-Line (1L) Pembrolizumab (pembro) + Carboplatin (carbo) + Paclitaxel (pacli) for Recurrent/Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC)

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Purpose/Objective(s): The standard-of-care (SOC) first-line treatment (1L) for R/M HNSCC consists of pembrolizumab (pembro) + platinum + fluorouracil (5-fluorouracil). However, 5-fluorouracil is associated with potential administration complications and related toxicity, creating the need for alternative chemotherapy combinations. The global, prospective phase 4 KEYNOTE-B10 study (NCT04489888) evaluated pembro + carboplatin (carbo) + paclitaxel (pacli) as 1L therapy for R/M HNSCC. Interim results of KEYNOTE-B10 showed promising antitumor activity for the initial 82 patients and manageable safety after a median follow-up of 8 months, suggesting that this 5-fluorouracil−free regimen could be a viable alternative for 1L R/M HNSCC. We report the protocol-specified final analysis including outcomes for all 101 enrolled patients.

Materials/Methods: Patients with previously untreated R/M HNSCC, regardless of their PD-L1 status, were administered pembro 200 mg IV Q3W (≤35 cycles) and ≤6 cycles of pacli 100 mg/m^2 IV Q1W (days 1 and 8) or 175 mg/m^2 IV Q3W and carbo AUC 5 mg/mL/min IV Q3W until PD, intolerable toxicity, or patient withdrawal. The primary end point was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points were DOR and PFS per RECIST v1.1 by BICR, OS, and safety.

Results: At February 20, 2023, data cutoff, treatment was ongoing for 15 patients (14.9%) while 86 (85.1%) discontinued treatment, primarily because of PD (n = 62, 61.4%). Median follow-up was 18.9 months (range, 9.1-27.0). Confirmed ORR by BICR was 48.5% (95% CI, 38.4-58.7); comprising 7 patients (6.9%) with confirmed CR and 42 (41.6%) with confirmed PR (table). Median (95% CI) PFS was 5.6 months (5.1-6.7), and OS was 13.1 months (9.6-15.2). Any-grade treatment-related adverse events (TRAEs) occurred in 96 patients (95.0%). Grade 3-5 TRAEs occurred in 76 patients (75.2%), most commonly decreased neutrophil count (44.6%) and anemia (19.8%).

Conclusion: The promising efficacy and safety data obtained from the final analysis of the KEYNOTE-B10 trial suggest that pembro + carbo + pacli

could be an additional treatment option to meet current clinical needs as a 1L therapy for R/M HNSCC.

Abstract 3 − Table 1

	Pembro + carbo + pacli N = 101
ORR by BICR, n (% [95% CI])	49 (48.5 [38.4-58.7])
CR by BICR, n (%)	7 (6.9)
PR by BICR, n (%)	42 (41.6)
PD-L1 CPS ≥1, n	81
ORR by BICR, n (% [95% CI])	36 (44.4 [33.4-55.9])
PD-L1 CPS ≥20, n	41
ORR by BICR, n (% [95% CI])	18 (43.9 [28.5-60.3])
DCR, n (% [95% CI])	76 (75.2 [65.7-83.3])
DOR, median (95% CI), mo	5.5 (4.2-6.7)
PFS, median (95% CI), mo	5.6 (5.1-6.7)
OS, median (95% CI), mo	13.1 (9.6-15.2)
12-mo OS rate, % (95% CI)	52.3 (42.1-61.5)
18-mo OS rate, % (95% CI)	37.8 (27.6-47.9)

4

A Phase II Trial of Personalized Immunotherapy in Patients (pts) with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M HNSCC) That Have Progressed on Prior Immunotherapy.

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Purpose/Objective(s): There is a great need for improvement in outcomes in pts with R/M HNSCC that have progressed on anti-PD-1 mAb (IO) and the development of a more personalized treatment (Tx) approach.
Materials/Methods: Our phase II prospective study evaluated a drug selection strategy based on immune gene expression. Included pts had progressed on prior IO and received ≤3 lines of Tx. All pts underwent a biopsy during screening that was analyzed via the OmniSeq immune report card (IRC). The IRC reports a panel of 397 genes as a relative rank score (RRS) where expression of each gene is compared to a reference population, normalized to a value between 1 and 100. If the CTLA4 vs LAG3 RRS difference was ≥ 15.2, pts were "selected" to receive Nivolumab (N) plus Ipilimumab (I) (if CTLA4 higher) or N + Relatlimab (R) (if LAG3 higher). If the CTLA4 vs. LAG3 RRS difference was < 15.2, pts were randomized 1:1 to N+I or N+R. The primary endpoint was the ORR by RECIST 1.1 of Tx in those "selected" for Tx. DCR (CR/PR/SD) was estimated with Wilson Score 95% confidence intervals. For RNA Seq analysis, proportion analysis of highly expressed genes (≥75 RRS) across groups were compared to <75 RRS. Fisher exact test was performed on each gene for the comparisons, genes with p<0.05 were filtered out to examine whether the proportion is higher or lower in a particular category.
Results: 20 pts were enrolled, and 18 were evaluable for ORR. Primary site was larynx/hypopharynx (5), oral cavity (2), oropharynx [11 (10 HPV+)]. Most recent Tx was IO monotherapy (11), chemo plus IO (5), or chemo (2). 9/18 pts were also platinum failure. Best response was SD in 5 patients. The DCR was similar in all 18 pts (28%) and by regimen N+R (n=11 27%), N+I (n=7, 28%). 6 pts were "selected" for Tx, all receiving N+R with a DCR of 33% (95%CI: 9.7, 70), median duration of SD of 133.5 days. 12 patients were randomized, with DCR of 25% (95%CI:8.9-53.2), median duration of SD of 55 days. We analyzed the highly expressed genes (≥75 RRS) from 26 pts [enrolled (20) + screened(6)]. Genes highly expressed in >90% of pts included: KRT5, TRIM29, and >50%: EGFR, GITR, KREMEN1, S100A8, TGFB1, CCNB2, LEXM. PRDM1 was expressed in a higher proportion of progressing pts (62%) vs. SD (0%) (p=.04). Comparing the most recent prior Tx, IO alone (n=16) vs. chemo (alone or with IO)(n=10), a higher proportion of chemo pts expressed: GNLY, OAS1, IFIT3, IDO2, IL12B (p<0.05) while TGFB1 was higher after IO alone (p=0.04).
Conclusion: Our unique study prospectively evaluated a Tx selection strategy based on immune gene expression. Although efficacy was low with both N+I and N+R, prospective selection was feasible and selected pts had a numerically higher DCR, with a longer duration of SD. This represents a first step toward a more personalized approach to treatment. Further gene expression analysis of this cohort is ongoing.

5

HPV Serology and Circulating Viral DNA for Detection, Genotyping, and Risk-Stratification in p16+ Oropharyngeal Cancer

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Purpose/Objective(s): The incidence of human papillomavirus-positive (HPV+) oropharyngeal cancer (OPC) has increased rapidly in North America. HPV serology has been proposed as a sensitive, scalable, and cost-effective early detection test. HPV seropositivity can precede clinical presentation of OPC by several years, so additional diagnostic and/or surveillance procedures may be necessary to optimize early cancer detection. The potential for HPV circulating tumor DNA (ctDNA) to confirm a diagnosis of OPC in seropositive individuals is poorly understood. Moreover, the concordance of baseline HPV serology and HPV ctDNA and their respective associations with cancer burden in OPC patients are not known. We hypothesized that plasma levels of HPV antibodies and HPV ctDNA are associated with disease burden in a cohort of p16+ OPC patients.

Materials/Methods: We analyzed pre-treatment peripheral blood plasma from 100 patients with non-metastatic p16+ OPC treated with definitive (chemo)radiotherapy. A multiplex ELISA was used for serologic evidence of HPV proteins (L1, E1, E2, E4, E6, E6) from 10 HPV genotypes, quantified by mean fluorescence intensity (MFI). Plasma HPV ctDNA was quantified by whole viral genome sequencing utilizing a custom HPV-targeted capture panel for 38 HPV genotypes (HPV-seq). Gross tumor volume (GTV) was obtained from the sum of all target contours on computed tomography simulation scans. Statistical tests Kruskal-Wallis and Pearson's r were used to compare the assays.

Results: Seropositivity and HPV ctDNA positivity were found in 100% of cases. Serological results indicated 10 genotypes, and HPV ctDNA results indicated 9 distinct genotypes; both assays identified HPV16 as the most prevalent genotype (98% for each). Among the 98 patients with detectable HPV16 within ctDNA, HPV16 E6 seropositivity demonstrated high sensitivity (95%), while E1 (50%), E4 (47%), E7 (66%), and L1 (63%) demonstrated considerably lower sensitivities. HPV ctDNA but not HPV16 E6 MFI was positively associated with disease burden as determined by T- and N-category (Table 1), and by GTV (ctDNA vs GTV, r=0.47 p=1.0e-06; E6 MFI vs GTV, r=-0.14 p=0.17).

Conclusion: This is the first report to compare HPV serology and HPV ctDNA sequencing in OPC patient plasma. Both tests were highly sensitive and could identify multiple oncogenic HPV genotypes. The level of HPV16 ctDNA but not HPV16 E6 antibodies in plasma was associated with disease burden. These findings have potential implications for early detection and prognostication.

Abstract 5 – Table 1: Comparison of HPV16 E6 (MFI) serology and HPV ctDNA quantification (copies/ml)

N-Category (UICC 8th Ed.)	N0 (n=3)	N1 (n=69)	N2 (n=24)	N3 (n=4)	P (Kruskall-Wallis)
Serology	10666	10422	9475	5772	0.34
ctDNA	602	4800	6151	55668	0.050
T-Category	T1 (n=24)	T2 (n=45)	T3 (n=16)	T4 (n=15)	
Serology	11014	10331	8569	8568	0.32
ctDNA	1719	9224	12397	3241	0.098

6

Ultrasensitive Liquid Biopsy in Patients with p16-Positive Oropharyngeal Cancer Using HPV-seq

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Purpose/Objective(s): Plasma HPV DNA could detect molecular residual disease (MRD) after (chemo)radiotherapy (CRT/RT) for oropharyngeal cancer (OPC). Whole HPV genome sequencing (HPV-seq) could both genotype and quantify HPV DNA more sensitively than digital polymerase chain reaction (dPCR). We compared HPV-seq and dPCR pre- and post-RT in a large, prospective OPC cohort. We hypothesized that HPV-seq is more sensitive and more accurately predicts recurrence by MRD.

Materials/Methods: We recruited patients (pts) with non-metastatic p16-positive OPC (TNM8 stage I-III) undergoing curative-intent CRT/RT. Each pt had peripheral blood plasma prospectively collected at pre-RT and 3-months post-RT. The primary endpoint was recurrence-free survival (RFS) and secondary endpoint was overall survival (OS). Time-to-event analysis was performed using the Kaplan-Meier method with log-rank tests and multivariable Cox regression. HPV-seq was performed using a validated hybrid capture panel targeting 38 HPV genomes and 15 recurrently mutated genes in OPC. dPCR was performed using a validated multiplexed assay targeting HPV16 E6/E7. HPV DNA levels were expressed as copies/mL plasma and log-transformed for statistical tests.

Results: We performed HPV-seq and dPCR on pre- and post-RT samples from 245 pts. Median follow-up was 52.3 (4.5-95.8) months, and 3-yr RFS was 87.9%. HPV-seq detected plasma HPV DNA in 237 (97%) pts pre-RT (HPV16-only: 161, non-HPV16: 16, mixed: 60) with 0.017-364867 copies/mL. Of pre-RT samples with HPV-16 reads detected on HPV-seq, HPV-16 dPCR was detectable in 202/221 (91%), with 0.32-37313 copies/mL on dPCR. Copies of HPV16 DNA per mL were strongly correlated between HPV-seq and dPCR (R=0.986). Post-RT, HPV-seq detected residual HPV DNA in 48 (20%) pts. Of these, dPCR detected 19 and did not detect 29, of which 6 had non-HPV16, and the other 23 had HPV16 with <1.37 copies/mL. Of pts with 3-year recurrence, post-RT detection of HPV DNA by HPV-seq predicted 16/23 (sensitivity=70%, NPV=95.5%, AUC=0.81) and by dPCR predicted 7/23 (sensitivity=30%, NPV=91.0%, AUC=0.63). Post-RT residual HPV DNA on HPV-seq was associated with poorer RFS (3-yr 58% vs. 96%, p<0.0001) and OS (3-yr 61.4% vs. 97.1%, p<0.0001). Of 192 pts with HPV16 undetectable by dPCR at post-RT, the 23 with residual HPV DNA detected by HPV-seq still had poorer RFS (3-yr 62.5% vs. 95.7%, p<0.0001) and OS (3-yr 75.0% vs. 96.9%, p<0.0001) than those with HPV-seq clearance. Adjusting for T and N staging, post-RT residual HPV16 DNA was independently prognostic of RFS and OS by either assay, with odds ratios for RFS of 14.91 [6.19, 35.94] for HPV-seq and 5.17 [2.09, 12.81] for dPCR.

Conclusion: Whole viral genome sequencing genotypes and quantifies plasma HPV DNA. Pts with residual HPV DNA had poorer RFS and OS, independent of stage. For HPV16, HPV-seq and dPCR are strongly correlated, but HPV-seq is more sensitive with higher negative predictive value and predicted 2.3x more 3-year recurrences in OPC pts.

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Novel Radioenhancer NBTXR3 Activated by Radiotherapy in Cisplatin-Ineligible Locally Advanced HNSCC Patients: Final and Exploratory Results of a Phase I Trial

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Purpose/Objective(s): New approaches are needed for frail or elderly patients with locally advanced head and neck squamous cell carcinoma (LA HNSCC) who are unfit to receive cisplatin with concurrent radiotherapy (RT). NBTXR3 is a first-in-class radioenhancer, composed of functionalized hafnium oxide nanoparticles, administered by a single intratumoral injection and activated by RT. NBTXR3 locally amplifies the anti-tumoral response of RT without adding toxicity to surrounding healthy tissue as shown in a randomized trial in soft tissue sarcoma. This two-part study: dose-escalation followed by the dose-expansion part reported here, evaluated the safety and preliminary efficacy for NBTXR3 activated by RT in elderly or frail patients ineligible to cisplatin.

Materials/Methods: Patients with previously untreated AJCC 8th Stage III-IVA or T3,T4 SCC of the oral cavity or oropharynx (OPC) ineligible to cisplatin were enrolled. Eligible patients received a single IT injection of NBTXR3 at the recommended dose (22% of the baseline tumor volume) followed by RT (IMRT 70 Gy in 35 fractions). The primary objectives of the dose expansion part were to test the recommended dose, to confirm its safety, and obtain preliminary evidence of efficacy. The secondary

objectives included the evaluation of progression-free survival (PFS) and overall survival (OS).

Results: 56 patients in the dose expansion part were treated from April 2019-January 2022; 44 patients were evaluable for objective tumor response. In the all treated (AT) population, median age was 72 years. 67% had age-adjusted Charlson Comorbidity Index scores ≥4, 55.4% had OPC (45.2% HPV+) and 80% had T3-4. Median injected volume of NBTXR3 was 13.6 [0.6-57.1] mL. Grade ≥ 3 treatment emergent adverse events (TEAE) reported as potentially related to NBTXR3 or to injection procedure were 1.3% all TEAEs reported, respectively. In the evaluable (EV) population, ORR of the NBTXR3 injected lesion was 81.8%; complete response rate was 63.6%. ORR of injected and non-injected lesions was 79.5%. Median PFS by independent central review was 11.4 mos (AT) and 16.9 mos (EV). Median OS was 18.1 mos (AT) and 23.1 mos (EV). PFS of injected lesion (LPFS) was 16.9 mos (AT) and not reached (EV). Exploratory analyses of additional endpoints will be presented.

Conclusion: NBTXR3 IT injection followed by activation with RT was confirmed to be feasible and well tolerated in elderly or frail patients with LA HNSCC and significant comorbidities. The high ORR suggests that NBTXR3+RT is effective in this elderly population ineligible to cisplatin with a high unmet medical need. These results reinforced by exploratory analyses support our ongoing phase III study comparing NBTXR3/RT± cetuximab vs. RT±cetuximab in platinum-based chemotherapy ineligible elderly patients with LA-HNSCC: NANORAY 312 (NCIT04892173).

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Phase I/II Study of A Novel MDM-2 Inhibitor (APG-115-Alrizomadlin) in p53 Wild Type Salivary Gland Cancers

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Purpose/Objective(s): Malignant salivary gland cancers (SGC) are rare tumors of the head and neck with no approved therapeutics in the recurrent and/or metastatic setting. The most common histology is adenoid cystic carcinoma (ACC) and the median progression free survival (mPFS) in patients with untreated disease is 2.8 months (mo). MDM2 gene amplifications are common in these tumors and preclinical evidence supports the activity of MDM2 inhibitors both as monotherapy (mono) and in combination (combo) with chemotherapy. APG-115/alrizomadlin is a potent oral small molecule MDM2 inhibitor. Based on these preclinical data, we hypothesized that APG-115 would have significant clinical activity in p53 wildtype (p53wt) SGC.

Materials/Methods: A phase 1/2 multicenter study was conducted to evaluate the safety and efficacy of APG-115 +/- carboplatin in p53wt SGC. Eligibility criteria included high grade malignant SGC, no evidence of a p53 mutation, and ≥20% progression by RECIST v1.1 in the preceding 12 mo. The primary endpoints were dose-limiting toxicity and overall response rate, secondary endpoints included PFS, duration of response, and overall survival. Data were continuously monitored and doses assigned using the time-to-event continual reassessment method. The trial design was

modified to a single arm study of APG-115 mono after safety meetings noted increased toxicities in the combo arm. As of 9/29/2023, there were 30 evaluable pts in the mono arm and 4 pts in the combo arm.

Results: Overall 82% (32/34) had stabilization of their previously progressive disease (clinical benefit rate 94%). An ORR of 10% and 25% were reported for the mono and combo cohorts, respectively, with a mPFS of 10.5 mo in the mono arm. In the mono treated cohort - ACC histology pts appeared to have a greater benefit (PR: 13%, SD 83%, mPFS 10.5 mo) compared to non-ACC (PR: 0%, SD 86%, mPFS 6 mo). 2 DLTs were reported. The most common treatment-related adverse events (TRAEs) of any grade included nausea (77%), fatigue (73%), and thrombocytopenia (50%). 70% had ≥ G3 TRAE. In the combo arm the most common TRAEs of any grade included: anemia (100%), thrombocytopenia (100%), and neutropenia (75%). All the pts on the combo arm had ≥ G3 TRAE. Updated ORR, PFS and survival data as well as results of correlative studies will be presented.

Conclusion: APG-115 monotherapy demonstrates promising antitumor activity among pts with p53*wt* SGC with an acceptable safety profile. Greatest apparent activity was seen in patients with ACC. This is the first study to evaluate the activity of MDM2 inhibition in patients with SGC. These data strongly support confirmatory clinical trials of MDM2 inhibitors in p53*wt* SGC, specifically ACC.

Abstract 8 − Table 1

	Arm A-Monotherapy	Arm A- ACC	Arm A-Non-ACC	Arm B-Combination
n	30	23	7	4
Best Response				
PR	3	3	0	1
SD	25	19	6	3
PD	2	1	1	0
Survival Outcomes*				
6 mo PFS	75% (59, 95)	89% (75, 100)	34% (11, 100)	75% (43, 100)
mPFS, mo	10.5 (8.1, ne)	10.5 (8.1, ne)	6 (5, ne)	10.3 (5.5, ne)
*95% CI, ne= Not estimable				

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A Phase II Single Arm Trial of Induction and Concurrent Vismodegib with Curative Intent Radiation Therapy for Locally Advanced, Unresectable Basal Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): Locally advanced, unresectable basal cell carcinoma (BCC) can be treated with radiation therapy (RT), but locoregional control (LRC) rates are unsatisfactory. Vismodegib is a hedgehog pathway inhibitor (HPI) active in BCC which can radiosensitize cancer cells in preclinical models. We evaluated the combination of vismodegib and RT for patients with locally advanced, unresectable BCC. The hypothesis was that the combination of the vismodegib and RT would yield higher rate of LRC than historically observed with RT or vismodegib alone.

Materials/Methods: In this multicenter, single-arm, phase II study, patients with locally advanced, unresectable BCC of the head and neck ≥2 cm in size and/or with nodal metastasis but without distant metastasis received 12 weeks of induction vismodegib at the FDA approved dose and frequency (150 mg orally once daily) followed by 7 weeks of concurrent vismodegib and RT to 66-70 Gy in 33-35 fractions. The primary endpoint was LRC rate at 1 year after the end of treatment. Secondary endpoints included objective response according to RECIST, progression-free and overall survival (PFS and OS), adverse events according to CTCAE v4.1 and patient reported quality of life (PRQOL) according to the Skindex-16. Tumor genomic sequencing was an exploratory endpoint in a subgroup of patients.

Results: Twenty-four patients received vismodegib; 5 were unable to complete 12 weeks of induction therapy. LRC was achieved in 91% (95% CI 68-98%) of patients at 1 year. Response rate was 63% (95% CI 38-84%) after induction vismodegib and 83% (95% CI 59-96%) following concurrent vismodegib and RT. With median follow up of 5.7 years, 1-year PFS and OS rates were 100% and 96%, and at 5-year PFS and OS rates 78% and 83%. Distant metastasis or BCC-related death has not been observed. The most frequent treatment-related adverse events were dysgeusia, fatigue and myalgias occurring in 83%, 75% and 75% of patients. Seven serious adverse events occurred in 4 patients, none of which were related to protocol therapy. No grade 4-5 treatment-related adverse events occurred. PRQOL demonstrated clinically meaningful improvements in all subscales, with emotions and functioning improvements persisting for a year after the end of treatment. All patients that underwent tumor sequencing were found to have an oncogenic loss of function mutation in *PTCH1*, but no functional alterations were detected in *SMO, SUFU* or *GLI1*.

Conclusion: This is the first prospective trial of RT for locally advanced, unresectable BCC of the head and neck and demonstrated the combination of vismodegib and RT yielded high rates of LRC and PFS, and durable improvements in PRQOL. In practice, this combined modality approach may improve the outcomes of select patients with locally advanced, unresectable BCC of the head and neck.

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A Phase 2 Multi-Center, Placebo-Controlled, Randomized Study to Assess the Safety and Efficacy of Parenteral TK-90 for Preventing Radiation-Induced Mucositis in Patients with Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): The aim of this research was to rigorously assess the clinical safety and therapeutic efficacy of parenteral TK-90, an anhydrouridine inhibitor targeting uridine phosphorylase, in ameliorating severe oral mucositis (SOM) in patients diagnosed with squamous cell carcinoma of the head and neck (SCCHN) undergoing radiation therapy (RT).
Materials/Methods: In Phase 2, a multi-center, placebo-controlled, randomized, assessor-blind investigation, the study enrolled 24 patients with non-metastatic SCCHN across four medical institutions from July 2022 to February 2023. Diverse modalities of RT (2D RT, 3D RT, Intensity-modulated RT) were administered at a daily dosage of 2.0 Gy, five days weekly, reaching cumulative dosages of 60-70 Gy. Participants were randomized to receive either 45 mg/kg of parenteral TK-90 or a placebo via intravenous administration, both pre-and post-RT sessions, concomitant with rigorous oral mucositis (OM) evaluations. The primary endpoints constituted the ascertainment of Grade 3- or 4 (SOM) incidences in TK-90 vs. placebo cohorts as quantified by the World Health Organization (WHO) scale. Secondary endpoints encompassed the evaluation of SOM duration and scrutinization of drug-related toxicity. Secondary endpoints included assessing the duration of SOMand evaluating toxicity related to the study drug.
Results: Demographic and treatment-related parameters were statistically balanced across both study arms. The median age of the enrolled participants was 50 years, with a range of 36 to 70 years, and a preponderance (79%) were male. Utilizing Fisher's exact test for statistical validation, TK-90 manifested a statistically significant reduction in SOM incidence in contrast to the placebo: 0.0% vs. 50.0% in the seventh week (p=0.014) and 8.3% vs. 75.0% in the ninth week (p=0.003). In addition, the Wilcoxon Rank-sum Test affirmed a significant decrement in SOM duration (p=0.026). Overall, 3 (12.5%) patients had Adverse events (AEs) that were probably related to the study drug. All those AEs were Grade 1 fever and infusion-related reactions and were resolved within 4 days of occurrence. One patient experienced unrelated serious cardiac arrest. No TK-90-related treatment-emergent serious adverse events (AEs) or discontinuations were reported.
Conclusion: Parenteral administration of TK-90 presents a promising and effective strategy for preventing radiation-induced OM in SCCHN patients. Notably, TK-90 demonstrates good tolerability, with no Grade 3- 4 AEs reported, and does not lead to an increase in RT-associated toxicities. These optimistic results merit additional validation in an upcoming, more expansive randomized study.

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Two-Year Intention-to-Treat Analysis for Tumor Outcome in Patients Treated with Avasopasem for Oral Cavity and Oral Pharynx Primaries

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Purpose/Objective(s): IMRT plus cisplatin (CRT) is established treatment for LAHNC, but ~70% of patients develop severe oral mucositis (SOM), often requiring feeding tube nutrition. Avasopasem (AVA) is an investigational small molecule selective dismutase mimetic converting superoxide to hydrogen peroxide, which may protect normal cells from, and potentially sensitize cancer cells to, RT (Anderson 2019, Sishc 2021). In a randomized, double-blind phase 3 trial, AVA substantially reduced duration and incidence of SOM versus placebo (PBO) without an adverse effect on safety or 1-yr survival (Anderson 2022). Present analysis assesses intention-to-treat (ITT) 1-yr tumor outcomes and 2-yr survival.
Materials/Methods: Patients with oral cavity (OC) or oropharynx (OP) LAHNC receiving 60-72 Gy of IMRT (≥50 Gy to ≥2 OM sites) plus cisplatin (weekly or q3 weeks) randomized 3:2 to IV AVA 90 mg vs PBO before each RT fraction. Tumor outcomes (LRC, PFS & DDC) were followed 1 year and overall survival (OS) 2 years, both for ITT and key subpopulations: Overall Tumor Stage; OC vs OP; HPV- vs HPV+; Definitive vs Post-op; QW vs Q3W cisplatin. Results were also compared to prior trial and recent literature.
Results: 455 patients were randomized, but 20 never received AVA or PBO, and 28 were excluded because of administrative suspension of dosing, leaving ITT safety/efficacy population of 407. Two-year OS was similar for AVA and PBO, 89% (95% CI: 84-93) vs 93% (95% CI: 88-96), respectively. Patients had similar one-year LRC (94% AVA vs 98% PBO), PFS (95% vs 98%), and DDC (96% vs 97%). Nine excess deaths occurred in AVA arm with clustering of 4 at 1 enrollment site. Four non-oncologic deaths occurred during CRT with disparate causes, and 4 excess deaths occurred late, 18 -21 months from randomization (1 progressive disease, 1 second cancer, 2 unknown). In HPV+ low-risk patients (n = 327) both arms had comparable or superior OS (AVA = 93%, PBO = 98%) to similar populations treated on RTOG 1016 (2y OS 90%) and the AVA phase 2b GT-201 study (93%). No antagonism of AVA on tumor control was evident in patients with high-risk disease: 2-year OS in patients with AJCC stage III/IVA/IVB (n=146) was 84% AVA vs 83% PBO, OC tumor site (n=59) was 76% vs 81%, and HPV negative (n=71) was 74% vs 74%, respectively. 80% of patients were treated definitively with CRT, with no detriment on 2-yr overall survival in this subgroup (92% AVA vs 95% PBO). There was no difference in OS based on cisplatin dosing schedule (QW 89% vs 93%, Q3W 90% vs 93%).
Conclusion: Based on 2-year ITT analysis, AVA does not seem to have oncologic detriment in both low and high-risk patients compared to PBO. Both arms performed better than previously published data for a mixed OC/OP, HPV+/HPV- population.

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Acute Toxicity Results from the Randomized Assessment of Cisplatin Dosing Interval for Ototoxicity (RADIO) Trial Comparing Chemoradiation (CRT) with Cisplatin Q3weekly to Weekly for Locally Advanced Squamous Cell Carcinoma of the Head and neck (LASCCHN)

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Purpose/Objective(s): The acute toxicities of CRT for LASCCHN patients (pts) remain challenging and may be influenced by the type and schedule of radiosensitizer. We report adverse effects (AEs) observed during CRT with different cisplatin schedules on the RADIO trial.

Materials/Methods: Adult pts ECOG 0-2 eligible for RADIO had histologically confirmed LASCCHN of oral cavity, oropharynx, nasal cavity, hypopharynx, larynx or PUK; were planned for primary curative CRT; had adequate baseline hearing and were suitable for q3weekly cisplatin. Pts received RT 70 Gy/35 fractions to gross disease and were randomized (stratified by tumor p16 status) to concurrent cisplatin either 100 mg/m^2 days 1, 22 and 43 or 40 mg/m^2 weekly x 7 weeks. Co-primary outcomes for RADIO were incidence of hearing loss determined by audiogram and hearing-related QoL both measured 1-year from start of treatment. Secondary outcomes included need for amplification, HRQoL and incidence of tinnitus, neuropathy and nephropathy. AEs were recorded prospectively using CTCAE v4.03 grading criteria. All pts provided informed consent for this REB approved trial.

Results: 99 eligible pts (85 males/14 females) median age 61 years (40-75) were enrolled at 3 centers in Ontario, Canada between Feb 2019 to June 2023. Baseline pt characteristics were well balanced between treatment arms. Most pts had oropharyngeal cancer (87%) and most tumors were p16-positive (93%). 50 pts received cisplatin q3weekly for 3 (74%), 2 (22%) or 1 cycle (4%); mean total dose 251.2 mg. 49 pts received weekly cisplatin for a median of 6 cycles (range, 3-7); mean total dose 247.3 mg. There were no treatment-related deaths. 87 pts had currently available AE data and most had multiple typical Grade 1-2 AEs. 7 pts (8%) reported only Grade 1 AEs. 33 pts (37.9%) reported 72 AEs ≥Grade 3: 32/15 pts treated q3weekly, and 40/18 pts treated weekly. More pts receiving q3weekly cisplatin had Grade 3 neutropenia (5 vs 2 pts) and AKI (2 vs 0 pts). More pts receiving weekly cisplatin had Grade 3/4 AEs (18 vs 15), Grade 3 dysphagia/mucositis (8 vs 4 pts) and anemia (2 vs 0 pts). One pt each on the weekly cisplatin arm had Grade 3 pulmonary embolism, Grade 4 acute psychosis and Grade 4 thrombocytopenia. Similar rates of acute Grade 3 dehydration, electrolyte disturbances, and weight loss were observed; as well as pt-reported ≥Grade 2 hearing impairment (8 vs 6 pts) and peripheral neuropathy (2 vs 2 pts).

Conclusion: RADIO participants had similar total cisplatin exposure by treatment arm. There were some differences in acute toxicity patterns

related to cisplatin schedule. Severe neutropenia and AKI appeared to be more frequent with q3weekly cisplatin, and total severe AEs including dysphagia/mucositis and anemia appeared higher with weekly cisplatin. AE data continue to be collected and will be reported. Precise conclusions about ototoxicity differences will be made based on the definitive 1-year primary audiometric and QoL endpoints of RADIO which will be analyzed and reported in 2024. (NCT03649048)

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Patient-Reported Outcomes and Financial Toxicity in Head and Neck Cancer (PaRTNer): Longitudinal Assessment of Financial Toxicity and Coping Mechanisms

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Purpose/Objective(s): Patients undergoing definitive radiation therapy (RT) for head and neck cancer (HNC) are at risk for financial toxicity (FT) given complex treatment and high symptom burden. The PaRTNer study was designed to longitudinally assess FT.

Materials/Methods: Single-institution, prospective study (NCT3506451) of adult patients with non-metastatic HNC undergoing definitive RT. Surveys at baseline, 3 mo, and 6 mo post-RT collected demographics, a validated FT measure (COST [score <26 indicating FT, with lower scores indicating worse FT]), and measures of cost coping. Paired t-tests, Wilcoxon Rank Sum tests, ANOVA, and Spearman correlation estimates were used to test associations.

Results: 60 patients were enrolled from 2019-2021. Most were white (76%) and male (68%). Median age was 61 (range 42-86). Most had completed at least some college (71%), and had employer-sponsored private insurance (55%). 50% were working at least part-time, and most earned >\$60k/yr (55%); median annual income was Median COST scores at baseline, 3 mo, and 6 mo post-RT were 25, 30, and 32, respectively (p<0.001, baseline vs 6 mo). Baseline COST score was associated with race, with white patients having higher COST scores than Asian or Black patients (p=0.02, median 27, 22, and 14, respectively; lower scores indicating worse FT). There was an association between sex and COST score (p=0.04, median score 22 female vs 28 male), and a positive correlation between higher COST score and higher annual income (p<0.0001, r=0.62). Older age, lower level of education, government-sponsored insurance, non-full-time employment, and higher number of ED visits were also associated with lower COST score (worse FT). To pay for cancer care, patients reported decreased spending on basics (26%) or leisure activities (44%); using savings (33%) or borrowing money (27%); and skipping medication doses (10%) or not filling prescriptions (19%) at baseline. These coping mechanisms were associated with lower COST scores (worse FT). In particular, patients who skipped medication doses had lower COST scores across all time points (baseline: 5 vs 26, p=0.001; 3 mo: 4 vs 24, p=0.02; 6 mo: 11 vs 34, p=0.04). At 6 mo post-RT, 31% had ongoing decreased work productivity. Mean COST scores for these patients were consistent with FT (<26) and significantly

lower than for those who were able to return to work full-time (10 vs 29, p=0.008).

Conclusion: Surveyed patients undergoing definitive RT for HNC experienced FT at baseline, and this improved post-RT. Non-white, female, and low-income patients are at higher FT risk. Even 6 mo after diagnosis, some patients continued to struggle with FT. They used cost coping measures like skipping medication doses and had ongoing decreased work productivity. These findings show that FT is both an acute and a late treatment-related toxicity.

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Long-Term Efficacy of Risk-Directed, De-Escalated Post-Operative Adjuvant Therapy for Surgically Resected Locally Advanced, Human Papillomavirus-Positive Oropharynx Squamous-Cell Carcinoma (HPV+ OPSCC): A Non-Randomized, Multi-Arm Phase 2 Trial

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Purpose/Objective(s): Post-operative adjuvant therapy is recommended for most patients with resected locally advanced, HPV+ OPSCC, and includes radiation therapy (RT) alone or with cisplatin. For patients with high-risk pathology (positive margin and/or extra-nodal extension [ENE]), cisplatin (cumulative dose 300 mg/m^2) is typically given with RT 60-66 Gy (POACRT). For patients with intermediate-risk pathology (lympho-vascular or peri-neural invasion, ≥2 involved regional lymph nodes, single involved lymph node >3 cm, and/or T_3 or N_2 pathology), POART 60-66 Gy is given alone, although a recent randomized phase II multi-institutional trial suggests select patients may be treated with 50 Gy. These treatments are curative in most patients; however, toxicity is substantial. In this non-randomized, multi-arm phase 2 trial, we assessed the efficacy of two de-escalated (de-) adjuvant therapy regimens in patients with surgically resected locally advanced, HPV+ OPSCC. Patients with high-risk pathology received de-POACRT (cisplatin 100 mg/m^2 x1 dose and 42 Gy RT given in 2 Gy daily doses). Patients with intermediate-risk pathology received de-POART (42 Gy) alone. Here, we report long-term efficacy outcomes for these patients.

Materials/Methods: Patients with operable AJCC 8th Edition clinical stage I-III (excluding $T_{1-2}N_0$, T_4, and N_3) HPV+ OPSCC underwent trans-oral robotic or laser surgery and selective neck dissection. Risk-directed adjuvant therapy included de-POACRT for high-risk pathology and de−POART for intermediate-risk pathology. Efficacy endpoints included relapse and death. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: We enrolled and treated 20 patients with de-POACRT and 30 patients with de-POART. Overall patient and tumor characteristics included median age 58 years (range 34-72), smoking history ≥10 pack-years 36%, primary pathologic tumor site (base of tongue 42%; tonsil 54%, unknown primary 4%), and AJCC clinical stage (I-76%; II-24%). Median

follow-up of all patients was 46.2 months (IQR 36.6- 52.7). All but 1 patient had follow-up of at least 32 months. Relapse occurred in 2 patients on de-POACRT and 1 on de-POART. Death occurred in no patients after de-POACRT and in 1 patient after de-POART (cause of death unknown, but disease-free 3 months earlier). In the de-POACRT cohort, estimated 4 year PFS was 90% and OS was 100%. In the de-POART cohort, estimated 4 year PFS was 97% and OS was 100%.

Conclusion: Among patients with surgically resected locally advanced, HPV+ OPSCC, 4 year PFS and OS were excellent in patients with high-risk pathology treated with one cycle of cisplatin and 42 Gy RT, and in patients with intermediate-risk pathology treated with 42 Gy RT alone.

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NRG-HN003: Phase I and Expansion Cohort Study of Adjuvant Pembrolizumab, Cisplatin and Radiation Therapy in Pathologically High-Risk Head and Neck Cancer with Exploratory Biomarker Correlatives

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Purpose/Objective(s): Patients with locoregional, pathologically high-risk HNSCC recur frequently despite adjuvant cisplatin-radiation therapy (CRT). Targeting PD1 may reverse immunosuppression induced by HNSCC and CRT.

Materials/Methods: We conducted a phase I trial (n=34) adding pembrolizumab (200mg q3 weeks) to adjuvant CRT, with correlative studies to identify biomarkers of clinical benefit. Eligible patients had resected HPV-negative, AJCC 7 stage III-IV oral cavity, pharynx, or larynx HNSCC, with extracapsular nodal extension or positive margin. We assessed PD-L1 expression using the 22c3 Ab in a CLIA laboratory test and correlated with disease-free survival (DFS) and overall survival (OS) using a combined positive score (CPS) threshold of ≥20/ or <20. The CPS threshold of 1+/< 1 could not be evaluated due to insufficient patients in the <1 group. DFS

and OS rates were estimated by Kaplan-Meier method, and groups were compared by 2-sided log-rank tests. Hazard ratios (HR; CPS ≥20/ or <20) were estimated by Cox models. To determine mechanisms and biomarkers of clinical benefit, additional exploratory analyses to assess the relationship between clinical outcomes and serum (Luminex, soluble checkpoints, cytokines, and chemokines), tumor/tissue (single-plex IHC, 7-color multispectral tumor staining, whole-exome sequencing, CD8 T cell infiltration, CD8/Treg ratio, and mutational status), and PBMC (spectral flow cytometry and T cell frequencies and activation states) biomarkers are being performed.

Results: Adding pembrolizumab to adjuvant CRT was well tolerated. Nine (26.5%) and 25 (73.5%) patients had CPS <20 or ≥20. At a median follow-up of 3.1 years (0.04-3.3), 15 (10) DFS (OS) events were reported, 3 (2) in the CPS <20 group and 12 (8) in the CPS 20+ group. Biomarker effect HR was 1.94 (95% confidence interval [CI] 0.54-6.89; p=0.30) for DFS and 1.70 (95% CI 0.36-8.00; p=0.50) for OS. Two-year DFS estimates were 77.8% (95% CI 50.6-100) for CPS <20 and 52.3% (95% CI 31.9-72.7) for CPS 20+. Two-year OS estimates were 77.8% (95% CI 50.6-100) for CPS <20 and 69.6% (95% CI 50.8-88.4) for CPS 20+.

Conclusion: In this small patient sample, no significant association of PD-L1 expression with clinical outcomes was identified. Circulating inflammatory cytokine and immune checkpoint biomarkers have been performed and are being correlated with clinical outcomes.

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FDG-PET-based Selective De-escalation of Radiotherapy for HPV-Related Oropharynx Cancer: Results from a Phase II Trial

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Purpose/Objective(s): Treatment de-escalation in HPV-related oropharyngeal squamous cell carcinoma (OPSCC) aims to minimize toxicity without compromising oncologic outcomes. We conducted a prospective phase II nonrandomized trial using FDG-PET imaging biomarkers to selectively de-escalate chemoradiotherapy (CRT). We hypothesized this would maintain locoregional control in all patients while decreasing toxicity in the de-escalated cohort.

Materials/Methods: Eligible patients had stage I-II p16+ or HPV+ OPSCC with baseline tumor FDG-PET-avidity. All were planned to receive 70 Gy to gross disease and 56 Gy to elective nodal regions in 35 fractions with concurrent weekly carboplatin/paclitaxel. Mid-treatment PET was performed at fraction 10. If metabolic tumor volume was reduced by ≥50%, CRT was completed at 54 Gy in 27 fractions. The primary objective was to demonstrate non-inferiority of 24-month locoregional recurrence (LRR) overall by comparing the upper 90% confidence interval (CI) to 25%. Secondary objectives were failure patterns, survival, ctDNA trends, mpMRI, and toxicity. Toxicity measures included patient-reported outcomes (UWQOL-RTOG, FACT-HN, XQ). Kaplan-Meier analyses were used for survival outcomes.

Results: Eligible patients (n = 84) were enrolled from 2018 - 2023; 90% male, 75% stage I, and 48% never-smokers. De-escalation criteria were met in 42% (n = 35). The 54 Gy cohort had fewer patients with T3 tumors (3% vs 20%, p = 0.02) and lower median baseline weight (188 vs. 207 lbs, p = 0.015); no other differences in distribution of baseline factors nor initial RT plans were found. Median follow up at this analysis was 28.9 mo overall, 31.6 mo for 54 Gy and 25.9 mo for 70 Gy patients. LRR at 24 mo was 7% (90% CI: 2% - 12.1%) in the entire cohort, 5% (90% CI: 0% − 10.5%) with 70 Gy, and 10% (90% CI: 1% - 18.2%) with 54 Gy. There were 5 LRR and 3 distant recurrences overall. Of 4 patients with only LRR, 3 were salvaged surgically without systemic therapy and have no evidence of disease, and 1 (70 Gy cohort) declined surgery. There was 1 cancer-related death after a distant-only recurrence in the 70 Gy cohort. Median weight loss from baseline in the 54 Gy cohort was significantly less at 1 mo (6.5% vs. 10.6%, p <0.001) and 3 mo (6% vs. 12.6%, p <0.001) post-RT. Use of feeding tube during RT or ≤1 mo post-RT was numerically better in 54 Gy patients (11% vs. 16%, p = 0.5). The 70 Gy cohort had one grade 4 (G4) carotid artery injury and one likely treatment-related death. The 54 Gy cohort had no G4+ toxicities, with less decrement from baseline in median UWQOL-RTOG scores for pain subscale at 1 mo (5 vs 10, p = 0.01) and mucus subscale at 12 mo (0 vs. 5, p = 0.2) post-RT. Remaining PRO instrument analyses are ongoing and will be presented.

Conclusion: Mid-treatment FDG-PET may be a reliable biomarker to selectively de-escalate radiation dose in early-stage HPV+ OPSCC to improve toxicity while preserving oncologic outcomes.

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Early Outcomes for A Single-Arm Phase I/II Trial of Selective Avoidance of Nodal VolumEs at Minimal Risk (SAVER) in the Contralateral N0 Neck of Patients with p16-Positive Oropharynx Cancer

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Purpose/Objective(s): Most patients with p16-positive oropharynx cancer (p16+OPC) receive contralateral elective nodal radiation therapy that improves regional control but increases acute and long-term toxicity. We hypothesize a validated volume reduction in the contralateral neck is effective with an improved toxicity profile in patients with p16+OPC receiving definitive or adjuvant radiation therapy.

Materials/Methods: Patients with newly diagnosed p16+OPC without contralateral nodal involvement treated with primary proton or photon-based (chemo)radiation or adjuvant (chemo)radiation following Transoral Robotic Surgery (TORS) were eligible for enrollment. The reduced contralateral nodal volume included regions of level II and III based on high risk locations for contralateral nodal disease. The primary endpoint was elective out-of-field contralateral nodal failure. Dosimetric comparisons between standard versus reduced elective nodal volumes were analyzed. Acute toxicity was collected using CTCAE v4.0.

Results: Fifty-two patients were enrolled of which 36 (69.2%) received definitive (chemo)radiation. Sixteen (30.8%) patients underwent adjuvant radiation following TORS of which 5 (31.2%) received concurrent platinum-based chemotherapy for high risk features. Proton therapy was used in 38 (73.1%) patients. There were no contralateral nodal failures at a median follow up of 15 months (range 1-24 months). For the first 20 patients enrolled, dosimetric comparison of the reduced contralateral elective nodal volumes to consensus elective nodal volumes demonstrated a decrease in the mean dose (18.5 Gy to 14.1 Gy [p<0.05]) and V30 Gy (21.3% to 11.6% [p<0.01]) of the contralateral parotid dose. Significant differences were independent of radiation modality or technology. Acute grade 3 toxicity was observed in 13 (25%) patients including 6 (11.5%) who received a PEG tube during treatment. There were no grade 4-5 acute toxicities, and at 6 months follow up no patients had retained a PEG tube.

Conclusion: Selective avoidance of nodal volumes at minimal risk in the N0 contralateral neck of patients with p16-positive oropharynx cancer can be safely performed while maintaining excellent regional control. Both dose to contralateral organs at risk and toxicities were favorable. Maturation of follow-up is ongoing to further support this de-intensification strategy.

Abstract 17 — Table 1

Feature	Total (n=52) %	(chemo) radiation (n=36) %	Surgical (n=16) %
Age at diagnosis, median, (range), y	57 (41 — 83)	60 (44 — 83)	54 (41-79)
Gender, n (%) Male Female	45 (86.5) 7 (13.5)	34 (94.4) 2 (5.5)	11 (68.8) 5 (31.3)
Race White Black	47 5	32 4	15 1
Site BOT Tonsil Multiple	21 (40.4) 24 (46.2) 7 (13.5)	14 (38.9) 15 (41.7) 7 (19.4)	7 (43.7) 9 (56.3) 0
cT stage 1 2 3 4	18 (34.6) 24 (46.2) 8 (15.4) 2 (3.8)	9 (25.0) 17 (47.2) 8 (22.2) 2 (5.5)	9 (56.3) 7 (43.8)
cN stage 0 1 3	7 (13.5) 42 (80.8) 3 (5.8)	6 (16.7) 28 (77.8) 2 (5.6)	1 (6.3) 14 (87.5) 1 (6.3)
Modality Photons Protons	15 (28.8) 37 (71.2)	10 (27.8) 26 (72.2)	5 (31.3) 11 (68.8)

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Criteria for the Diagnosis of Extranodal Extension Detected on Radiological Imaging in Head and Neck Cancer: HNCIG International Consensus Recommendations

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Purpose/Objective(s): Pathological evidence of extranodal extension (pENE) is known to be a negative prognostic factor in head and neck cancer (HNC). The available evidence suggests that radiologically or imaging-detected extranodal extension (iENE) is also associated with worse clinical outcomes. Although the reliable detection of iENE before initiation of treatment may help guide treatment selection, the diagnostic criteria and terminology used to report iENE are not widely agreed upon. The Head and Neck Cancer International Group (HNCIG) conducted a Delphi survey with the aim of developing a framework for decision-making on the most important areas of iENE diagnostic criteria and terminology requiring consensus.

Materials/Methods: All 21 international member groups of the HNCIG were invited to nominate a practicing radiologist with HNC expertise to join the global consensus panel. A three-round modified Delphi process with 18 international radiology experts representing 14 national clinical research groups was completed. Online questionnaires via a survey platform included four main sections pertaining to iENE: diagnostic criteria, inter-observer agreement, the impact of core biopsy, and classification systems.

Results: We generated consensus recommendations on the terminology and criteria for iENE to harmonize clinical practice and research. Overall, we achieved consensus on 47 items. The experts strongly agreed that there is no difference in iENE features between HPV-positive and HPV-negative HNC. Regarding iENE features, the experts strongly agreed that indistinct nodal margin, extension into perinodal fat, extension into adjacent structures, and conglomerate/matted/coalescent nodes should all be used as criteria by which to identify iENE, while nodal necrosis and capsular thickening should not be used as criteria for identifying iENE. The experts also agreed that "conglomerate", "matted", and "coalescent" do not describe different things. Importantly, we also proposed a new 5-tier classification system to aid diagnosis, which was supported by the majority of respondents over existing systems but which will require clinical validation. The experts strongly agreed in support of using a standardized classification system and synoptic reporting for iENE. The recommendations have been endorsed by 19 national organisations, representing 34 countries.

Conclusion: These guidelines will serve to standardize definitions and classifications to aid reporting in both clinical practice and research. We have also proposed a new classification system for the diagnosis of iENE that requires validation before wider clinical implementation.

Poster Q&A Sessions

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Surrogate Endpoints in p16-Positive Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): The increased incidence of HPV-related cancers has motivated efforts to optimize treatment paradigms for these excellent-prognosis patients. Validation of surrogates for overall survival (OS) could expedite the evaluation of new therapies. We sought to validate candidate intermediate clinical endpoints (ICE) in trials assessing definitive treatment of p16-positive oropharyngeal cancer with (chemo)radiation.

Materials/Methods: A retrospective review of five multicenter randomized trials (NRG/RTOG 9003, 0129, 0234, 0522, 1016) was performed. Eight ICEs were considered as potential surrogates for OS: freedom from local progression (FLP), freedom from regional progression (FRP), freedom from distant metastasis (FDM), freedom from locoregional progression (FLRP), freedom from any progression (FFP), locoregional progression-free survival (LRPFS), progression-free survival (PFS), and distant metastasis-free survival (DMFS). A two-stage meta-analytic framework was used to evaluate the ICEs, with $R^2 \geq 0.7$ as criteria for clinically relevant surrogacy.

Results: In total, 1,373 patients with p16-positive oropharyngeal cancer were analyzed. Median follow-up was four years. For the first condition, correlating the ICE with OS at the individual and trial level, FDM and the three composite endpoints LRPFS, DMFS, and PFS were highly correlated with OS at the patient level (Kendall's $\tau > 0.85$) and at the trial arm level ($R^2 > 0.75$). For the second condition, correlating treatment effects of the ICE and OS, the composite endpoints LRPFS, DMFS, and PFS met criteria with R^2 of 0.89, 0.97, and 0.92, respectively. Treatment effects on the remaining ICEs were less highly correlated and did not meet surrogacy validation criteria for OS for the second criterion.

Conclusion: LRPFS, DMFS, and PFS are validated surrogates for OS in p16-positive oropharyngeal cancers treated with (chemo)radiation and may serve as clinical trial endpoints.

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Radiotherapy for Older Patients with Oropharyngeal Cancer

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Purpose/Objective(s): Previous research has estimated that the optimal radiotherapy utilisation (RTU) rate for patients with head and neck cancer is 74%. However, there is limited data on the actual RTU rate for older patients with head and neck cancer and in particular, older patients with oropharyngeal cancer. The aims of this research were to determine the actual RTU rate, radiotherapy dose, comorbidity, and survival rate according to age group for patients with oropharyngeal cancer.

Materials/Methods: Linked Queensland Cancer Register, radiotherapy and hospitalisation data from the Queensland Oncology Repository from 2012 to 2021 was used to determine the number of patients diagnosed with Oropharyngeal cancer. Analysis of the actual RTU rate, radiotherapy dose received, level of comorbidity, and survival data for the following age groups, <65 years, 65-74 years, 75-84 years and 85+ years was undertaken.

Results: Between 2021-2021, 3044 people were diagnosed with Oropharyngeal cancer. HPV positive disease was identified in 64% of the cohort. Only 2% (46) were aged 85+ years and 9% (271) were aged 75-84 years. For those aged 85+ years, 43% received radiotherapy versus 73% for people aged 75-84 and 81% aged 65-74 years. The most common radiotherapy dose for those aged 65-74 years was 66 Gy + (68%) versus 48% for those aged 75-84 years. A comorbidity score of 2+ for those aged 65-74 years occurred in 9% of people versus 37% of those aged 85+ years. The 2-year survival rate for patients aged 65-74 years was 77% versus 26% for patients aged 85+ years.

Conclusion: For patients with oropharyngeal cancer, the actual radiotherapy utilisation rate and the proportion of patients receiving 66Gy+ decreases with increasing age. The 2-year survival rate also decreases with increasing age. The number of comorbidities increases with increasing age. Further work is required to determine the relationship between the comorbidity score and the actual RTU rate, and other reasons for the potential reduction in the RTU rate.

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Feasibility of Adaptive Radiation Therapy for Human-Papilloma Virus-Positive Oropharyngeal Cancer Patients Using MR-Guided RT

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Purpose/Objective(s): Human-papilloma virus (HPV)-positive oropharyngeal cancer (OPC) is a potentially curable disease with a rising incidence in the United States. Despite improved radiation therapy (RT) techniques, toxicities remain a concern. Adaptive RT (ART) can reduce radiation to organs-at-risk (OARs) without sacrificing tumoricidal dose to target volumes, but there are barriers to routine implementation. These include (1) technical barriers to ART and (2) timing of ART for shrinking tumor volumes or changes in body contours (such as weight loss or contracture of OARs). Magnetic resonance (MR)-Linacs allow for frequent, online, and standardized plan adaption, made possible by improved visualization of tumors and OARs as well as an integrated planning system. This study aims to: (1) develop an ART workflow protocol using an online adapt-to-shape approach on our MR-Linac while (2) identifying barriers to performance (such as treatment times and the influence to quality of life) and (3) characterizing quantitative imaging biomarkers during RT.

Materials/Methods: Sixteen eligible participants with non-metastatic HPV+ OPC will be enrolled. All participants will undergo simulation on our institution's MR-Linac. Participants will receive concurrent chemoRT with a dose prescription of 70 Gy in 35 fractions on the MR-Linac. ART planning will occur every 5th fraction of RT (i.e. the 6th, 11th, 16th, 21st, 26th, and 31st fractions). At 3-months follow-up, participants will undergo another MRI scan on the MR-Linac. The primary endpoint is to assess the accuracy of ART by (1) calculating the percent difference between initial and weekly ART plans and (2) confirming accuracy of deformable imaging registration. Secondary endpoints include (1) treatment times, calculated from guidelines set by the MR-Linac Consortium Head and Neck Tumor Site, as well as (2) quality of life measurements using study questionnaires (i.e. EORTC QLQs Core 30 and H&N43) at all study timepoints. As an exploratory endpoint, quantitative imaging biomarkers of tumor and nodal volume regression will be descriptively characterized.

Results: This study is a trial-in-progress and has not reached pre-specified endpoints for analysis.

Conclusion: MR-Linacs are underutilized in the treatment of OPC patients, despite previous validation of clinically acceptable head and neck RT plans. For OPC patients, replanning is often static (i.e. at one timepoint), offline, and limited in standardization. This work will help clarify the role of MR-guided ART in HPV+ OPC: its feasibility, quality, and overall patient experience.

Clinical Trial Registry Number (NCT): NCT05849142

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Biomarker-Driven Radiation Therapy Dose Reduction after Transoral Robotic Surgery for the Treatment of HPV-Positive Oropharyngeal Cancer

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Purpose/Objective(s): HPV-driven oropharyngeal squamous cell cancer (OPSCC) has a high cure rate and a high burden of treatment-related toxicities. Transoral robotic surgery (TORS) is a treatment option for patients with early-stage disease. Most patients will be recommended adjuvant RT. ECOG 3311 was a phase 2 trial demonstrating that patients with intermediate pathologic risk factors treated with 50 Gy of adjuvant RT had similar survival as those receiving the current standard 60 Gy of adjuvant RT. However, 50 Gy is still associated with meaningful toxicity, specifically with respect to impaired swallowing function. Circulating tumor HPV DNA (ctHPVDNA) is a sensitive marker of tumor recurrence. We posit that HPV-driven OPSCC patients with intermediate pathologic risk factors and an undetectable post-operative ctHPVDNA are a subset of patients with particularly excellent prognosis that are candidates for further de-escalation of therapy. We initiated a trial treating those patients with 36 Gy of adjuvant RT based on the hypothesis that swallow function (as measured by the MD Anderson Dysphagia Inventory (MDADI)) will be improved at one year compared to historical controls from ECOG 3311.

Materials/Methods: We opened a single institution study (NCT05387915) including patients with pT1-2, N0-1, M0 HPV-related OPSCC who had TORS resection of their primary site and neck dissection. Inclusion criteria include patients with <10 pack-year smoking history or a <30 pack-year smoking history if >10 years since last tobacco consumption. Pathologic criteria include a set of intermediate risk factors (close margin (1-4 mm), perineural invasion, 2-4 positive lymph nodes or a single lymph node >3 cm, and no ENE). Patients must have a detectable pre-operative ctHPVDNA. A ctHPVDNA is drawn 7-14 days post-operatively; if negative, patients receive 36 Gy of adjuvant RT in 2.4 Gy daily fractions; if positive, they receive care per the discretion of the treating radiation oncologist. If the final surgical margin at the the primary site is >2mm, patients are eligible to have the primary tumor site omitted from the radiation volume. Our primary endpoint is 1-year composite MDADI score. Secondary endpoints include overall/progression-free survival and other quality of life metrics. The study is powered to detect an 8.5-point improvement in MDADI composite score at one year over the historical control from ECOG 3311 Arm B. With an alpha of 0.05 and a power of 0.90 we require 27 evaluable patients. Accounting for dropout, we aim to enroll 33 total patients.

Results: We have been open for approximately one year at a single institution and have enrolled 13 patients thus far. We have plans to open at two additional sites..

Conclusion: This ongoing study of ctHPVDNA-guided adjuvant RT in patients with HPV-driven OPSCC continues to accrue well.

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Adjusted RECIST Criteria for Assessing Time to Recurrence in Patients with Fully Resected Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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Purpose/Objective(s): RECIST criteria to assess response and progression in solid tumors were published in 2000 and updated to Version 1.1 in 2009. For patients with resected SCCHN and without macroscopic residual disease, no imaging-based criteria exist for the multidisciplinary team to jointly assess time to recurrence, and many components of RECIST 1.1 do not apply (eg, baseline target and nontarget lesions). However, some aspects of RECIST 1.1 criteria are applicable, including size increase thresholds for relapses in lymph nodes, indicating RECIST disease progression in patients without imaging-assessed macroscopic disease at baseline.
Materials/Methods: We developed adjusted RECIST 1.1 criteria for assessing recurrence in resected SCCHN and other solid tumors. These criteria are being evaluated in the ongoing, phase 3 XRay Vision study of xevinapant vs placebo plus radiotherapy in patients with resected, high-risk locally advanced SCCHN deemed ineligible to receive cisplatin (NCT05386550). The US Food and Drug Administration has reviewed a protocol and independent review charter based on these new criteria and stated that they have no issues or concerns with them at this time.
Results: In the adjusted RECIST 1.1 criteria, baseline assessment will only confirm the absence of radiographically detectable disease. The subsequent appearance of an unequivocal new non-nodal malignant lesion will be diagnostic of disease recurrence. With respect to lymph nodes, imaging will be acquired at baseline; however, baseline measurement of normal nodes will be performed retrospectively if the node later becomes enlarged (≥10 mm in short axis diameter [SAD]). Nodal recurrence will be confirmed by FDG-PET, biopsy, or in the absence of biopsy, ≥1 node that is ≥10 mm in SAD and increased by ≥5 mm vs baseline without nonmalignant cause. For equivocal findings (eg, very small and uncertain new lesions), treatment may continue until recurrence is confirmed by biopsy or the next imaging assessment. If relapse is confirmed at the next imaging assessment, the date of relapse should be recorded as the earlier date when relapse was suspected.
Conclusion: Adjusted RECIST 1.1 criteria to evaluate time to recurrence in patients with fully resected SCCHN are proposed. These criteria also may be applicable across adjuvant treatment settings in a variety of solid tumors, such as resected primary breast cancer.

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Comparison of Induction Cisplatin, Docetaxel, and 5-Fluorouracil to An Induction Platinum Doublet Regimen for Locally Advanced Human Papillomavirus-Associated Oropharyngeal Cancer

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Purpose/Objective(s): Management of locoregionally advanced (LA) human papillomavirus-positive oropharyngeal squamous cell carcinoma (HPV(+)OPSCC) often entails induction chemotherapy (IC) followed by definitive chemoradiation. The standard IC regimen for head and neck cancer, docetaxel, cisplatin, and 5-fluorouracil (TPF), has a high rate of toxicity. Due to the chemosensitivity of HPV(+)OPSCC, platinum-taxane doublets are often used as IC with less toxicity. No study to date has compared TPF to a platinum-taxane doublet IC regimen. The goal of this study is to compare response rates, overall survival (OS), and complications of TPF and platinum-taxane doublet IC regimens in patients with HPV(+) OPSCC undergoing treatment with curative intent.
Materials/Methods: In this retrospective analysis, patients with treatment-naive HPV(+)OPSCC treated with induction TPF were compared to patients treated with an induction platinum-taxane doublet. Tumor characteristics, responses to IC and chemoradiation, rate of hospitalization, and OS were collected.
Results: 59 patients (22 TPF and 37 platinum-taxane doublet) from July 2010 to December 2022 were included. 30 patients received carboplatin/ paclitaxel and 7 cisplatin/docetaxel. The average age was 61.1 years (range 46−83) and 84.7% of patients were male. Staging is shown in Table 1. There were no differences in completion of IC (81.2% completed TPF vs. 91.2% completed platinum doublet, p = 0.407). All patients responded to IC with a higher rate of complete response (CR) in the TPF group (TPF CR 38.1% vs. platinum doublet CR 8.8%; TPF partial response (PR) 61.9% vs. platinum doublet PR 91.2%; p = 0.014). There was no difference in response after completion of definitive chemoradiation (TPF: CR 77.2%, PR 9.1%, progression or metastasis 13.6% vs. platinum doublet: CR 75.7%, PR 16.2%, progression or metastasis 8.1%; p = 0.660). There were also no differences in hospitalizations for adverse events (36.3% in TPF vs. 40.5% in platinum doublet, p = 0.789) or recurrence (13.6% in TPF vs. 2.7% in platinum doublet, p = 0.141). The 5-year OS was 81.9% in the TPF group and 81.5% in the platinum doublet group; there was no significant difference in OS (p = 0.495).
Conclusion: Compared to patients who received IC with TPF, patients who received a platinum-taxane doublet regimen had similar OS, response after definitive chemoradiation, rate of hospitalizations, and rate of recurrence. IC with a platinum-taxane doublet for LA-HPV(+)OPSCC appears to be non-inferior to TPF and could be a de-escalation strategy for patients who are not candidates for TPF. Further prospective comparison in a clinical trial is warranted.

Abstract 105 − Table 1

Table 1	TPF	Platinum doublet
T-stage		
1	3 (13.6%)	6 (16.2%)
2	5 (22.7%)	7 (18.9%)
3	4 (18.2%)	5 (13.5%)
4	10 (45.5%)	19 (51.4%)
N-stage		
0	0 (0%)	1 (2.7%)
1	1 (4.5%)	9 (24.3%)

(Continued)

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Table 1	TPF	Platinum doublet
2	19 (86.4%)	23 (62.2%)
3	2 (9.1%)	4 (10.8%)
M-stage		
0	18 (81.8%)	37 (100%)
1	4 (18.2%)	0 (0%)

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Clinical Outcomes of Human papillomavirus (HPV) Testing Discordance in Oropharyngeal Squamous cell Carcinoma

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Purpose/Objective(s): HPV status is routinely assessed in newly diagnosed oropharyngeal squamous cell carcinoma (OPSCC) because of its prognostic significance. p16 immunohistochemistry (IHC) is typically used as a surrogate for HPV presence without direct assessment of HPV status, such as through PCR or in situ hybridization. In this study, we analyzed the discordance between p16 IHC and HPV status in patients treated with definitive (chemo)radiation (CRT) for OPSCC and any potential association with treatment outcome.

Materials/Methods: Retrospective study was performed with IRB approval. Patients undergoing radiotherapy (RT) or CRT for OPSCC at Duke University Medical Center between January 1, 2005 through December 31, 2021. Patients with positive p16 IHC but without HPV subtype were noted for further DNA PCR testing. Inclusion criteria: ≥18 years of age with available treatment records and completion of treatment. Exclusion criteria: previously treated head and neck cancer primary, metastatic or recurrent disease, or treatment at an outside facility. Associations between HPV and p16 IHC status, patient demographics (age, race, sex, tobacco use history), tumor stage (AJCC 8th edition), treatment modality, recurrence patterns and overall survival were extracted from the medical record. Time to event outcomes (OS, DFS, and LRC) were calculated from the date of diagnosis using the Kaplan-Meier method and compared between groups using the log-rank test. Categorical data was summarized with count (frequency) and compared using the chi-square test or Fisher's exact test as appropriate.

Results: 62 patients were analyzed who had p16 IHC and confirmed HPV status by PCR. 51 patients (82%) were HPV+/p16+. There was no difference in AJCC 8th edition group stage. There was also no difference between smoking status or pack years between the two groups. OS, DFS, and LRC at 3 years for all patients were 87% (95% CI: 79.0% - 95.8%), 77.2% (95% CI: 67.4% - 88.5%), and 88.5% (95% CI: 80.8% - 96.9%), respectively. OS at 3 years for HPV+/p16+ and HPV-/p16+ were 88.2% (95% CI: 79.7% - 97.5%) vs 81.8% (61.9% - 100%), respectively (p=0.058). DFS at 3 years for HPV+/p16+ and HPV-/p16+ were 80.3% (95% CI: 70.0% - 92.0%) vs 63.6% (40.7% - 99.5%), respectively (p=0.083). LRC at 3 years for HPV +/p16+ and HPV-/p16+ were 90.2% (95% CI: 82.3% - 98.7%) vs 80.0% (58.7% - 100%), respectively (p=0.083).

Conclusion: The data suggest worse survival for OPSCC patients with discordant HPV DNA and p16 positivity, although the sample size was not adequately powered to be conclusive. Further prospective studies with a larger patient population are warranted to determine if testing concordance prior to treatment could be used to refine therapeutic decision making.

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XRay Vision: A Phase 3 Study of Xevinapant Plus Radiotherapy (RT) for High-risk, Cisplatin-ineligible Patients with Resected, Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA SCCHN)

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Purpose/Objective(s): The current standard of care for patients (pts) with resected LA SCCHN who are at high-risk of disease recurrence and are cisplatin eligible is chemoradiotherapy (CRT; cisplatin + RT). For pts who cannot receive cisplatin, treatment options are limited, and there is currently no treatment specifically recommended by international guidelines. Xevinapant, a first-in-class, small-molecule inhibitor of apoptosis protein inhibitor, has been shown to restore cancer cell sensitivity to apoptosis, thereby enhancing the effects of chemotherapy and RT. In a randomized phase 2 study in pts with unresected LA SCCHN, xevinapant + CRT was associated with a 53% lower risk of death after 5 years of follow-up and a 67% lower risk of death or disease progression after 3 years of follow-up vs placebo + CRT. In preclinical SCCHN models, xevinapant + RT alone also demonstrated antitumor activity. These promising clinical and preclinical data provide a strong rationale for combining xevinapant + RT in cisplatin-ineligible pts with LA SCCHN.

Materials/Methods: XRay Vision (NCT05386550) is a randomized, double-blind, placebo-controlled, phase 3 study comparing xevinapant or placebo + intensity-modulated RT (IMRT) in pts with resected LA SCCHN who are ineligible for cisplatin and have a high risk of relapse. Eligible pts must have histologically confirmed cancer of the oral cavity, oropharynx, hypopharynx, or larynx; undergone surgery with curative intent 4−10 weeks before the start of treatment (if possible, it is recommended to start treatment within 8 weeks from surgery); high risk of relapse; no residual disease by CT scan; and ineligible for cisplatin (meeting ≥1 of the following criteria: eGFR <60 mL/min/1.73 m^2; grade ≥2 audiometric hearing loss or grade ≥2 tinnitus; grade ≥2 peripheral neuropathy; and if aged ≥70 years old, unfit according to the G8 questionnaire [score ≤14] or ineligible for cisplatin due to age limit according to national guidelines). Other eligibility criteria include ECOG PS of 0−2 and adequate hematologic and hepatic function. Approximately 700 eligible pts will be randomized to oral xevinapant (200 mg/day; Days 1−14 of a 3-week cycle) or placebo for 3 cycles + standard fractionation IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week) followed by 3 cycles of xevinapant or placebo. The primary endpoint is disease-free survival. Secondary endpoints include overall

survival, time to subsequent cancer treatments, safety, and health-related quality of life. Pts will be followed up until the last pt has been assessed for 60 months post randomization or until premature treatment discontinuation. Enrollment is ongoing in 21 countries worldwide, including the US, Mexico, and countries in South America, Europe, and Asia. The study started in October 2022, and recruitment is ongoing.

Results: Pending

Conclusion: Pending

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Enfortumab Vedotin (EV) in the Previously Treated Advanced Head and Neck Cancer (HNC) Cohort of EV-202

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Purpose/Objective(s): The prognosis of patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (SCC) is poor (median overall survival [OS] 10−13 mo), and effective treatments are needed. The cell-adhesion molecule Nectin-4 is expressed in a majority of HNCs. EV is a Nectin-4−directed antibody−drug conjugate approved as monotherapy in previously treated locally advanced or metastatic (la/m) urothelial carcinoma (UC) and, in the US, with pembrolizumab for previously untreated la/mUC ineligible for cisplatin. EV was evaluated in previously treated HNC in EV-202 (NCT04225117).

Materials/Methods: In this open-label phase 2 study, pts with la/m solid tumors enrolled in tumor-specific cohorts. In this cohort, pts had HNC not amenable to curative-intent treatment, radiographic progression on/after the last regimen, progression/relapse/discontinuation for toxicity after 1 platinum-based therapy for la/m disease, and ≤2 lines of cytotoxic therapy in the la/m setting. Pts had received prior programmed cell death protein 1/ligand 1 (PD-1/L1) inhibitor unless contraindicated. Pts received intravenous EV 1.25 mg/kg on days 1, 8, and 15 of each 28-d cycle (C) until disease progression or discontinuation criteria were met. Primary endpoint was confirmed objective response rate (ORR) per investigator assessment.

Secondary endpoints were duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) per investigator assessment; OS; and safety/tolerability. Exploratory endpoints included immunogenicity, pharmacokinetic parameters, and pt-reported outcomes.

Results: As of April 11, 2022, 46 pts were enrolled; median follow-up was 9.3 mo. Median age was 65 y, 87.0% of pts were men, and 52.2% had ≥3 prior lines of systemic therapy in the metastatic setting. Forty-five pts had SCC; 1 had adenocarcinoma. Confirmed ORR was 23.9%; DCR was 56.5%. Median time to response was 1.7 mo. Median DOR was not estimable. Median PFS and OS were 3.9 and 6.0 mo, respectively. Common treatment-related adverse events (TRAEs) were alopecia (28.3%), fatigue (26.1%), and peripheral sensory neuropathy (23.9%). Grade ≥3 TRAEs occurring in >1 pt were anemia and decreased neutrophil count (both n=2). TRAEs of special interest were skin reactions (45.7%), peripheral neuropathy (32.6%), dry eye (6.5%), and hyperglycemia (4.3%). No antitherapeutic antibodies against EV were detected. Serum EV decreased substantially from end-of-infusion concentrations before subsequent doses in C1, while plasma concentration of free monomethyl auristatin E (drug component of EV) remained high between days 1 and 15 of C1. Median global pain assessment score was 4/10 at baseline, with numeric reduction in scores (indicating pain improvement) in C3 and beyond.

Conclusion: EV demonstrated antitumor activity with manageable AEs in pts with heavily pretreated HNC post-platinum and PD-1/L1 inhibitor.

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Systematic Implementation of Effective Quality Assurance Processes for the Assessment of Radiation Target Volumes in Head and Neck Cancer

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Purpose/Objective(s): Significant heterogeneity exists in clinical quality assurance (QA) practices within radiation oncology departments, with most chart rounds lacking prospective peer-reviewed contour evaluation. This has the potential to significantly affect patient outcomes, particularly for head and neck cancers (HNC) given the large variance in target volume delineation. With this understanding, we incorporated a prospective systematic peer contour-review process into our workflow for all patients with HNC. This study aims to assess the effectiveness of implementing prospective peer-review into practice for our National Cancer Institute-Designated Cancer Center and to report factors associated with contour modifications.

Materials/Methods: Starting in November 2020, our department adopted a systematic QA process with real-time metrics, in which contours for all patients with HNC treated with RT were prospectively peer-reviewed and graded. Contours were graded with green (unnecessary), yellow (minor), or red (major) colors based on the degree of peer-recommended modifications. Contours from November 2020 through September 2021 were included for analysis.

Results: 360 contours were included. Contour grades were made up of 89.7% green, 8.9% yellow, and 1.4% red grades. Physicians with >12 months of clinical experience were less likely to have contour changes requested than those with <12 months (8.3% vs. 40.9%; p<.001). Contour grades were significantly associated with physician case load, with

physicians presenting more than the median number of 50 cases having significantly less modifications requested than those presenting less than 50 (6.7% vs. 13.3%; p=.013). Physicians working with a resident or fellow were less likely to have contour changes requested than those without a trainee (5.2% vs. 12.6%; p=.039). Frequency of major modification requests significantly decreased over time after adoption of prospective peer-contour review, with no red grades occurring >6 months after adoption.

Conclusion: This study highlights the importance of prospective peer contour-review implementation into systematic clinical QA processes for HNC. Physician experience proved to be the highest predictor of approved contours. A growth curve was demonstrated, with major modifications declining after prospective contour review implementation. Even within a high-volume academic practice with subspecialist attendings, over 10% of patients had contour changes made as a direct result of prospective peer-review.

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Oncological Outcomes of Partial thickness Calvarial Resection for Locally Advanced Scalp Malignancies

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Purpose/Objective(s): Traditionally, locally advanced scalp malignancies have been managed through composite, full-thickness calvarial resection. The aim of this study is to explore the surgical technique of partial calvarial resection for locally invasive scalp malignancies without medullary space invasion, employing a burr-down approach. This study aims to provide a comprehensive examination of its clinical applications and the postoperative oncological outcomes it yields.

Materials/Methods: This retrospective case series included 26 patients 18 years of age or older with a diagnosis of scalp cancer infiltrating the calvarial region and pericranium without infiltration of medullary space. All surgical procedures were performed at a tertiary medical center from 2012 to 2022. Comprehensive patient records were reviewed to gather data on demographics, prior medical/surgical history, the nature and duration of adjuvant therapy, imaging results, surgical outcomes, and postoperative oncological results.

Results: 26 patients with cancerous scalp lesions necessitating calvarial resection for deep margin control were identified in 22 men and 4 women. Mean age at diagnosis was 72 years. The most common histopathological diagnosis was Squamous cell carcinoma (n=15), basal cell carcinoma (n=2), melanoma (n=4), sarcoma(n=1), and non-squamous cell carcinoma skin (n=1). Partial removal of the calvarial lesions was achieved in all patients without any intraoperative complications. Twelve patients received adjuvant consisting of the following modalities: radiation (6), chemotherapy (1), immunotherapy (1), a combination of immunotherapy and radiation (2), and a combination of chemotherapy and radiotherapy (2). There were a total of 7 recurrences: local (n=3,11%), regional(n=3,11.5%), distal (n=1,3.8%). Long term local control was achieved in (n=24,88.4%) of patients. The average time from surgery to the last recorded follow-up was 19.1 months, and the average time from surgery to cancer recurrence was 15.1 months.

Conclusion: Partial calvarial resection represents a viable, safe, and effective surgical technique for cancerous tissue removal, reducing risks associated with full thickness calvarial resection, and enhancing soft tissue healing when compared to the established gold standard.

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One Year Experience of a Radiation Oncology Semi-weekly Head & Neck Contour Peer Review at a Single Institution

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Purpose/Objective(s): Because head and neck radiotherapy is complex, relying solely on a weekly chart review is inadequate for evaluating radiation oncology contours. Implementing a dedicated semi-weekly examination of all head and neck contours prior to radiation treatment planning, allowing for comprehensive assessment of images and treatment targets, may result in improved patient outcomes. Conducting a thorough assessment of all head and neck contours also exposes resident physicians to a greater volume of patient contours for education purposes.

Materials/Methods: In total, 74 consecutive head and neck cancer patients treated between August 2022 to September 2023 were discussed in a semi-weekly head and neck contour peer review prior to radiation treatment planning. Three head and neck radiation oncologists as well as four resident physicians participated. Attendance for all participants were logged. Modifications to the volumes were tracked and stratified into no changes/minor changes/major changes. If no changes were made, the plan was cleared for treatment planning. Minor changes were defined as changes to margins or nodal coverage. Major changes were defined as changes to dose, fractionation scheme, or treatment to bilateral neck.

Results: An average of 1.61 patients were discussed per review. Given the allotted time, on average this allowed for up to 18 minutes of discussion per patient. In contrast, our departmental chart rounds is allotted 1 hour for upwards of 40 patients to be discussed per patient (1.5 minutes per patient). In total, 24/74 patients underwent minor changes (32.4%) and 1 patient underwent a major change (1.3%). Overall, 7/74 patients (9.5%) of the patients were re-irradiation cases.

Conclusion: A semi-weekly, dedicated 30-minute head and neck contour review session is not only achievable but also highly practical. Further exploration of head and neck contours facilitates the incorporation of modifications into a patient's treatment strategy. In addition, discussing both primary and re-irradiation cases expands a resident physician's exposure to a greater variety of patients.

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Comparison of TTMV-HPV DNA to Gold Standard PET for Evaluation of Treatment Response in HPV-Associated Oropharyngeal Cancer after Definitive Treatment

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Purpose/Objective(s): The rise in oropharyngeal squamous cell carcinoma (OPSCC) is being driven by human papillomavirus (HPV)-associated disease. The standard of care in diagnosis and surveillance is tissue diagnosis guided by imaging, especially in the non-surgical treatment. There is interest in utilizing plasma tumor tissue-modified (TTMV)-HPV DNA in diagnosis and surveillance. The goal of the study was to compare (TTMV)-HPV DNA against the gold standard, PET-CT in OPSCC managed with definitive therapy.

Materials/Methods: This was a retrospective IRB exempt study. Patients with HPV-associated OPSCC treated with definitive concurrent chemoradiation (CRT), definitive radiation alone (RT), or surgery followed by

postoperative radiation who completed treatment from 2018 to 2023 at two treatment sites were reviewed. All patients underwent a 3-month post--treatment PET-CT scan and TTMV-HPV DNA. Additional TTMV-HPV DNA, imaging, and biopsies were ordered based on provider preference. Imaging response was assessed using Neck Imaging Reporting and Data System (NI-RADS) risk classification.

Results: Our cohort consisted of 68 patients, predominantly male (88.2%) with a median age of 66. Half of the cohort were never smokers. Cancer staging was as followed: Stage I (39.7%), II (50%), and III (10.3%) The majority (94.1%) of patients received definitive CRT, with 95.6% of these patients receiving a radiation dose of 70 Gy. 179 total TTMV-HPV DNA tests and 88 PET scans were obtained. Pre-treatment TTMV-HPV DNA was available for 60.3% of patients. Six patients (8.8%) were found to have disease failure; in two of these patients, TTMV-HPV DNA indicated failure well ahead of imaging. In this study, NI-RADS was found to have a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 83.3%, 90.3%, 45.5% and 98.2% (one false negative, 6 false positives). TTMV-HPV DNA was found to have a sensitivity, specificity, PPV and NPV of 66.7%, 98.4%, 80.0% and 96.8% (2 false negatives, 1 false positive).

Conclusion: TTMV-HPV DNA has comparable NPV and much higher PPV when compared to gold standard PET for the surveillance of HPV-related head and neck cancers. In addition to standard post-treatment imaging, TTMV-HPV DNA has the potential to serve an important role in reducing the need for repeated imaging and subsequent invasive procedures. Further prospective studies are warranted.

Author Disclosure: R. Song: None. P. Sun Cao: None. K. Sura: None.

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Induction Chemotherapy for Oropharyngeal Cancer: A Single Institution Retrospective Review

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Purpose/Objective(s): Head and neck cancers place healthy tissues in close proximity to tumor volumes, increasing toxicity risk. Induction chemotherapy (IC) allows pre-chemoradiotherapy cytoreduction. We hypothesized that treating patients with oropharyngeal cancer (OPC) to the post-induction volume would decrease grade 3+ toxicity compared with the pre-induction volume.

Materials/Methods: All OPC patients treated with curative-intent radiotherapy (RT) 70 Gy in 35 fractions with or without chemotherapy between 2013 and 2022 were selected. The subgroup treated with IC was identified. Demographic, treatment, toxicity, and efficacy data were compiled through manual chart review. Statistical software was used for evaluating local control (LC), overall survival (OS), and progression-free survival (PFS) from date of initiation of treatment to date of last followup or death using the Kaplan-Meier method. For induction patients, plan review determined whether pre-chemotherapy or post-chemotherapy volumes were contoured.

Results: 262 patients were identified. 45 patients had received IC prior to RT. For the entire cohort, median age 62 years (range 40-88), 16% female, 62% ECOG 0 and 33% ECOG 1, 96% squamous, 73% HPV+, and 65% with past smoking history. <1% cT0, 12% cT1, 28% cT2, 24% cT3, 34% cT4; 15% cN0, 14% cN1, 64% cN2, 7% cN3, with 98% cM0. Patients who received IC had a higher numerical rate of cT4 (43 vs 33%, p=0.185) or cN3 disease (14% vs 5%, p=0.10) compared to the cohort who did not receive IC. Of the 45 patients who received IC, 97% received a platinum-taxane doublet and 40% also received 5-fluorouracil. Post-induction, 6 patients (11%) experienced complete response, 2 (4%) progressive disease,

and 32 (58%) partial response; imaging was unavailable in the remainder. 78% of patients who received IC had a post-chemotherapy gross tumor volume (GTV) contoured. There was no detectable difference in grade 3+ toxicity between the patients who had IC followed by RT to pre-chemotherapy GTV vs. those with IC followed by RT to post-chemotherapy GTV (p=0.72). Patients who received IC prior to RT did not have improvement in LC, OS, or PFS compared with patients who were treated with RT alone without IC.

Conclusion: In this post-hoc retrospective single institution cohort, IC did not appear to change efficacy outcomes, consistent with published data. In patients treated with IC, there did not appear to be a difference in grade 3+ toxicity for patients who received RT to the post-chemotherapy GTV. Study limitations include small sample size, non-uniform IC regimens, and retrospective toxicity data collection. Larger prospective studies are needed to determine if post-IC GTV RT will result in decreased long-term toxicity.

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A Pilot Study Evaluating Selective Minimal Residual Disease Directed Adjuvant Radiation in Human Papilloma Virus Associated Oropharynx Carcinoma

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Purpose/Objective(s): Human papilloma virus (HPV)-associated oropharynx squamous cell carcinoma (OPC) is associated with excellent outcomes and has led to de-escalation efforts to reduce treatment toxicity. In the post-operative setting, adjuvant therapy is recommended based on traditional pathologic factors and additional biomarkers are needed to select optimal candidates for therapy de-escalation. Cell-free tumor DNA (ctDNA) is an emerging method of cancer surveillance and detecting minimal residual disease. HPV ctDNA can be detected prior to clinically apparent recurrence. In our pilot study we hypothesize that undetectable post-operative HPV ctDNA can be used to select patients for active surveillance, in which adjuvant radiation is omitted or delayed until patients develop detectable HPV ctDNA (cohort A). We also hypothesize that undetectable HPV ctDNA can be used to select for post-operative chemoradiation de-escalation to 30 Gy with concurrent chemotherapy (cohort B) in patients with positive margins or extracapsular extension (NCT05307939).

Materials/Methods: Subjects are eligible for trial enrollment if they have: detectable pre-operative HPV-16 ctDNA (min 50 copies/mL), undergone surgical resection of all gross disease, and undetectable post-operative HPV ctDNA. All patients must also have a minimum of one of the following pathologic criteria: AJCC 7 pT1N1/pT2N1/pT3 disease, N2 disease, unknown primary (pT0N1-2b) status post neck dissection, lympho-vascular invasion (LVI), peri-neural invasion (PNI), or close margin (<3 mm), microscopic positive margin, or extracapsular extension (ECE). Patients who meet the aforementioned criteria who do not have positive margins or ECE are eligible for active surveillance (Cohort A) without immediate adjuvant therapy. Patients with microscopic positive margins or extracapsular extension are eligible for immediate de-escalated adjuvant chemoradiation (Cohort B). During active surveillance, Cohort A patients are observed and

are treated with delayed adjuvant radiation if they develop detectable HPV ctDNA without radiographic evidence of disease. Patients with microscopic positive margins or extracapsular extension are treated with de-escalated post-operative chemoradiation: 30 Gy in15 fractions with concurrent chemotherapy (bolus cisplatin or carboplatin/5-fluorouracil). The primary objective is to evaluate the one year pathologically confirmed PFS (n=30). For each cohort, if at least eighty-five percent of evaluable patients are disease progression-free and alive at the end of one year of follow-up, the cohort will be declared promising and worthy of further investigation. Secondary objectives include evaluating one and two year locoregional PFS, one and two year overall survival, HPV ctDNA PFS patient report quality of life, and patient reported financial toxicity.

Results: TBD

Conclusion: TBD

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HyperlynX: A Phase 1b Safety Study of Xevinapant, Weekly Cisplatin, and Radiotherapy in Patients with Unresected Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): The current standard of care for patients with unresected locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) is cisplatin 100 mg/m^2 every 3 weeks (Q3W) with concomitant radiotherapy (RT). Cisplatin once a week (QW) (NCCN Guidelines Category 2B and ESMO Guidelines II, A) is an alternative regimen to cisplatin 100 mg/m^2 Q3W that is increasingly being adopted given the unfavorable adverse event profile of cisplatin 100 mg/m^2 Q3W and the improved hydration associated with the QW regimen; however, direct comparisons from randomized confirmatory clinical trials in the definitive setting are pending. Xevinapant is a first-in-class, potent, oral, small-molecule IAP (inhibitor of apoptosis protein) inhibitor that is thought to restore cancer cell sensitivity to apoptosis, thereby enhancing the effects of chemotherapy and RT. In a randomized, phase 2 study of xevinapant + chemoradiotherapy (CRT; cisplatin 100 mg/m^2 Q3W) in patients with unresected LA SCCHN, the primary endpoint of improved locoregional control was met. This regimen was associated with a 53% lower risk of death after 5 years of follow-up and a 67% lower risk of death or disease progression after 3 years of follow-up vs placebo + CRT. Here we describe an open-label, phase 1b study that aims to evaluate the tolerability and safety of xevinapant when added to cisplatin QW + RT in patients with unresected LA SCCHN.

Materials/Methods: HyperlynX (NCT06056310) will enroll patients with histologically confirmed, unresected LA SCCHN of the oropharynx (HPV-negative only), hypopharynx, and/or larynx (stage III, IVA, or IVB) eligible for definitive CRT. Main inclusion criteria include evaluable tumor burden per RECIST 1.1, ECOG PS 0−1, and adequate organ function. Main exclusion criteria include evidence of metastatic disease (stage IVC), and primary tumor site unknown or in the nasopharyngeal sinuses, paranasal sinuses, nasal cavity, salivary gland, thyroid gland, parathyroid gland, or skin. Approximately 40 eligible patients will receive 6 cycles of xevinapant (200 mg/day; Days 1−14 of a 21-day cycle), initiated in combination with cisplatin QW and intensity-modulated RT (70 Gy in 35 fractions, 2 Gy/fraction, 5 days/week) for the first 3 cycles. The primary endpoint is the occurrence of dose-limiting toxicity−like events. Secondary endpoints include safety, objective response, progression-free survival, locoregional control, and time to subsequent cancer treatments. Patients will be followed up until the last patient on study has reached their 18-month visit or until premature treatment discontinuation. The study started in October 2023 and will enroll patients in 6 countries worldwide

Results: Pending

Conclusion: Pending

Author Disclosure: N.F. Saba: Grant/research funding; BMS, Exelixis, Astra Zeneca, Exelixis, BionTech, TOSK. Honoraria; Aduro, AZ, Eisai, Exelixis, Merck, EMD Serono, Kura, Vaccinex, CUE, BionTech, GSK, TOSK, Seagen, Flamingo, Infinity, Inovio,Aveo, BMS, Cornerstone, Celldex, Surface Onc, Astex, Immugene, Faron, Coherus, Adagene, Fulgent, Nanobiotix, Astra Zeneca, . A. Sukari: None. F. Forget: None. A. Popovtzer: None. J. Rubio Perez: None. J. Park: None. M. Yang: None. M. Sato: None. M. Kuipers: None. R. Ito: None. S. Salmio: None.

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A Vaccine (PDS0101) Alone or in Combination with Pembrolizumab for the Treatment of Locally Advanced Human Papillomavirus-Associated Oropharynx Cancer

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Purpose/Objective(s): PDS0101 is a novel, investigational HPV-targeted immunotherapy that stimulates a potent targeted T cell attack against HPV-positive cancers utilizing a mixture of HPV16 E6 and E7 peptides pools delivered subcutaneously with cationic (positively charged) lipid nanoparticles. Initial studies of PDS0101 in combination with pembrolizumab in patients with metastatic HPV16-positive recurrent/metastatic HNSCC demonstrated clinical activity with notable polyfunctional HPV16-specific CD4 and CD8 T cell activation. Limited data exist in the curative intent setting. MC200710 (NCT05232851) is an ongoing prospective window of opportunity study of neoadjuvant PDS0101 with or without pembrolizumab prior to surgery or chemoradiation.

Materials/Methods: Patients with high risk locally advanced HPV16-positive oropharyngeal carcinoma, defined as multiple or bilateral nodes, radiographic extranodal extension, or lymph nodes >6cm receive two cycles of PDS101 with or without pembrolizumab. The two cycles are given 21 days apart and patients undergo restaging prior to surgical resection. The primary objectives are safety in addition to determining pathologic response and ctDNA response (ctHPVDNA, liquid biopsies). The pathologic response (pTR) is defined as necrosis, keratinous debris, giant cells/histiocytes as percentage of total tumor bed area. Patients will be considered responders with a pTR1 (10-49%) or greater or if they have >= 50% decreased in ctHPVDNA from baseline.

Results: Eight of a planned 20 eligible patients have been accrued on study. An observed response rate of at least 20% for either pathologic response or ctHPVDNA response will be deemed worthy of further investigation for each arm. Secondary endpoints include radiologic response, progression free survival, and overall survival. Correlative analyses include immunologic query of peripheral blood mononuclear cells (PBMCs) for HPV16-specific immune response over time and in relation to pathologic and ctDNA assessment.

Conclusion: MC200710 is a trial in progress investigating the pathologic and ctDNA response to two cycles of neoadjuvant PDS0101 with or without pembrolizumab prior to surgery in patients with HPV associated oropharyngeal carcinoma.

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Outcomes in Patients with Oral Cavity Squamous Cell Carcinomas with Respect to Initiation of Chemotherapy and Adjuvant IMRT Timing

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Purpose/Objective(s): Patients with advanced oral cavity squamous cell carcinoma (OCSCC) have high recurrence rates. The current treatment paradigm consists of definitive surgery followed by risk-adapted adjuvant radiation therapy (RT) with or without concurrent chemotherapy. We hypothesized that initiating chemotherapy on the same day as RT and shorter interval between surgery and starting RT would improve oncological outcomes.

Materials/Methods: We performed a single-institution retrospective review of patients with OCSCC treated with adjuvant IMRT +/- chemotherapy after surgery from July 2002-August 2021. Univariate analysis of predictors for locoregional control (LRC), distant metastasis-free survival (DMFS), and overall survival (OS) were performed using Cox regression, with p-value <0.05 considered significant (statistical software).

Results: 479 patients with OCSCC were identified with a median age at diagnosis of 59 years. 65.1% were male, 72.9% had a smoking history, and 70.1% had a history of alcohol use. Almost half of patients had pT4 tumors (48.6%), 39.5% had lymphovascular invasion, 40.5% had extranodal extension, and 63.7% had perineural invasion. Median RT dose was 63 Gy (IQR 60-66 Gy). Most patients did not receive chemotherapy (45.5%), while 41.5% received cisplatin-based chemotherapy, and 9.6% received carboplatin-based chemotherapy. Median follow-up was 32 months (IQR 12-69). 3-year LRC, DMFS, and OS for all patients were 73.0%, 59.6%, and 61.6%, respectively. When considering chemotherapy timing relative to RT initiation, 7.3% started before RT (median 5 days prior to RT; IQR 2-7), 32.2% started both on the same day, and 15% started chemotherapy after RT (median delay of 6 days; IQR 1-7). Outcomes for patients receiving chemotherapy are in Table 1. Timing of chemotherapy initiation relative to RT was not significantly associated with LRC, DMFS, or OS. On univariate analysis for predictors of OS, T category (P=0.009), perineural invasion (P=0.010), extranodal extension (P<0.001), N category (P<0.001), and time from surgery to RT initiation (<6, 6-8, >8 weeks, p=0.007) were significant.

Conclusion: In summary, this single institution study shows that delayed initiation of RT after surgery is associated with significantly worse overall survival, but chemotherapy timing relative to RT does not confer worse outcomes in patients with OCSCC who received definitive surgery followed by adjuvant IMRT.

Abstract 117 − Table 1

Chemotherapy Timing	3yr LRC	3yr DMFS	3yr OS
All	69.7%	52.1%	53.8%
Prior	69.4%	54.8%	54.6%
Same	72.4%	53.2%	54.7%
After	63.9%	48.6%	51.6%
p-value	0.408	0.932	0.828

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Predictors of Occult Nodal Involvement in Clinically Node Negative Primary Parotid Carcinoma: An Updated NCDB Analysis

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Purpose/Objective(s): Primary Parotid Carcinomas (PPC) comprise a wide array of histologies, each with varying propensity for local invasion and cervical nodal involvement. Upfront surgical excision of the primary tumor constitutes the standard of care for PPC, but there exists little consensus regarding management of the clinically negative neck (cN0). We conducted a clinicopathologic correlative analysis of the National Cancer Database (NCDB) to identify predictors of occult nodal involvement in PPC to guide elective neck management.

Materials/Methods: The NCDB was queried for adults diagnosed from 2010-2020 with cN0M0 PPC who underwent adequate surgical resection (defined as subtotal to radical parotidectomy with >/=18 nodes examined) without pre-surgical treatment. Pathologic T-classification, tumor size, histology, grade, lymphovascular space invasion (LVSI), gender, and age at diagnosis were specified *a priori* as variables of interest. The primary

outcome, occult nodal positivity (*i.e.* cN0 but pN+), was assessed by univariable (UVA) and multivariable (MVA) logistic regression, depicted as odds ratios (OR) and corresponding 95% confidence intervals (95%CI) with a prespecified threshold for statistical significance of $p<0.05$. Recursive partitioning analysis (RPA) was then performed to hierarchically categorize patients according to occult nodal disease risk.

Results: From an initial 51,663 patients with PPC 1,899 met inclusion criteria and were included for analysis, of whom 1,047 (55.1%) had occult nodal involvement. By UVA, the incidence of occult nodal positivity was significantly higher with male sex; age 51 and older; high grade; pT2 status or greater; histology of adenocarcinoma, salivary duct carcinoma, or carcinoma ex-PA; tumor size >2cm; and LVSI. On MVA, tumor size, age, and gender were no longer significantly associated with occult nodal involvement; however, LVSI (OR 8.3, 95%CI 6.3-10.8), carcinoma ex-pleomorphic adenoma (OR 3.6, 95%CI 1.7-7.7), adenocarcinoma (OR 3.5, 95%CI 2.2-5.5), salivary duct carcinoma (OR 3.62, 95%CI 2.2-6.1), pT3 (OR 1.9, 95%CI 1.1-3.3), pT4 (OR 3.1, 95%CI 1.8-5.4), and high grade (OR 2.7, 95%CI 2.0-3.5) remained significant. On RPA evaluating LVSI, histology, pT, and grade, LVSI was the strongest predictor of occult nodal involvement (87% if LVSI+ vs 32% if LVSI−).

Conclusion: LVSI appears to supersede tumor histology, grade, size, and pT status as the strongest risk factor for occult nodal involvement in PPC. To our knowledge, this is the largest series to evaluate this pathologic feature. Further research into this heretofore underappreciated risk factor and its implications for management of the cN0 neck is warranted.

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Combinatorial Immunotherapy and Associated Tumor Metabolic Stress in Pre-clinical HNSCC Mmodels

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Purpose/Objective(s): The combination of conventionally fractionated radiation (conRT) and anti-PD1/PD-L1 has underperformed, speaking to a lack of understanding in the interaction between conRT and the immune response. To begin to address this issue, we have undertaken a comprehensive evaluation of conRT and PD-1/PD-L1 in pre-clinical models.

Materials/Methods: We utilized MOC2 cell lines (+/- CRISPR knock out (KO) of PD-L1) to generate flank tumors in either immunodeficient (Nu/nu) or immunocompetent (C57Bl/6) mice (n=6-10/group) which were treated with 2 Gy x 9d +/- anti-PD1 mAb (250 ug/week x 2) and evaluated for effects on tumor response, measured as tumor volume on day 14 post-conRT. One way ANOVA and with post-hoc comparisons were performed on these values. Additionally, select tumors were analyzed via multi-channel flow cytometry, bulk RNA-Seq, and reverse phase protein array (RPPA). For RNA Seq data, differences between each individual group were analyzed using a moderated t statistic, with adjustment for multiple testing performed by fitting a beta uniform mixture (BUM) model. For RPPA data, two-way ANOVA with post-hoc comparisons were performed. Additional analysis of RNA Seq data to predict immune infiltrate was

performed utilizing TIMER2.0, which provides data from 6 models of predicting immune infiltrate. Ingenuity pathway analysis (IPA) was performed on RNA-Seq and RPPA data.

Results: Interestingly, a modest repression of tumor grow due to PD-L1 KO was observed in Nu/Nu mice (p=0.04), while no effect was seen in the C57Bl/6 model (p=0.3). However, taken as a whole, the combination of conRT and PD-L1 KO in the C57Bl/6 model led to the most numerically meaningful reduction in TGD (p=3e-2 vs. PD-L1 KO; p=3e-3 vs. conRT), with a similar magnitude of effect when conRT was combined with PD1 mAB in a follow-up experiment (p=0.005). Between group comparison of RNA-Seq and RPPA data from tumors collected ∼14-20 days post conRT, followed by IPA analysis of differentially expressed targets identified some of the most significantly affected pathways in the conRT + PD-L1 KO groups being repression of oxidative phosphorylation (p=4.2e-4) from the RNA seq data, accompanied by repression of PI3k/Akt (p=3.9e-20) and an activation of AMPK signaling (p=3.8e-11) in the RPPA. Finally, analysis of predicted immune infiltrate depended upon the methodology used, however a significant reduction in several macrophage lineages was observed in multiple models (CIBERSORT, CIBERSORT-ABS, QUANTISEQ and xCELL). Analysis of flow cytometry data is ongoing.

Conclusion: Tumor analysis reveals a potential long-term reduction in oxidative phosphorylation with a concordant upregulation of AMPK signaling in PD-L1 KO tumors treated with conRT pointing to metabolic targeting as a potential therapeutic sensitization strategy.

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Tubarial Gland Sparing with Intensity-Modulated Radiation Therapy for Oropharyngeal Cancers: A Pilot Study of Dosimetric Feasibility

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Purpose/Objective(s): Tubarial glands have been newly identified as a potential organ at risk (OAR) for head and neck cancer radiation therapy. However, the feasibility of sparing them is yet to be determined. In this study, we hypothesized that intensity-modulated radiation therapy (IMRT), which is widely utilized in the treatment of oropharyngeal carcinoma, would reduce the mean dose to the tubarial glands without a significant difference in target coverage.

Materials/Methods: With approval from the Institutional Review Board, seventeen patients with oropharyngeal carcinoma who received curative intent definitive radiation therapy were included in the study. Patient baseline and tumor characteristics were extracted from electronic medical records. Tubarial glands were delineated for each patient and the treatment plans were re-optimized to limit the mean dose to the new OARs to as low as reasonably achievable. Each patient's dosimetric parameters from the clinically treated IMRT plan and the newly re-optimized plan were recorded and a paired t-test was performed to compare the mean dose for tubarial glands and target coverage (D99 for high-risk, intermediate-risk, and low-risk clinical target volumes) between the clinical plan and the re-optimized plan.

Results: Among the 17 patients, 10 (59%) had tonsil and 7 (41%) had base of tongue primary sites. All patients received definitive radiation (66-70 Gy/30-35 fractions) with concurrent cisplatin. Mean tubarial gland volume was 4.23 cc (Interquartile range [IQR]-3.6-4.7 cc) on the left and 4.25 cc (IQR-3.57-4.85 cc) on the right. The clinical plans had a mean dose of 49.7 Gy (IQR-34-65 Gy) and 27.7 Gy (IQR-8.9-50.5 Gy) for the ipsilateral and contralateral tubarial glands, respectively. The difference in mean doses between the clinical and re-optimized plans were 4.9 Gy (95% CI: 3.3-6.6 Gy; $p<0.01$) and 7.0 Gy (95% CI: 5.0-8.9 Gy; $p<0.01$) for the ipsilateral and contralateral tubarial glands, respectively. Based on the distance between

the target volume and tubarial gland, a difference in the mean dose of 0.2-13.5 Gy was observed, and 7 patients (41%) had ≥10 Gy reduction in dose to either side. A small decrease in high risk target coverage was noted, but all re-optimized plans met departmental dosimetric goals (mean difference in HR-CTV D99% - 0.8% (95% CI: 0.48-1.26%; p<0.01), IR-CTV D99% - 0.7% (95% CI: -2.35-3.78; *p*=0.62) and LR-CTV D99% - 1.4% (95% CI: -3.04-5.94; *p*=0.5).

Conclusion: This pilot study demonstrates the dosimetric feasibility of tubarial gland sparing with IMRT for oropharyngeal carcinoma. Dosimetric constraints for this new OAR need to be determined with larger studies.

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EVOLVE: Evaluating the Safety of and Quality of Life in De-escalated Head and Neck Irradiation in HPV + Oropharynx Cancer in Non/Minimal Smokers in the Community Setting

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Purpose/Objective(s): Previous studies at large academic centers have shown that de-escalation of adjuvant radiotherapy for selected patients with human papillomavirus-associated oropharyngeal squamous cell carcinoma in non-smokers/minimal smokers has similar rates of disease control with reduced toxicity and stable quality of life. The purpose of this study was to confirm the reproducibility of these findings in a community cancer center setting.

Materials/Methods: Adults with HPV mediated squamous cell carcinoma of the oropharynx with ≤ 10 pack year smoking history T0-T4N0-N2M0 (AJCC8, including unknown primary p16+ minimal smokers) and with negative margins (if surgical arm) were enrolled on this prospective observational study. Initial surgical resection was performed if an R0 resection was anticipated AND if the surgeon would anticipate a good functional outcome post-operatively. Adjuvant radiotherapy was as per Ma *et al* JCO 2019. Induction chemotherapy with de-escalated radiotherapy to complete responders was undertaken when surgical resection was not deemed optimal. Platinum eligible induction chemotherapy was as per Marur *et al* JCO 2017. Platinum ineligible induction chemotherapy was as per Chen *et al* Lancet Oncology 2017. The primary endpoint was cumulative incidence of local/regional recurrence and 2 year PFS by Kaplan Meier method. Secondary endpoints included quality of life as determined by Head and Neck PRO (FACT-H&N, EORTC QLQ-C30 and H&N35), and overall survival. The study was closed after 70/80 patients were accrued given published Phase III data supporting the practice.

Results: Accrual was from February 2019 to September 2023 with median follow-up of 31.8 months. 44/70 (63%) underwent surgery followed by de-escalated chemoradiotherapy with ENE present in 29.5% of those patients. The remainder underwent induction chemotherapy followed by response adapted de-escalated chemoradiotherapy. Overall survival was 100% for the surgical group, 95% for the induction chemotherapy followed by chemoradiotherapy group. Local/regional control at 2 years was 93%. PFS was 89.7% for all patients at 2 years. Patients with no ENE had 96.3% PFS compared to ENE+ patients with 83.3% PFS at 2 years p=0.16. Mean sum EORTC QOL HN35 at enrollment was 52.5 compared with 47.1 at 24 months (p=0.083) demonstrating numerically improved quality of life after treatment.

Conclusion: In the community setting, de-escalation of radiotherapy is safe and effective without significant detriment to quality of life.

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Predictors of Treatment Failure in Young, Non-Smoking, Non-Drinking Patients with Squamous Cell Carcinoma of the Oral Tongue

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Purpose/Objective(s): A history of significant alcohol and tobacco use are known risk factors for the development of squamous cell carcinoma of the oral tongue (SCCOT). Despite a documented rise in disease incidence in young patients with no known risk factors, little is understood about the pathogenesis and clinical outcomes in this cohort. High rates of treatment failure in these patients, when compared to older patients with SCCOT and no risk factors, warrants further study. We aim to identify specific demographic, clinical, or pathological predictors of treatment failure in young, SCCOT patients with no prior drinking or smoking history.

Materials/Methods: A retrospective review of patients presenting to a large, academic center with SCCOT was performed. Patient demographics, surgical pathology, and clinical outcome data were collected. Patients were included if their age at diagnosis was ≥18 and ≤45 years old. Treatment failure was defined as locoregional failure (LRF). Potential predictors of treatment failure were evaluated using univariate and multivariate Cox regression analyses. A similar cohort included patients aged >45 years and was used as a validation group to determine if the predictors identified were unique to our population of interest.

Results: Of the 85 patients included, 41 were young (48%) and 44 were older (52%). The average age for each cohort was 36.1 and 61.3 years, respectively. 40 were female (47%), 20 young (49%) and 20 older (45%). For the young cohort, a history of dental procedures or oral disease was a significant predictor of LRF on univariate analysis (HR: 3.96, CI: 1.59-9.85, p=0.003). Disease site also appeared to play a role, with a dorsal lesion significantly predicting LRF (HR: 4.67, CI: 1.87-11.67, p=0.001). All other variables, including patient BMI, sex, advanced staging, positive margins, perineural invasion, and time to surgery were not significant. In the multivariate model, the presence of a dorsal lesion was still statistically significant, while adjusting for a history of dental procedures or oral disease (HR: 3.51, CI: 1.34-9.15, p=0.01). In the older cohort, these patient characteristics were not significant predictors of LRF.

Conclusion: Our analysis suggests that predictors of treatment failure in young, SCCOT patients with no known risk factors may exist. The location of disease on the dorsal tongue, a relatively rare subsite, was a significant predictor of LRF and unique to this cohort of young patients. These findings may aid in guiding treatment, but research is needed to identify potentially unknown predictors of poor outcomes, such as the role of genetic predispositions or the oral microbiome, in this unique cohort of young, non-smoking, non-drinking SCCOT patients.

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Prognostic Factors for Locoregional Control in Early-Stage Oral Tongue Squamous Cell Carcinoma Treated with Partial Glossectomy and Elective Neck Dissection

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Purpose/Objective(s): Patients with early-stage oral tongue squamous cell carcinoma (OTSCC) are generally considered low-risk for recurrence and typically do not receive adjuvant radiotherapy. We aimed to identify pathologic factors associated with locoregional recurrence in this population.
Materials/Methods: A retrospective chart review was conducted of patients with AJCC 8th edition pT1-2N0 OTSCC who underwent partial glossectomy and elective neck dissection without adjuvant treatment between 2015-2021. Pathology reports were reviewed for tumor size, depth of invasion (DOI), glossectomy specimen margin and final tumor bed margin status, and the presence of perineural invasion (PNI) or lymphovascular space invasion (LVSI). Patients with prior head and neck radiotherapy or positive final margins were excluded, resulting in 110 patients in the final analysis. Locoregional control (LRC) and overall survival (OS) were estimated by the Kaplan-Meier method. Multivariate analysis was performed using a Cox proportional hazards model to identify prognostic factors for LRC.
Results: Median follow-up was 45.6 months. Median patient age was 62 years. Sixty (54.5%) patients were male, and 39 (35.5%) were current or former smokers. The cohort contained 46 (41.8%) pT1 tumors and 64 (58.2%) pT2 tumors. Median number of lymph nodes dissected was 33, median tumor size was 16mm, and median DOI was 5mm. PNI was noted in 18 (15.3%) cases, LVSI was identified in 4 (3.6%) cases, and 9 (8.2%) cases had positive glossectomy specimen margins. Three-year LRC/OS was 88.0%/92.5% for all-comers, 92.0%/95.2% for pT1 disease, and 85.0%/90.5% for pT2 disease. On multivariate analysis, DOI (HR=1.31 (95% CI: 1.06-1.63), p=0.01), presence of LVSI (HR=6.90 (95% CI: 1.42-33.65), p=0.02), and positive glossectomy specimen margins (HR=6.66 (95% CI: 1.60-27.78), p=0.009) were associated with inferior LRC. Three-year LRC was 66.7% with positive glossectomy specimen margins and 89.5% without. Three-year LRC was 0.0% with positive LVSI and 89.4% without. Among the 8 patients who experienced regional failure, 5 (62.5%) recurred in the ipsilateral neck only, 2 (25.0%) failed in the bilateral neck, and 1 (12.5%) experienced an isolated contralateral neck recurrence.
Conclusion: In patients with pT1-2N0 OTSCC who underwent partial glossectomy and elective neck dissection, DOI, presence of LVSI, and positive glossectomy specimen margins, despite final negative tumor bed margins, were all associated with inferior LRC. Patients with these risk factors may be considered for adjuvant radiotherapy to optimize disease control.

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A Phase II Trial of Xevinapant in Combination with Post-Operative Cisplatin and Radiotherapy for High Risk Head and Neck Cancer

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Purpose/Objective(s): Patients with head and neck squamous cell carcinoma (HNSCC) who have high risk clinicopathologic factors after surgery are at high risk for locoregional recurrence despite multimodal therapy. This risk is particularly high for patients who are found to have early recurrence during preparation for post-operative radiotherapy. Xevinapant is an oral inhibitor of apoptosis (IAP) antagonist that has demonstrated early evidence of efficacy in combination with 7 weeks of radiation and cisplatin in a phase II trial, with a tolerable safety profile. A phase III trial of definitive radiation, cisplatin, and xevinapant is underway. In this phase II study, we hypothesize that the addition of xevinapant to post-operative chemoradiotherapy with weekly cisplatin will improve disease free survival for this high risk population.
Materials/Methods: Subjects will be eligible for trial enrollment if they have: new diagnosis of HNSCC who have undergone surgical resection of all known gross disease who meet one of the following criteria: 1) surgical margin <5mm and 2 or more intermediate clinicopathologic risk factors (T3/4, N2b-3 disease, PNI or LVI) 2) extranodal extension or positive surgical margins or 3) biopsy proven early gross recurrence prior to RT. Patients must be within 10 weeks of surgery at the time of enrollment to be eligible, and all efforts will be made to begin radiation within 6 weeks of surgery. We anticipate that >= 85% of patients will have cancers of the oral cavity. Patients with HPV-related oropharyngeal cancers are not eligible. Eligible patients will undergo PET/CT simulation to identify evidence of early recurrence. Patients will be treated with post-operative radiotherapy (60-66 Gy in 30-33 fractions), weekly cisplatin (40mg/m2), with concurrent and adjuvant xevinapant. Patients who have evidence of gross recurrence will be treated to 70 Gy / 35 fractions of radiotherapy and 7 weeks of weekly cisplatin. Xevinapant will be dosed 200 mg / m2 days 1-14 every 21 days per cycle. The trial will enroll 54 patients. The primary endpoint is 12-month disease free survival. The cumulative incidence of locoregional failure, overall, survival, treatment related adverse effects, and patient reported quality of life.
Results: TBD
Conclusion: TBD

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Patterns of Recurrence and Predictors of Outcome in Cervical Esophageal Carcinoma Patients Treated with Definitive Chemoradiation

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Purpose/Objective(s): Cervical esophageal carcinoma (CEC) is a rare form of esophageal cancer that is typically locally advanced at diagnosis and often carries a poor prognosis. The aim of this study was to evaluate patterns of recurrence and therapy-related toxicities in patients treated with chemoradiation therapy (CRT).
Materials/Methods: Patients were retrospectively identified with CEC who underwent CRT between 2012 and 2023. Toxicities were defined as per CTCAE v5. Locoregional control (LRC), progression free survival (PFS), and overall survival (OS) were estimated with Kaplan Meier (KM) analysis. Cox regression analysis were used for univariate analyses (UVA) and multivariate analyses (MVA).
Results: Twenty-eight consecutive patients were included for analysis with a median age of 65 years. The majority of patients were female (n=20; 71.4%), had a prior history of cancer (n=14; 50%), had squamous cell carcinoma histology (n=24; 85.7%), were Stage IV (n=11; 39.3%), and had a median pack-years for current and former smokers of 42.5 pack-years. The

median dose of radiotherapy was 66 Gy (range 45-70 Gy), and patients were treated with concurrent cisplatin (n=17; 60.7%), carboplatin (n=7; 25%), or oxaliplatin (n=2; 7.1%); 2 (7.1%) patients declined chemotherapy. Acute grade 3 (n=6; 21.4%), 4 (n=1; 3.6%), and 5 (n=1; 3.6%), as well as late grade 3 (n=6; 21.4%) and 4 (n=1; 3.6%) radiation therapy-related toxicities were observed. The most common acute and late grade 3+ toxicities were radiation dermatitis (n=5; 17.8%) and esophageal stricture (n=7; 25%), respectively. One patient died as a result of aspiration pneumonia one month after completion of CRT. Two patients were treated after CRT with nivolumab maintenance therapy; both are currently alive with no evidence of disease. Median follow up for the cohort was 28 months. The 2-year LRC, PFS, and OS were 53.7%, 50.3% and 55.3%, respectively. Eleven patients experienced disease progression, with 36.7% local, 9.1% regional, 18.2% distant, and 36.4% simultaneous locoregional and distant progression. Carboplatin-containing chemotherapy was associated with improved OS (HR 0.084, 95%CI 0.007-0.961, p=0.046). Factors associated with worse OS included ECOG performance status 2 (HR 20.2, 95%CI 1.6-253.7; p=0.02), history of any prior cancer (HR 7.0, 95%CI 1.5-32.5; p=0.013), and smoking pack-years (HR 1.03, 95%CI 1.001-1.060; p=0.043).

Conclusion: Cervical esophageal carcinoma is a rare and challenging disease with suboptimal outcomes. Efforts to improve locoregional control and distant progression after CRT should be evaluated for this patient population.

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Adjuvant Treatment Deintensification after Transoral Surgery for Human Papillomavirus-Positive Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): The safety and oncologic efficacy of a primary surgical approach, or transoral robotic surgery (TORS) with neck dissection, is well-established for early stage OPSCC. Given high rates of survival, particularly for human papillomavirus (HPV)-associated OPSCC, there is increasing interest in treatment deintensification strategies.

Materials/Methods: We designed a prospective, non-randomized phase II trial (NCT05119036) to deintensify adjuvant treatment for patients undergoing primary surgical therapy for early-stage HPV+ OPSCC. Inclusion criteria include adults (ECOG PS 0-2) with accessible/resectable cT1-2 HPV+ OPSCC, with cN0 or mobile cN1-2 nodal staging (AJCC8). Unknown primaries are included if the primary is fully resected at the time of TORS, or if the palatine/lingual tonsils are thoroughly resected and negative. Exclusion criteria include contraindications to anesthesia, incomplete adjuvant radiation, prior head and neck radiation, other cancer within 3 years, and distant metastasis. Pathology is used to assign one of three arms: (1) observation (negative margins, negative or single positive node; (2) 44 Gy/22fx adjuvant radiation (negative margins, ≤4 positive nodes with ENE ≤ 2mm); or (3) 54Gy/27fx adjuvant radiation (negative margins, ≤4 positive nodes with ENE > 2mm or >4 positive nodes with ENE < 2mm). Of note, chemotherapy is not used. In cases of adjuvant radiation, ipsilateral neck radiation is given for primary palatine tonsil or glossotonsillar sulcus tumors with < 1cm extension onto the tongue base. For other primary sites, if bilateral neck dissection is performed and contralateral neck nodes are negative or there is only a single positive node without ENE, only ipsilateral radiation is prescribed. Otherwise, if only ipsilateral neck dissection is performed, the contralateral neck receives reduced radiation (40Gy/22fx or 50Gy/27fx for arms 2 and 3). The primary endpoint is

2-year disease free survival, and secondary endpoints include locoregional control, overall survival, distant metastasis, toxicity profiles (NCI-CTCAE), swallowing-related quality of life (MDADI), and gastrostomy tube dependence rates.

Results: The study began in May 2022 at two sites. As of this writing, 59 subjects have accrued out of 75 subjects. Preliminary data analysis is planned for 2025.

Conclusion: Despite interest in deintensification strategies for HPV+ OPSCC, there is no consensus on best treatment strategies. This prospective study of de-escalated adjuvant treatment for early-stage HPV+ OPSCC treated with primary surgery will assess the safety and oncologic efficacy of this approach compared to historical controls, while more clearly defining the safety of eliminating adjuvant chemotherapy.

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Implications of Rapid Molecular Responses to Induction Chemotherapy (IC) in Human Papilloma Virus (HPV) Head and Neck Squamous Cell Carcinoma (HNSCC).

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Purpose/Objective(s): Patients with locally advanced (LA) HPV HNSCC are treated with various types of IC and/or standard (sd) or reduced dose (rd) of chemoradiation (CRT). Chemotherapy only (TPF) or with immunotherapy (TP-PD1) are the main IC types used prior to CRT or surgery. Tumor tissue modified viral HPV DNA (TTMV) is a sensitive and specific biomarker for HPV+ HNSCC. Therefore, TTMV may be useful to match patients with the appropriate intensity of treatment while minimizing toxicity. However, how TTMV levels may be used to guide the treatment of HNSCC is not yet established.

Materials/Methods: Patients with LA HPV+ HNSCC with high-risk features (radiographic ECE, T4 primary, ≥N2c) and <20 pack-year (py) smoking history or deemed unresectable were treated with IC TPF followed by rdCRT (56 Gy) with weekly carboplatin in responders; sdCRT (70 Gy) was used in clinical non-responders. Current smokers or those with ≥20 py underwent IC (TPF, TP or TP-PD1) with sdCRT. Patients were eligible for rdCRT if they had a significant clinical response to IC were participating in the QB2 trial (NCT02945631). Regeneron trial patients received TP-Cemiplimab IC followed by sdCRT are also continuing adjuvant Cemiplimab alone for 6 months (NCT05376553).

Results: 23 subjects treated between 2/4/21-8/11/23, who had pre- and post-IC TTMV data were included in our analysis. 16/23 received IC with TPF, 1/23 TP and 6/23 TP-PD1. 21 subjects received 3 cycles of IC. 2 subjects received 2 cycles of IC only: 1 in TPF 1 in TP − PD1. Median pre-IC TTMV was 8082, and median follow up time from treatment start was 16 months with an average of 8.0 data points. 9/23 subjects had full clearance TTMV after 1 cycle of IC (7 in TPF, 2 in TP-PD1), 9 after 2 cycles (7 in TPF, 2 in TP-PD1), and 3 after 3 cycles of IC. 1 subject still had abnormal TTMV after 3 cycles and underwent 7000 cGy. 1 patient had a positive pre TP-PD1 IC TTMV, with no levels drawn during IC however TTMV was negative when sd CRT began. TTMV testing was done for all 19 subjects after completion CRT and all were negative, 4 are still completing tx or pending post tx results. All subjects in addition to standard surveillance

have TTMV testing done during their surveillance visits. 2 subjects developed recurrent HPV HNSCC after CRT, both locoregional, first cleared TTMV after 2 cycles and second after 3 cycles of IC.

Conclusion: Full clearance of TTMV occurred in a large fraction of patients after 1 cycle of IC and majority of patients 2 cycles. In this small study set, all the HNSCC recurrences occurred in patients delayed TTMV IC responses. The small sample size of our study lacks the statistical power to demonstrate that the failing to attain full clearance of TTMV after/during IC is associated with a poor prognosis. However it is our hope that early TTMV dynamics can be studied in a larger cohorts as a tool to stratify patients and match appropriate treatment intensity to patient risk factors.

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ENID: Phase II Trial of Definitive Chemoradiation with Elective Nodal Irradiation Dose De-Escalation for P16 Positive Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): HPV-related oropharyngeal squamous cell carcinomas (OPSCCs) have a better overall prognosis and head and neck irradiation is associated with significant acute and late toxicities, therefore this has been an area of active evaluation of de-escalation strategies. Among them is a reduced dose to the elective lymph nodes. The purpose of this study is to report the initial evaluation of lower dose (40 Gy in 20 fractions) to the elective lymph nodes while delivering usual high dose (70 Gy in 35 fractions) to the FDG PET defined gross disease. The primary objectives were to demonstrate improved quality of life using questionnaires and PEG tube use. The secondary objectives were to demonstrate acceptable locoregional control.

Materials/Methods: This phase II study enrolled patients with HPV related OPSCC who were staged as AJCC 8th edition T1-3, N1-2, M0, and excluded active smokers. All patients were treated with 40 Gy to the known disease and elective lymph nodes, and a subsequent boost was delivered to the PET defined gross disease for an additional 30 Gy in 15 fractions. In addition, patients' baseline/pretreatment data was recorded. Patients completed baseline questionnaires including the Edmonton Symptom Assessment System (ESAS), NCCN distress, and the EORTC QLQ-H&N35 questionnaires. These questionnaires were completed at each clinically defined follow-up visit up through two years post-treatment. Physician assessment of key toxicities (taste, dry mouth, dysphagia, weight loss and mucositis) were recorded as well. The 3-mont post treatment PET scan was used for disease assessment, with additional scans obtained if there was less than a CR.

Results: In this initial analysis a total of 12 patients have completed at least 6 months of follow up. Of the 12 patients, 91.67% were male, 33.33% had never smoked, and 50% had a BMI over 30. A total of 3 patients required PEG tube placement. With one patient lost to follow up after 6 months, the locoregional control was 100% at 6 months, and the 1-year RFS was 100%. Two patients had less than CR at the first PET scan, and were confirmed to have achieved CR with a subsequent PET. Grade 2 or higher toxicities were reported by 9 patients during treatment, 6patients at 1 month post treatment and 0 patients at 3 months post treatment. QOL assessment also demonstrated a rapid improvement in the first 3 months after treatment.

Conclusion: This study reports encouraging outcomes for a de-escalation strategy delivering lower dose to the elective lymph nodes while maintaining high control rates. Using FDG PET as the primary target delineation and using standard IMRT techniques, this is a potential strategy that could be readily employed by other centers and in future studies.

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Arytenoid-Sparing Intensity-Modulated Radiotherapy for Early-Stage Glottic Cancer

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Purpose/Objective(s): Standard treatment for early-stage glottic cancer with 3D-conformal radiotherapy (3D-CRT) offers durable long-term local control. Carotid-sparing intensity-modulated radiation therapy has become more widely used in an attempt to decrease toxicities. In this study, we demonstrate initial dosimetric results of a novel approach called arytenoid-sparing IMRT (AS-IMRT), which is aimed at reducing speech and swallowing toxicity.

Materials/Methods: We identified 26 patients with Stage 0-1 glottic cancer treated with radiation alone to 63 Gy in 28 fractions between 2017 and 2022. We selected two representative patients to assess dosimetric feasibility of AS-IMRT and compare organ-at-risk doses to 3D-CRT. We developed a novel target volume delineation protocol for bilateral and unilateral AS-IMRT. Arytenoid sparing was not done if tumor extended to the posterior 1/3 of the true vocal cord on that side, as determined by laryngoscopy. Carotid sparing was done bilaterally in all AS-IMRT plans. Clinical goals included planning target volume coverage $D_{95\%} > 95\%$ and $D_{100\%} > 90\%$, spared arytenoid(s) $D_{mean} < 40$ Gy, and carotid $D_{mean} < 20$ Gy and $D_{max} < 30$ Gy.

Results: We generated AS-IMRT and 3D-CRT plans for one patient with bilateral arytenoid-sparing and one patient with unilateral (right) arytenoid-sparing. Table 1 describes the dose statistics when comparing 3D-CRT to AS-IMRT plans in these patients. Substantial sparing of the pharyngeal constrictor D_{mean} and the carotid D_{max} and D_{mean} occurred for both bilateral and unilateral AS-IMRT approaches. However, when attempting to spare only the right arytenoid, the clinical goal could not be met even on the spared side (right arytenoid D_{mean} 5225 cGy) due to proximity of the treated left arytenoid.

Conclusion: We have created a novel IMRT technique incorporating sparing of both arytenoids and carotids for early-stage glottic cancer. We have demonstrated dosimetric feasibility of this technique when compared to 3D-CRT, especially in the scenario of bilateral arytenoid sparing. We intend to complete comparative planning for the remainder of our cohort to optimize this technique and better understand its limitations. Ultimately, we plan on designing a prospective trial to evaluate whether this approach will lead to clinical benefits, including mitigating treatment-related dysphonia and dysphagia.

Abstract 129 — Table 1

Structure	Unilateral (Right) AS (cGy)		Bilateral AS (cGy)	
	3D	AS-IMRT	3D	AS-IMRT
R Arytenoid D_{mean}	6492	3812	6491	5224
L Arytenoid D_{mean}	6447	3918	6494	6346
Constrictors D_{mean}	5691	3633	5289	3528
Esophagus D_{max}	6504	6226	6407	6541
Esophagus D_{mean}	2433	1582	2757	1900
L Carotid D_{max}	6632	2750	6477	2899
L Carotid D_{mean}	3908	1319	3773	1399
R Carotid D_{max}	6609	2839	6535	2915
R Carotid D_{mean}	3441	1433	4413	1364

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Randomized Clinical Trial of Tele-Surveillance and Remote Symptom Monitoring Compared to Standard Surveillance for HPV-Associated Oropharynx Cancer with No Evidence of Disease on Post-Treatment Imaging

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Purpose/Objective(s): The incidence of Human Papilloma Virus (HPV) associated oropharyngeal cancer has risen rapidly over the past two decades with excellent prognosis and high rates of locoregional control. Post-treatment PET/CT for oropharyngeal cancer has a very high negative predictive value. Despite the improved outcomes for HPV-associated oropharyngeal cancer and the predictive value of post-treatment PET/CT, national guidelines for post-treatment surveillance of oropharyngeal cancer do not distinguish according to HPV status. The benefits and costs of various post-treatment surveillance regimens for patients with no evidence of disease on post-treatment PET/CT are unknown. Telemedicine with remote patient monitoring is a novel strategy to surveil patients while reducing the burden of traditional follow up regimens. This randomized clinical trial will test the hypothesis that tele-surveillance is non-inferior to standard surveillance for detection of progression-free survival (PFS) events (NCT05048459).

Materials/Methods: Eligible patients have a diagnosis of HPV associated squamous cell carcinoma of the oropharynx with no evidence of disease on PET/CT imaging within 9 months of completing radiation therapy. No evidence of disease is a multi-disciplinary consensus determination by the patient's radiation, medical, and surgical oncologist. Patients are randomized 1:1 between standard surveillance according to institutional and national guidelines vs tele-surveillance with remote patient monitoring. Patients in the tele-surveillance arm have an annual tele-visit and remote patient monitoring every 6 months. All patients will complete the EORTC QLQ-C30, EORTC QLQ-HN43, and COST: A FACIT questionnaires annually as well as blood collection every 6 months for circulating tumor HPV DNA. The primary endpoint is 2-year PFS with a noninferiority margin of 12% for tele-surveillance. Sixty patients will be randomized between arms. Secondary endpoints include patient reported global and head and neck specific quality of life, locoregional control, distant metastases, overall survival, patient reported financial toxicity, cost of surveillance approach, physician and patient satisfaction, and detection of recurrence with circulating tumor HPV DNA.

Results: TBD

Conclusion: TBD

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App-based Interactive AI Guiding Physicians in Real Time to Avoid Radiation Treatment Complications

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Purpose/Objective(s): With improved effectiveness of contemporary treatment, head and neck cancer patients have longer projected life expectancies and commonly develop late treatment adverse effects. Mountains of AI data aim at predicting outcome, few, if any, aim at preventing the foreseeing unfavorable outcome from happening. The purpose of this study was to develop an app-based interactive artificial intelligence (AI) to allow physicians to modify radiation treatment planning in real-time to avoid treatment related complications.

Materials/Methods: Five hundreds and fifty-six dose-volume histograms (DVH) of temporal lobes from 278 patients who underwent IMRT with concurrent chemotherapy for nasopharyngeal carcinoma at a single institution were used to predict temporal lobe toxicity. Median follow-up was 66 months. Temporal lobe injury was defined as development of new T1 enhancement on MRI with or without surrounding T2 edema. Patients were randomly divided into two groups. First group consists of 268 temporal lobes, of which 80% were used for training and 20% for testing. The remaining cases were used for validation. Various machine learning classification algorithms were compared individually and in combination. Scikit-learn machine learning library in Python was used to find the optimum neural network architecture for DVH analysis.

Results: Support vector machine with selected combined features in the low-dose (p-value <0.001), medium-dose (p-value = 0.04), and high-dose (p-value <0.001) regions achieved an AUC of 0.94 and a true positive rate (TPR) of 100%. Deep learning neural network yielded an AUC of 0.94 and a TPR of 95%. We built an application (app) to analyze the planned treatment course using the above models, and to provide real-time feedback regarding the potential complications. When necessary, the application offers the "best" alternative radiation profile similar to the planned one, and such that the consensus of the used models predicts no complications. For instance, in the example below (Figure 1), the app is presented with the dose profile for the planned treatment course with an increment ranging from 5 to 10Gy. The app warns the physician by displaying the planned treatment course in red and recommends an alternative "safer" profile, shown in green, with a 25% reduction in the volume of the temporal lobe receiving 70Gy (V70Gy) to mitigate the risk of temporal lobe injury. Live demonstration of the app with clinical cases will be presented.

Conclusion: A user-friendly mobile-based app with fast response time has been created that helps physicians to predict and avoid treatment complications in real-time.

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Detectable Circulating Tumor Tissue Modified Viral (TTMV)-HPV DNA in Non-Oropharyngeal Head and Neck Cancers

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Purpose/Objective(s): Plasma ctHPVDNA is detectable prior to treatment in ~90% of patients with HPV-OPSCC and has shown utility in the dynamic monitoring of treatment response and detecting recurrences (4, 5, 6). Recent data has demonstrated ctHPVDNA to be detectable in patients with sinonasal and nasopharyngeal primary tumors (7). Herein, we present our early experience of ctHPVDNA detection in non-oropharyngeal HPV-associated head and neck cancers using an ultrasensitive multianalyte droplet polymerase chain reaction assay that tests for cell free tumor tissue modified viral (TTMV)-HPV DNA (liquid biopsies).

Materials/Methods: The medical record of all head and neck cancer patients at our institution seen from April 2022-September 1, 2023 were

reviewed. HPV status was determined by immunohistochemical staining of tumor tissue for p16 and in-situ hybridization for high risk subtypes of HPV, per our institutional standard procedures. TTMV-HPV DNA results, patient demographic information, clinical data, and were obtained from chart review.

Results: We identified 20 patients with non-oropharyngeal HPV-associated head and neck cancers in whom TTMV-HPV DNA was assessed. All cancers were p16 positive and HPV was tested in 8/20 and was positive in 7/8. Of these 20 patients, 15 patients had assessment TTMV-HPV DNA prior to treatment. This included 3 patients with SCC of the nasopharynx, 3 patients with sinonasal SCC, 1 patient with SCC of the posterior pharyngeal wall, 3 patients with SCC of unknown primary, 1 patient with SCC of the oral tongue, 2 patients with SCC of the larynx, 1 patient with cutaneous SCC, and one patient with sinonasal neuroendocrine carcinoma of the ethmoid sinus. Pre-treatment TTMV-HPV DNA was detectable in 13/16 with a median value of 7,808 (range 0-98,950). 11 had TTMV-HPV16 DNA positivity, 1 -HPV18, 0-HPV 33, 1 -HPV 35. TTMV-HPV DNA was undetectable in patients with the following primary sites: T4N0 subglottic SCCA (HPV positive), and pT2N0 SCC of the nasal cavity (HPV positive).

Conclusion: Circulating TTMV-HPV DNA is detectable in non-oropharyngal HPV-associated head and neck cancers. More research is needed to validate the sensitivity, specificity, and clinical utility of TTMV-HPV DNA in non-oropharyngeal HPV-associated head and neck cancers.

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AI-ing Microenvironment Improves Prediction of Extracapsular Nodal Extension in Oropharyngeal Carcinoma

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Purpose/Objective(s): Deintensification for early-stage oropharyngeal carcinoma includes surgery +/- adjuvant radiation therapy without the use of concurrent chemotherapy. Pathologic findings of nodal extracapsular extension (ECE), however, obligate the use of postoperative concurrent chemotherapy in these patients. Machine learning (ML) and deep learning (DL) algorithms using clinical annotations or CT images have yielded less than optimal ECE prediction with AUCs of 0.58-0.85. We hypothesized that interplay between involved nodes and peritumoral environment plays a pivotal role in ECE determinants. The purpose of this study was to investigate if AI-ing the microenvironment of nodal metastasis can enhance ECE prediction.

Materials/Methods: Between 2016 and 2022, 171 patients with newly diagnosed resectable oropharyngeal carcinoma underwent upfront transoral robotic surgery and neck dissection at our institutions. In all these patients, high-resolution CT scans were done preoperatively and were concluded to have no evidence of ECE by experienced head and neck radiologists. Median age was 63 years. Radiomics and topological features from the nodal and perinodal microenvironment were extracted to generate predictive models.

Results: There was a total of 264 pathological lymph nodes. Of these positive nodes, 20% exhibited ECE with a ECE of <1 to 10mm. Extraction of radiomics features of the nodal microenvironment, in addition to nodal metastasis, improves AUC from 0.76 to 0.87. Analysis of topological

features of the perinodal region, in addition to nodal metastasis, improves AUC from 0.61 to 0.79. Multimodal predictive model employing both radiomics and topological features yields an AUC of 0.94. Inclusion of HPV status in our multimodal further improved the performance with an AUC of 0.95, a true-positive rate of 100%, and a true-negative rate of 90%.

Conclusion: AI-ing microenvironment of nodal metastasis enhances robustness of ECE prediction in patients with oropharyngeal cancer.

Author Disclosure: R. Paul: None. J. Richmon: None. A.W. Chan: None.

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Access to Head and Neck Cancer Specialists: A Geospatial Analysis of U.S. Travel Time

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Purpose/Objective(s): Head and neck cancers (HNC) present unique clinical challenges due to their anatomical location and complex treatment approaches, necessitating specialized care from a multi-disciplinary team. Understanding disparities in access to HNC specialists is crucial to ensure equitable treatment for patients. This study aims to assess geographic disparities across the United States using geospatial analysis.

Materials/Methods: HNC specialist locations were identified using two complimentary data sources: the American Society of Clinical Oncology and data from the U.S. News and World Report doctor finder, which included physicians that: self-reported a primary specialty in medical, radiation, or surgical oncology and reported HNC as a subspecialty. Specialists were matched to unique entries in the NPPES NPI Registry. Travel time to the nearest specialist from U.S. Census population-weighted county centroids were computed for all U.S. counties using the Travel Time API. Median travel time by U.S. region, metro/non-metro status, and population density are reported. Statistical analyses were conducted using Spearman's rank correlation and Wilcoxon tests to account for non-normality.

Results: Across 3,141 U.S. counties the median estimated travel time to the nearest of 1,107 HNC providers was 96 minutes (1.6 hours). Spearman's rank correlation test showed that a lower population density was associated with longer travel time ($r = -.6$, $p < .001$), demonstrating a continuum in disparity in access to specialized care. However, there were still disparities observed between counties with similar populations: as an example, Travis County, TX (Austin) and El Paso County, TX (El Paso) have relatively similar populations (1,290,188 vs. 865,657 persons) but disparate travel time (14 vs. 237 minutes). A Kruskal-Wallis test showed that median travel time (in minutes) varied significantly by region (Midwest 111, Northeast 57, South 87, West 147; χ^2 (3) = 328.83, $p < .001$) and by specialist type (Medical 114, Surgical 122, Radiation 125; χ^2 (2) = 26.51, $p < .001$). Metro areas had lower median travel time than non-metro areas (58 vs. 120 minutes; Wilcoxon $p < .001$).

Conclusion: The geospatial analysis revealed substantial disparities in access to HNC specialists across the U.S which may contribute to health outcomes. Further investigation into the causes of these disparities and contextualizing these results within HNC epidemiology will allow for the identification of healthcare "deserts" where need and access to care are imbalanced. These results can be leveraged to identify solutions to optimize resource allocation to improve patient access to HNC specialists.

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Geographical Disparities in the Management of Early-Stage Oropharyngeal Squamous Cell Carcinoma (OPSCC) in the United States (US)

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Purpose/Objective(s): To identify treatment modality variations for OPSCC within the US based on social determinants of health (SDOH), treatment facility characteristics, and distance to facility.

Materials/Methods: The National Cancer Database (NCDB) was analyzed for patients with OPSCC from 2004-2018. Patients with OPSCC were included if age > 40 years, overall stage I-III, and intent to cure treatment. Data on treatment modality, SDOH, Charlson-Deyo comorbidity score (CDCS), oropharyngeal subsite, treatment facility type and location, and distance to the treatment facility were collected.

Results: 2,176 patients met inclusion criteria (mean age: 60.9 years, range 40-90; 1,730, 83.3% male). 1,927 (93.5%) were White, 1,947 (97%) non-Hispanic, 60 (3%) Hispanic, and 97 (4.7%) Black. 30% of patients live in areas with above average high school diploma attainment. Most patients had insurance (1,997/2,055; 97.2%) with the majority having private insurance. 731 (38%) had an annual income of >$63,333. 92% (1,998) of patients had a CDCS of 0 or 1 and the majority had cT1 (826, 39.7%) or cT2 (1,252; 60.3%) tumors and a base of tongue subsite (n=1777, 82%). Patients were treated most commonly in an academic research program (1,014, 53.5%) or in a comprehensive community cancer program (CCCP) (598, 31.5%). The most common treatment modality was chemoradiation (CRT; n= 1310, 60%), followed by radiotherapy alone (RT; n= 257, 12%). A total of 511 (23%) patients underwent surgery, most commonly with adjuvant CRT (201/511, 39%) or RT (139/511; 27%). Treatment modality did not vary with CDCS (p= 0.1858), race/ethnicity (p=0.438), education (p= 0.1659), income (p= 0.8764) or insurance (p= 0.7925). When analyzing by facility-specific treatment variables, patients with a higher CDSC were more likely to be treated with RT+C. Treatment modality per disease subsite varied significantly (p= 0.0122), with surgery the preferred treatment for base of tongue and soft palate and RT+CT for tonsil. Higher confidence levels were obtained when looking at treatment modality per disease subsite after adding facility-specific treatment variables (p= 0.0004). Academic research programs were more likely to treat OPSCC with surgery when compared to a CCCP, which favored RT (p= 0.0081). The South Atlantic region is more likely to use RT over surgery, while the West North Central region is more likely to use surgery (p= 0.042). Additionally, patients traveled further to receive surgery compared to travel distance for RT (p= 0.0194).

Conclusion: Across the US, non-operative therapy is more commonly offered to patients with early stage OPSCC than surgical therapy. This is impacted by facility type, geographic location, the distance patients drive to their treatment facility, CDCS, and tumor subsite. Disparities in access to treatment exist and may influence treatment modality selection for OPSCC.

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Addressing Positive Multi-Cancer Early Detection Tests in Head and Neck Surgery: Experience with Head and Neck Work Up for High-Risk Referrals

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Purpose/Objective(s): Multi-cancer early detection (MCED) tests offer population-based screening for cancer using minimally invasive blood-based sampling and are now commercially available on a self-pay basis. Patients may be identified as at risk for head and neck cancer (HNC) based on a positive signal and predicted site of origin. Detailed information about subsite of origin is not available. There are currently no consensus guidelines available for HNC providers to direct work up or surveillance for these patients. We report an early case series which highlights considerations when evaluating patients referred for a positive commercially obtained MCED test.

Materials/Methods: Retrospective chart review of patients referred to Otolaryngology-Head and Neck Surgery (Oto-HNS) with an at risk MCED result. Patients who were enrolled in unpublished prospective clinical trials were excluded.

Results: Three patients were identified as high risk for HNC and one patient had a positive lymphoma MCED test (mean age: 70.8 years, range: 50-87; 3 male). All were asymptomatic. *Patient 1* was at risk for HNC on MCED and had an abnormal oropharyngeal exam, H&N CT, PET/CT, and was diagnosed with pT2N1M0 p16(+) oropharygeal squamous cell carcinoma (HPV(+)OPSCC). *Patient 2* was at risk for HNC and had a neck mass on exam, abnormal H&N CT, abnormal PET/CT, tested positive for circulating tumor HPV DNA (ctHPVDNA), and was diagnosed with pT2N1M0 HPV(+)OPSCC. *Patient 3* was at risk for HNC and lung on MCED, had a normal H&N exam, an indeterminate 8-9 mm deep lobe parotid mass on H&N CT, H&N MRI, and H&N US, and a thigh mass on PET/CT, and was diagnosed with high grade undifferentiated pleomorphic sarcoma of the thigh. Due to the small size of the parotid mass, location, patient age and pressing comorbidities, radiographic surveillance with MRI and exam in 6 months was recommended. *Patient 4* was referred to Oto-HNS for a positive lymphoma MCED test for H&N exam, and had no abnormal findings on exam or PET/CT. This patient is undergoing surveillance with MRI and exam in 6 months. The average time from MCED test result to clinical diagnosis was 42 days (range: 26-56 days).

Conclusion: In this case series, 67% (2/3) of patients referred with a positive MCED result suggesting HNC were diagnosed with HPV(+)OPSCC. We recommend that positive H&N MCED results be . Currently, work up should include a thorough H&N examination including flexible laryngoscopy and focused CT imaging. The performance of tissue of origin classifiers for squamous malignancies may be less accurate, supporting the use of a PET/CT scan in this setting. ctHPVDNA may be a useful adjunct for indeterminate imaging and physical exam findings. For a patient with no cancer identified, development of clear guidelines are warranted.

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Clinical Validation of Nuclear Factor Kappa B (p65) Among Head and Neck Cancer Patients at One Institution

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Purpose/Objective(s): Head and neck cancers (HNCs) is one of the most common and fatal tumors with varying incidence across sub-Saharan Africa and worldwide. Nuclear factor kappa B (NF-kB), a transcription has been implicated in chronic inflammation and malignant tumors including HNC. However, there is paucity of data on NF-kB (p65) clinical relevance in HNC with no known published data in Ghana or any other African country. This study assessed NF-kB (p65) expression and its association with various clinicopathological variables in HNC patients.

Materials/Methods: 112 head and neck tumors including 50 malignant and 62 benign tissues were used to examine NF-kB (p65) expression using immunohistochemistry. The NF-kB (p65) protein expression patterns were correlated with the patients clinicopathological features using the chi square test.

Results: The study revealed that NF-kB (p65) was expressed in 66 (58.9%) of head and neck tumors with a significant relationship to gender status, and type of tumor. High NF-kB (p65) expression in malignant tumors was twice that of benign tumors (60% versus 29%) respectively. The high NF-kB (p65) expression was more frequently associated with male patients. There was no association between NF-kB (p65) expression in malignant tumors and as age, tumor location, biopsy type, laterality, lymphovascular invasion, perineural invasion. The area under the curve predictive value of NF-kB (p65) was 0.656 with a sensitivity of 62.5% and specificity of 68.8%, positive predictive value of 68% and negative predictive value of 71% (p <0.0001).

Conclusion: This first study in Ghana (Africa) revealed that NF-kB (p65) is highly expressed particularly in male patients with head and neck cancers. High NF-kB (p65) expression may affect the prognosis of HNCs and could be explored as a probable biomarker and therapeutic target in HNCs.

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Introduction of Routine Postoperative PET/CT prior to Adjuvant Head and Neck Radiation Therapy

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Purpose/Objective(s): Routine clinical practice does not include postoperative positron emission tomography (PET)/CT prior to postoperative radiation therapy (PORT) for head and neck cancer. Besides logistical challenges in obtaining postoperative PET/CT within six to eight weeks after surgery, interpreting PET/CT findings in the postoperative setting can also be difficult. However, given the potential for residual or rapidly recurrent disease, postoperative PET/CT may help identify the need for additional diagnostic evaluation or alter adjuvant therapy. There are limited data evaluating the utility of postoperative PET/CT prior to PORT for head and neck cancer. We sought to evaluate the use and clinical relevance of postoperative PET/CT prior to PORT.

Materials/Methods: In this retrospective, single-institution cohort study, we identified patients with head and neck cancer between January 1, 2013 and April 1, 2023 who received a postoperative PET/CT prior to PORT. We extracted electronic medical record data supplemented with manual chart review to collect patient and disease-related information. We measured the rates of clinical management alterations, defined as changes in radiation treatment plans (such as boosting or inclusion of new targets), additional diagnostic workup, changes in systemic therapy plans, or additional surgery, as a result of postoperative PET/CT findings.

Results: The cohort included 133 patients who received a postoperative PET/CT prior to PORT. The mean age at diagnosis was 65 years (standard deviation: 15 years) and 90 (67.2%) were male. Regarding primary site, 34 (25.6%) were oral cavity, 21 (15.8%) were oropharynx, and 78 (58.6%) were other sites including sinonasal, salivary gland, skin, and thyroid. The mean time from surgery to postoperative PET was 37 days (standard deviation:

24 days), and the mean time from postoperative PET/CT to start of PORT was 20 days (standard deviation: 22 days). A total of 84 (63.2%) and 52 (39.0%) of patients started radiation more than 6 and 8 weeks after surgery, respectively. A total of 48 (36.1%) patients experienced a change in management as a result of the PET/CT findings: 44 (91.7%) had a change in radiation plan; 15 (31.2%) underwent additional diagnostic workup; 9 (18.8%) had a change in systemic therapy plan; and 2 (4.2%) underwent additional surgery.

Conclusion: In patients with head and neck cancer who received postoperative PET/CT prior to PORT, a meaningful proportion underwent additional diagnostic evaluation and/or experienced an alteration in adjuvant therapy because of the PET/CT findings. To our knowledge, this series represents one of the largest to date. Future research will seek to identify those who are most likely to benefit from a postoperative PET/CT and determine whether a normal PET/CT safely allows for delaying the start of radiation, for example to provide additional time for wound healing or accommodate patient logistical challenges.

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Phase 1 Study of the Tissue Factor−Targeting Antibody-Drug Conjugate XB002 in Patients with Advanced Solid Tumors (JEWEL-101): Design of Expansion Cohorts for Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): Despite recent advancements in therapy, patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) have a relatively poor prognosis after chemotherapy and immune checkpoint inhibitors (ICIs), with a median survival of ∼9 months, highlighting a need for novel treatments. Tissue factor (TF) is a factor VII/VIIa receptor involved in initiating the extrinsic coagulation pathway, and its overexpression has been associated with poor prognosis in several tumor types, including SCCHN. XB002 is a novel antibody-drug conjugate (ADC) composed of a TF-targeting monoclonal antibody conjugated to zovodotin, an auristatin-based payload with a protease-cleavable linker. The zovodotin linker-payload is designed to lower off-target deconjugation vs other auristatin-based ADCs. In preclinical studies, XB002 displayed antitumor activity without affecting coagulation. The first-in-human, phase 1, open-label, multicenter JEWEL-101 study (NCT04925284) is evaluating XB002 in patients with advanced solid tumors. The maximum tolerated and/or recommended doses of XB002 alone and in combination with nivolumab or bevacizumab will be determined in a dose-escalation stage. Preliminary efficacy and safety will be determined in a tumor-specific cohort expansion stage. Here we present the design of the expansion stage for the SCCHN cohorts.

Materials/Methods: Patients in the SCCHN cohorts must have an inoperable, locally advanced, metastatic, or recurrent tumor, and an ECOG PS of 0−1. Patients must have measurable disease per RECIST v1.1, with the primary tumor located in the oral cavity, oropharynx, hypopharynx, or glottic larynx (nasopharyngeal carcinoma ineligible). Patient must have received 1−3 prior lines of therapy, including a prior platinum-containing chemotherapy and, if eligible and considered a local standard of care, prior ICI and/or anti-EGFR therapy. Additionally, radiographic progression during or following last systemic anticancer therapy is required. Prior treatment with TF-targeting or auristatin-based ADCs is not allowed, and patients with significant ocular disorders are excluded. Concomitant anticoagulants

are permitted, and patients with peripheral neuropathy are eligible, provided it is grade <2 and does not impact activities of daily living. SCCHN patients will be randomized between 2 cohorts and will either receive XB002 alone or XB002 in combination with nivolumab. The primary outcome is objective response rate per RECIST v1.1 by investigator. Secondary outcomes include safety, pharmacokinetics, immunogenicity, progression-free survival, duration of response, and overall survival. Enrollment is ongoing with recruitment at sites in the United States, Europe, and the Asia-Pacific region.

Results: TBD

Conclusion: TBD

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A Phase 2 Clinical Trial of Pembrolizumab with Radiation Following Progression on anti-PD-1 Therapy in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): Treatment options for patients (pts) with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) who have progressed on anti-PD-1 directed therapy are limited. Some of these pts may have more limited disease (oligo) progression that may be amenable to radiation therapy (RT). RT has not been tested prospectively in this setting.

Materials/Methods: We performed a Phase 2 trial investigating focused RT with concurrent pembrolizumab (pembro) in pts with SCCHN whose disease progressed on prior PD-1 blockade. Cohort A allowed RT to a single lesion while Cohort B allowed for RT to up to 6 lesions. The primary endpoint was overall progression-free survival (PFS) at 3 months. A two-stage design was used in each cohort with the goal to distinguish 3-month (mo) PFS >65% vs. 35%. Cytometry by time of flight (CyTOF) evaluated circulating immune populations in peripheral blood samples obtained at baseline and over the course of therapy.

Results: Eighteen pts were enrolled, 6 in Cohort A and 12 in Cohort B. Eight (44%) pts had HPV+ disease (3 in Cohort A, 5 in Cohort B); 16 received prior chemoRT to the HN. Median number of metastases were 8.5 (Cohort A, range 1,>10) and 2 (Cohort B, range 1,>10). The most common protocol RT dose was 40 Gy in 5 fractions (n=9). The two most common sites of radiation were head and neck (n=10) and lung (n=10). Treatment was generally well tolerated with 2 pts experiencing grade 3 toxicity (fatigue, esophagitis) and 2 pts grade 4 toxicity (laryngeal edema, bleeding), all in Cohort B. Median PFS for Cohort A was 1.8 mo (95% CI 0.7-32.9 mo) with one pt progression-free at 3 mo (17%); therefore, this cohort did not proceed to the second stage. In Cohort B, median PFS was 6.5 mo (95% CI 3.3-10.2) with 8/12 pts progression free at 3mo (67%). PFS was associated with smaller RT target (prescription isodose <80cm3, p=0.04), 1-2 vs. >2 metastases (p=0.01), and RT to >50% of metastases (p<0.0001). Median OS was 7.6 mos (95% CI 0.7-32.9 mo) in Cohort A and 10.2 mos in Cohort B (95% CI 6.0-49.7 mo). CyTOF identified that the fraction of circulating CD8+ central memory T-cells (Tcm) was higher at baseline (mean freq. 3.0% vs. 0.9%) and remained elevated following cycle 2 of pembro (mean freq. 3.2% vs. 0.6%), in pts progression free >3mo. Expression of the trafficking and homing marker CXCR5 was also elevated on treatment (p adj.= 0.03) in memory B-cells from pts with PFS>3 mo.

Conclusion: This prospective phase 2 trial evaluated RT in R/M SCCHN pts following disease oligo-progression on prior anti-PD-1 therapy. RT/pembro resulted in more promising outcomes when RT was used to target the majority/entirety of measurable disease, with median PFS exceeding 6mo. Multiplexed immune cell measurements identified potential biomarkers that may help select patients who may benefit from integrated RT following progression on anti-PD-1 therapy.

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Comparative Efficacy of KEYNOTE-B10 Regimen as First-Line (1L) Therapy in Recurrent/Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC): A Network Meta-Analysis (NMA) with Aggregate-Level Matching

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Purpose/Objective(s): In KEYNOTE-B10, a phase IV, single-arm trial, the combination of pembrolizumab+carboplatin+paclitaxel (referred to as the B10 regimen) demonstrated antitumor activity with a manageable safety profile as 1L therapy for R/M HNSCC. Due to the single-arm design of KEYNOTE-B10, an NMA was conducted using methodologies to incorporate data from a disconnected trial into a connected network of randomized controlled trials (RCT) to estimate the comparative efficacy of the B10 regimen versus other interventions in 1L R/M HNSCC.

Materials/Methods: A systematic literature review (SLR) was conducted on June 30, 2023 to identify RCTs evaluating relevant interventions in the target population. The objective response rate (ORR) from the interim analysis of KEYNOTE-B10 was extracted and compared with all trials in

the network. Aggregate-level matching (ALM) was used to integrate the KEYNOTE-B10 trial into the connected network by matching it to the RCT within the network with the closest trial design and patient population, thus creating a new pseudo-RCT. The best matching patient population was determined as that with the smallest sum of absolute standardized differences across the following characteristics: age, sex, race, ECOG performance status, metastatic disease, tumor location, human papillomavirus infection, and tumor stage at diagnosis.

Results: The SLR identified 25 trials, of which 6 matched the eligibility criteria of KEYNOTE-B10 and were included in the ALM/NMA. KEYNOTE-048 had the smallest overall difference in patient characteristics/highest number of balanced variables compared to KEYNOTE-B10, with the latter being incorporated as a new treatment arm in the former. Results from the fixed-effects NMA for the B10 regimen are summarized in Table 1. For ORR, the B10 regimen was more efficacious compared to the platinum +5FU, platinum+taxane, platinum, 5-fluorouracil, and methotrexate regimens. There was no statistically significant difference in ORR between the B10 regimen and pembrolizumab+platinum+5-fluorouracil, cetuximab +platinum+5-fluorouracil, and cetuximab+platinum+taxane.

Conclusion: This NMA including interim results from KEYNOTE-B10 demonstrates improved or comparable ORR outcomes versus alternative 1L R/M HNSCC interventions. Once available, analyses should be completed utilizing the final analysis of KEYNOTE-B10 as well as survival outcomes.

Abstract 141 − Table 1: Results of Fixed-Effects NMA

Comparators	Pembrolizumab + Platinum + Taxane ORR odds ratios (95% confidence interval)
Pembrolizumab + Platinum + 5-fluorouracil	1.35 (0.81, 2.23)
Cetuximab + Platinum + 5-fluorouracil	1.3 (0.78, 2.16)
Platinum + 5-fluorouracil	**2.95 (1.52, 5.76)**
Platinum + Taxane	**3.57 (1.46, 8.85)**
Cetuximab + Platinum + Taxane	1.27 (0.69, 2.35)
Platinum	**6.86 (2.53, 18.78)**
5-fluorouracil	**9.18 (3.27, 26.30)**
Methotrexate	**9.74 (3.59, 28.13)**

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Proton Re-Irradiation in the Adjuvant Setting for Head and Neck Squamous Cell Carcinoma with High Risk Features

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Purpose/Objective(s): For patients with head and neck squamous cell carcinoma (HNSCC), locoregional failure and second primary tumors are common indications for adjuvant re-irradiation (re-RT). Given an absence of clear consensus on the role of adjuvant reRT, we sought to evaluate histopathologic risk factors of HNSCC patients and their resulting outcomes after adjuvant re-RT with proton therapy.

Materials/Methods: We conducted a retrospective analysis of HNSCC patients who underwent salvage surgery at our institution followed by adjuvant re-RT with proton therapy over 1.5 years. All included patients received prior radiotherapy. The Kaplan-Meier method was used to evaluate recurrence-free survival (RFS) and overall survival (OS).

Results: The cohort included 22 patients, with disease subsites including oropharynx, oral cavity, hypopharynx, larynx, and nasopharynx. Depending on adverse pathologic features, adjuvant re-RT to 66Gy (68% of cohort) or 60Gy (32%), with (59%) or without (41%) concurrent systemic therapy was administered. The majority (86%) completed re-RT with no reported treatment delay; 3 patients experienced grade >=3 acute Common Terminology Criteria for Adverse Events (CTCAE) toxicity and no patient required enteral feeding tube placement during re-RT. Median follow-up was 21.0 months (IQR 11.7-25.2 months). Five patients had biopsy-proven disease recurrences a median of 5.9 months (IQR 3.8-9.7 months) after re-RT. RFS was 90.5%, 70.4%, 65.0% at 6, 12, and 24 months, respectively. OS was 100%, 79.2%, and 79.2% at 6, 12, and 24 months, respectively. Four patients had osteoradionecrosis on imaging a median of 13.2 months (IQR 8.7-17.4 months) after re-RT, with two requiring surgical intervention.

Conclusion: Adjuvant re-RT for HNSCC patients was well-tolerated and offered reasonable local control in this high risk cohort, but appears to be associated neck irradiation. Further study and longer follow-up could help define optimal patient management in this patient population.

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Can Circulating Tumor DNA be Utilized as a Marker to Guide High-Risk Head and Neck Squamous Cell Patients Treatment?

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Purpose/Objective(s): The purpose of the study was to define whether circulating tumor DNA (ctDNA) can be used as a measure to detect minimal residual disease (MRD) following surgical intervention in high-risk positive patients for head and neck squamous cell carcinoma (HNSCC).

Materials/Methods: IRB approval was obtained through our institution. Patients with HNSCC with surgical resection of their tumor were enrolled. Of these, 28 patients had ctDNA levels determined post-operatively (n = 28) using the Signatera test. Data were extracted from electronic medical records by trained abstractors.

Results: The patient cohort (20 male and 8 female) had an average age of 67.0 ± 9.82 years at the time of surgery. Patients were assessed using The Eastern Cooperative Oncology Group (ECOG) functional scores, with 17.9% scoring 0, 75.0% scoring ECOG 1, and 7.14% of patients with ECOG 2 or 3. All patients had primary laryngeal or oral cavity cancer, including gingival, tongue, and mandibular. The study had two patients with pathologic Stage I cancer, three with Stage II, five with Stage III, eleven with Stage IVA, and seven with Stage IVB. One patient received neoadjuvant

chemotherapy prior to surgery. There were 19 high-risk positive cancers, defined as positive extranodal extension or positive margins during surgery. 15 of these 19 patients patients received adjuvant chemotherapy and radiation, with or without a platinum agent, depending on their chemotherapy eligibility. In these high-risk patients, 18 had data in the post-operative period, prior to adjuvant therapy, for which 61.1% had positive ctDNA. Conversely, there were 9 patients without high-risk features, of whom only two had positive MRD post-operatively, and two with disease recurrence. There was a significantly lower tumor recurrence in the patients without high-risk features compared to those with high-risk features (22.9% vs. 54.5%, respectively) which correlated with ctDNA. At the time of data collection, 7 patients had disease recurrence for which 5 were post-operative ctDNA positive. Two patients were ongoing adjuvant treatment and follow-up without recurrence data.

Conclusion: ctDNA was detected frequently in the HNSCC patients with high-risk features post-operatively. Although we have a small number of the patients, the patients with recurrence following adjuvant treatment had high rates of positive ctDNA after the surgery. Therefore post-operative ctDNA for high-risk patients may be prognostic and considered in clinical trials designed for treatment intensification.

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Sequential Treatment Use in Clinical Practice for U.S. Patients with Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

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Purpose/Objective(s): Since the approval of pembrolizumab monotherapy in the platinum-refractory setting for R/M HNSCC in 2016 and the subsequent approval of pembrolizumab alone or in combination with chemotherapy in first-line (1L) in 2019, pembrolizumab-based therapy has become a standard of care. To better understand current real-world practice patterns, this study assessed the use of sequential systemic treatment from 1L to 2L for patients with R/M HNSCC.

Materials/Methods: A retrospective cohort study was conducted using the Flatiron Health Advanced Head and Neck database. The study cohort included adult patients with R/M HNSCC who initiated 1L systemic therapy between 07/01/19 and 12/31/22 with follow-up through 06/30/23. Patients were excluded if they received platinum treatment ≤6 months prior to 1L therapy, had head and neck cancer subtypes other than SCC of the hypopharynx, larynx, oropharynx, or oral cavity, or were treated in a clinical trial.

Results: A total of 1879 patients were included. Median age was 67 years (IQR: 60, 74). Most were male (77.1%) and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 (71.7%). HPV-positivity was reported in 70.8% (602/850) of tested oropharyngeal cancers. Table 1 shows the 1L treatment utilization with over half patients (58.9%) received pembrolizumab with or without chemotherapy in 1L. Patients who received 1L pembrolizumab monotherapy had the oldest age (median: 70 years), the highest proportion of ECOG≥2 (21.2%) and CPS≥1 (85.5%). Approximately 39.5% received a 2L therapy, 47.9% had no subsequent line of therapy at the end of follow-up, and 12.5% died during or after 1L therapy. Cetuximab-based regimens were the most used 2L therapy (25.1%), followed by pembrolizumab alone (23.1%) and platinum-based chemotherapy (14.5%). Of 231 patients starting pembrolizumab alone in 1L who later received subsequent treatment, 14 (6.1%) had platinum and 5-fluorouracil

added, 41 (17.7%) had other chemotherapy added, and 27 (11.7%) were retreated with pembrolizumab alone.

Conclusion: Pembrolizumab alone or in combination with chemotherapy were the most widely used in 1L for R/M HNSCC; over 40% of patients received other 1L therapies. Patients receiving pembrolizumab alone in 1L had different characteristics favoring older, more frail patients. Understanding the sequential use of immunotherapy is important to inform optimal management of patients with R/M HNSCC.

Abstract 144 − Table 1: 1L Treatments Used in R/M HNSCC

1L Treatment	N (%)
Pembrolizumab monotherapy	617 (33.7%)
Pembrolizumab + platinum + 5-fluorouracil	299 (16.4%)
Other pembrolizumab-based regimen	161 (8.8%)
Platinum monotherapy	278 (15.2%)
Platinum + taxane	158 (8.6%)
Nivolumab-based regimen	123 (6.7%)
Cetuximab-based regimen	104 (5.7%)
Other chemotherapy	87 (4.8%)
Note: Excluded 52 patients receiving 1L/2L therapy not deemed for R/M HNSCC per guidelines and oncologists' review	

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Platinum/taxane/pembrolizumab vs Platinum/5-fluorouracil/pembrolizumab in recurrent/metastatic Head and Neck Squamous Cell Carcinoma (r/m HNSCC)

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Purpose/Objective(s): Pembrolizumab +/- chemotherapy is standard therapy for r/m HNSCC. Despite regulatory approval of platinum/5FU/pembrolizumab, a taxane is often substituted for 5FU due to convenience and tolerability. We aimed to characterize nationwide use patterns and compare outcomes between the two regimens.

Materials/Methods: Patients in a real-world US database with r/m HNSCC treated from 2017-2022 with pembrolizumab plus platinum-based chemotherapy (either taxane or 5FU) were included. Demographic and cancer-specific characteristics were summarized. Overall survival (OS) was estimated using Kaplan-Meier methodology, and compared between groups using log-rank test and multivariable Cox regression. Time on treatment, number of cycles, receipt of second-line therapy, and toxicities were summarized and compared between groups.

Results: Of 438 patients, 320 (73%) received 5FU and 118 (27%) received a taxane. Taxane use became more frequent over time and was higher in academic vs community practices (51% vs 23%, p<0.001); within community sites, Northeast states had highest taxane use (28%). OS did not differ between taxane and 5FU groups (mOS 12.2 vs 13.4 months, p=0.662). On multivariable Cox regression, HR for death associated with taxane vs 5FU was 0.99 (95%CI 0.71-1.38). Receipt of 2L therapy was numerically higher for 5FU patients (46%) compared to taxane patients (35%, p=0.071). Grade ≥3 anemia was more common in taxane patients (33% vs 20%, p=0.003), whereas grade ≥3 lymphopenia and thrombocytopenia were numerically higher in 5FU patients.

Conclusion: In patients with r/m HNSCC undergoing chemoimmunotherapy, rates of taxane vs 5FU use vary by academic setting and geographic region. There was no difference in survival between platinum/taxane/pembrolizumab and platinum/5FU/pembrolizumab. Platinum-taxane appears to be a non-inferior alternative to platinum-5FU when combined with pembrolizumab for r/m HNSCC, and should be allowed in clinical trials and included in guidelines.

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Initial Experience of Proton-Based Stereotactic Body Radiotherapy for Head and Neck Reirradiation

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Purpose/Objective(s): Up to 50% of patients with head and neck cancer (HNC) may recur after initial treatment, which often includes a combination of surgery, chemotherapy, and radiation. Reirradiation is an effective treatment option with high rates of local control. Hypofractionated regimens may be desirable due to high biologically effective doses, however they can be complicated by high rates of toxicity. Intensity-modulated proton therapy (IMPT) plans have dosimetric advantages compared to standard photon plans. We sought to review initial patient tolerance and treatment outcomes of proton-based stereotactic body radiotherapy (SBRT) for reirradiation of HNC.

Materials/Methods: A single institution retrospective review of HNC patients treated with proton-based SBRT for reirradiation in the head and neck from July 2020 to December 2022 was performed. Acute and late toxicities were prospectively recorded. Patient reported outcomes were assessed prior to and at completion of treatment using the MD Anderson Symptom Inventory (MDASI) and EQ-5D5L visual analogue score (VAS). Planning outcomes and dosimetry parameters, including GTV volume, conformity (CI and R50), and PTV coverage were evaluated. Local control and overall survival were estimated using the Kaplan-Meier method. Paired t-test was used to compare continuous variables.

Results: 9 patients were treated with proton SBRT to 10 lesions in the head and neck. Most patients had squamous cell carcinoma histology (89%). All patients received a biologically effective dose of at least 58.5 Gy at initial course. Patients were reirradiated at median time of 2 years following prior head and neck radiotherapy (range 0.4, 15.8). The most commonly used dose and fractionation for reirradiation was 40 Gy (range 34, 40) in 5 fractions. Three patients received immunotherapy during treatment. Average gross target volume (GTV) was 9.1 cc (1.7, 28.6). The mean conformity index was 1.0 (0.6, 1.1) and mean R50% was 4.0 (2.3, 6.7). PTV V100% was 86.0% on average (54.9% − 96.2%). No patients developed a new grade 3 or greater toxicity during treatment or at last follow up. Comparing pretreatment to end of treatment timepoints, there was no significant increase in the mean VAS (55 to 62, p = 0.10), with no significant change in the mean MDASI symptom (2.5 to 2.4, p = 0.77) or interference (3.7 to 3.2, p = 0.63) scores. Local control was 100% at last follow up or death. Median overall survival was 0.8 years.

Conclusion: Proton-based SBRT for reirradiation of HNC is well tolerated with high rates of local control and median overall survival consistent with other reports in this population. Further follow up is necessary to assess tumor control and toxicities.

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Characteristics and Survival of Patients with Primary and Secondary Distant Metastasis of Oropharyngeal Squamous Cell Carcinoma (OPSCC)

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Purpose/Objective(s): OPSCC generally carries a favorable prognosis, particularly for HPV+ patients. However, distant metastasis (DM) occurs in 15-20% of patients. Most DM occurs following curative-intent treatment, but a proportion of patients present with primary DM. We sought to describe the characteristics and survival of patients with primary vs secondary DM OPSCC, including differences in the clinical presentation and prognosis from the time of presentation with DM.

Materials/Methods: This retrospective analysis examined OPSCC cases recorded at a tertiary academic center with three major geographic sites. We collected demographics, tumor staging, HPV status, sites of metastasis, treatment modalities, and survival from the time of DM. Kruskal-Wallis and Chi-Square tests were used to assess differences between groups. Kaplan-Meier analysis was used to estimate median overall survival.

Results: Of 132 patients with DM-OPSCC (2006-2020), 18 had primary and 114 had secondary DM. Median follow-up was 32.4 months. The primary DM group was significantly older at the time of DM diagnosis (65.5 vs 59.6 years, p = 0.04) . Findings are summarized in Table 1. The risk of death was higher in those who did not undergo metastasis-directed therapy (MDT) (HR 2.65, 95% CI 1.64 - 4.27), those who did not receive checkpoint inhibitors (IO) (HR 1.76, 95% CI 1.02 - 3.03), or those who did not undergo surgical metastasectomy (HR 4.72, 95% CI 2.09 - 10.68). The median time until onset of secondary DM after initial OPSCC diagnosis was 1.2 years (range 0.2 - 7.5 years). In patients who received curative intent surgery, extranodal extension was identified in 84% of specimens. For those who underwent curative-intent surgery for their primary tumor, 84% (68/81) had extranodal extension and 56% were pN2 or higher.

Conclusion: To our knowledge, this is the largest single center analysis of DM(+)OPSCC. Patients with primary DM were older, more likely to be HPV-negative or unknown HPV-status, and had shorter survival time from DM diagnosis compared to those with secondary DM. Patients treated with MDT, IO, and metastasectomy had significantly increased survival, though this finding likely reflects lower disease burden. This analysis demonstrates that primary DM(+)OPSCC carries a poor prognosis, but that aggressive treatment of secondary DM following initial curative-intent therapy has a median survival after DM of nearly 5 years.

Abstract 147 − Table 1

	Primary met	Secondary met	Met site (% with involvement)	Primary met	Secondary met
N	18	114			
Median Age at Dx	68.9	59.5	lung	44.4	49.1
% Male	83.3	90.4	mediastinum	50	27.2
HPV positive	22.2	75.4	bone	33.3	20.2
HPV negative	44.4	11.4	liver	16.7	12.3
HPV unknown	33.3	13.2			
% T4 − 8th ed	not fully staged	22.1	Median OS after DM (years)	0.8	1.7
% N2+ - 8th ed		26.9			
			Entire cohort		
% resected	23.5	80.7		Received tx modality:	
% definitive chemoradiation	5.9	19.3	Median OS after DM (years)	yes	no
% palliative chemo	77.8	48.2	MDT	4.7	1.1
% IO	16.7	24.6	metastasectomy	NR	1.2
% metastasectomy	5.6	18.4	IO	3.7	1.1
% radiation to DM	11.1	44.7			

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FIERCE-HN: A Multicenter, Randomized, Placebo-controlled, Phase 3 Study of ficlatuzumab + cetuximab in pts w/ recurrent or Metastatic (R/M) HPV-negative Head and Neck Squamous Cell Carcinoma (HNSCC)

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Purpose/Objective(s): For patients with R/M HNSCC, current treatments are palliative with anti-PD-1 checkpoint inhibitor +/- platinum and 5-fluorouracil chemotherapy for first-line followed by taxanes, methotrexate, and cetuximab as later-line options. The median overall survival (OS) for R/M patients is 10-13 months, and those with HPV-negative HNSCC face the worst outcomes.[1] Ficlatuzumab is a humanized IgG1 mAB against HGF, the ligand for the c-MET tyrosine kinase receptor. HGF/c-MET pathway dysregulation is frequently observed in HPV-negative HNSCC. In a phase 2 study, ficlatuzumab 20mg/kg plus cetuximab 500mg/m^2 every 2 weeks was assessed in R/M HNSCC patients that were anti-PD-1, cetuximab, and platinum-resistant, a pan-refractory population with a median PFS of 2 months[2]. In this study, HPV-negative patients had a progression-free survival (PFS) of 4.1 months, median OS of 7.4 months, and overall response rate (ORR) of 38% (6/16; 2 CR, 4 PR)[2]. The objective of the FIERCE-HN study is to compare the efficacy/safety of ficlatuzumab+cetuximab vs placebo+cetuximab in patients with R/M HPV-negative HNSCC.

Materials/Methods: FIERCE-HN is an international, multicenter, randomized, double-blind, placebo-controlled phase 3 study. Major enrollment criteria include confirmed primary diagnosis of HPV-negative R/M HSNCC; primary tumor of oropharynx, oral cavity, hypopharynx, or larynx; failed or intolerant to previous anti-PD-1/PD-L1 and platinum chemotherapy; no more than 2 prior lines of anticancer therapy; no prior treatment with cetuxiumab/alternative EGFR inhibitors in the R/M setting. Patients with feeding tubes are eligible. Approximately 410 patients will be randomized 1:1:1 to Arm A: ficlatuzumab 10mg/kg plus cetuximab 500mg/m^2, Arm B: ficlatuzumab 20mg/kg plus cetuximab 500mg/m^2, or Arm C:

placebo plus cetuximab 500mg/m^2. Treatments will be on Days 1 and 15 of a 28-day cycle. An interim analysis will be done to determine optimal dose of ficlatuzumab for further study progression when 70 patients each in Arms A and B have completed their first restaging scans (the inferior ficlatuzumab arm will be discontinued; final target n of ~163 in each the optimal ficlatuzumab and control arms). The primary endpoint is OS; additional endpoints include PFS, ORR, DCR, DoR, safety, PK/PD, QoL, and antidrug antibodies. A total of 239 events are required to have 87.5% power to detect a difference assuming a true HR=0.67 in favor of the optimal ficlatuzumab+cetuximab arm after the interim analysis. Analysis will use a 1-sided log-rank test at a significance level= 0.025 and the uniformly most powerful conditionally unbiased criterion to control the Type 1 error.

Results: TBD

Conclusion: TBD

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Safety and Toxicity of Iopofosine I-131 with External Beam Radiation Therapy (EBRT) in Recurrent or Metastatic Head and Neck Cancer (HNC): Results of a Phase 1 Study

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Purpose/Objective(s): Retreatment of recurrent HNC is often limited by tumor adherence to critical structures or normal tissue tolerance to radiation therapy. Iopofosine I-131 (CLR 131) is a novel targeted small molecular phospholipid ether (PLE) drug conjugate that delivers iodine-131 selectively to malignant tumor cells optimized through specialized regions called lipid rafts. Radiation exposure is selective to cancer cells due to the interaction of the PLE with the highly enriched lipid rafts of the plasma membrane, which are non-reliant on cell surface markers. In this trial, CLR 131 given with a reduced dose of EBRT will be safe and produce favorable tumor response rates.

Materials/Methods: All patients (pts) must have previously received treatment with curative intent radiotherapy to the HN region. Pts may have metastatic disease, as long as the site of recurrence is eligible for radiotherapy and takes precedence over systemic treatment. Eligible pts must demonstrate uptake of CLR 131 as indicated via SPECT/CT imaging after administration of a CLR 131 test dose. Pts received 2 doses of CLR 131 (days 1 and 8) with SPECT/CT imaging performed to quantitate the biodistribution of CLR 131. The Monte Carlo method was utilized to calculate the absorbed dose of CLR 131 by the targeted tumor. Pts subsequently received EBRT to complete the designated radiation dose outlined in the standard of care reirradiation plan (60-70 Gy).

Results: Sixteen pts were consented, and 12 were treated on study. Four pts were ineligible (2 had insufficient CLR 131 uptake, 2 had rapidly progressive disease). Six pts were treated at first recurrence, 6 pts had multiply recurrent disease, and 2 pts had metastatic disease. All pts completed treatment with CLR 131 and EBRT. One pt died from aspiration pneumonia unrelated to CLR 131 but possibly related to EBRT. The median total absorbed tumor dose of CLR 131 was 6.23 Gy [range 2.65 - 8.69 Gy]. Eight pts experienced gr 4 non-DLT hematologic toxicities (2 anemia, 8 leukopenia, 5 thrombocytopenia) at least probably attributed to CLR 131, which was consistent with the

expected toxicity profile. The hematologic toxicities occurred during weeks 6-8 from the first dose of CLR 131, and resolved within 3 weeks without sequelae. There were no treatment related gr 3-4 non-hematologic toxicities.

Conclusion: CLR 131 at a fractionated dose of 15.6 mCi/m2 in combination with EBRT was safe and tolerable in pts with recurrent/metastatic HNC. Observed myelosuppression was consistent with the known toxicity profile of CLR 131. The Monte Carlo method provides a novel approach for calculating the tumor-absorbed dose of radionuclide agents, allowing for accurate tumor targeting and personalized dosing strategies in future combination therapy studies, which may improve efficacy and reduce toxicity.

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Deep Learning-Based Prognostic Prediction for Early Stage Laryngeal Cancer Patients Post-Radiotherapy: Utilizing 3D CBCT and EMR Data

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Purpose/Objective(s): Radiation therapy is a predominant treatment method for early-stage laryngeal cancer patients. The primary objective of this study is to predict the prognosis of recurrence in this specific patient group. Our study cohort comprises patients with stages 0-2, who have undergone radiation therapy with a curative intent rather than for palliative care. In this research, we endeavor to introduce a deep learning-based survival analysis model that harnesses data from multiple modalities obtained during radiation therapy.

Materials/Methods: We amassed EMR data and intra-treatment CBCTs from 198 laryngeal cancer patients across five top-tier hospitals. From the CBCTs, only slides encompassing the larynx within the head and neck were selected and processed using Cubic spline interpolation, crafting 3D CBCT images with a depth set at 32. Depending on the EMR data, procedures like One-Hot encoding, Logit transformation, and Boxcox were applied. The 3D CBCTs fed into six sequential 3D CNN models, while the structured data informed a singular MLP model, generating feature maps. These maps coalesced and transferred to a Discrete-Time Model for survival function extrapolation. The finalized model was fine-tuned using hyperparameters like model type, learning rate, and discretization range, with the validation set's C-index guiding the objective function.

Results: Of the 198 patients studied, 96.5% were males and 3.5% females. Age-wise, 11.1% were ≤55, 36.4% between 55-65, 35.4% from 65-75, and 17.1% were ≥75. Imaging stages showed 6.6% at stage 0, 69.2% at stage 1, and 24.2% at stage 2. The 5-year survival rates were as follows: overall 0.9697, progression-free 0.8485, and recurrence-free 0.8636. Table 1 presents the top 5 models selected from a combination of the 10 distinct 3D CNN Models and 4 Discrete-time models, resulting in a total of 40 developed models. Both internal and external validations for these selected models yielded a C-index of 0.7 or higher and a Brier score of 0.16 or below.

Conclusion: Based on the results, we can infer that the deep learning-based survival analysis model proposed in this study, focusing on multi-modality, successfully predicts the prognosis concerning the duration until recurrence.

Abstract 150 − Table 1: Inference Performance of Deep Learning-Based Survival Analysis Model

Survival Model (CNN + Discrete-Time model)	Internal validation		External validation	
	C-index	Brier score	C-index	Brier score
SeResNext101 + N-MTLR	0.836	0.133	0.774	0.129
SeResNet152 + Nnet-survival	0.805	0.151	0.767	0.127
SeResNet50 + PMF	0.775	0.158	0.760	0.137
SeResNext50 + Nnet-survival	0.790	0.145	0.750	0.146
EfficientNetB1 + N-MTLR	0.808	0.153	0.748	0.150

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Outcomes and Genomic Landscape of Patients Treated with Re-Irradiation for Recurrent Head and Neck Cancer Using Pencil Beam Scanning Proton Therapy: The Maryland Proton Treatment Center Experience

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Purpose/Objective(s): Re-irradiation (re-RT) for recurrent head and neck cancer (rHNC) after prior HNC RT is clinically challenging given prior radiation of nearby organs at risk (OARs). We describe clinical outcomes and toxicity of pencil beam scanning proton therapy (PBS-PT) for recurrent HNC, and report genomic alterations associated with patterns of failure to improve clinical decision making.

Materials/Methods: We performed a retrospective analysis of rHNC patients treated at a single institution with PBS-PT. Baseline demographic, disease and treatment characteristics were recorded. Clinical outcomes were estimated using the Kaplan-Meier method. Univariable (UVA) and multivariable analyses (MVA) were performed to assess patient, disease, and treatment related factors. Acute and late grade 3+ toxicities were assessed per CTCAE v5.0. Next generation sequencing (NGS) and genomic analyses were performed on available samples.

Results: Eighty-nine patients treated with PBS-PT for rHNC between 2016 and 2022 with a median follow-up of 12 months (range 0-71) were included. The 1- and 2-year local control rates were 80.8% (95% CI: 70.8-90.8) and 66.2% (95% CI: 50.7-81.7) and 1- and 2-year distant metastasis free survival (DMFS) were 41.0% (95% CI: 30.0-52.0) and 26.3% (95% CI: 15.7-36.9). Median overall survival (OS) was 13 months (95% CI: 9.3-16.7). On UVA and MVA, smaller gross tumor volume was associated with improved OS (HR 1.002, p=.004), DMFS (HR 1.002, p=0.004) and progression free survival (PFS) (HR 1.002, p=0.014). There were 35 late grade 3 or higher toxicity events (30.3%), including one patient that suffered late grade 5 osteoradionecrosis resulting in sepsis. Patients with higher candidate gene specific mutation burden (genes with odds-ratio >2, p<0.05) had inferior PFS. In addition, *TP53*, *NOTCH4* and *ARID1B* mutations were associated with inferior DMFS (OR>2, p<0.05). Of the top 28 highly mutated genes (mutated in ≥ 3 samples in either group, odd ratio>2), TP53 was the most frequently mutated gene in DMFS alive group with Met(78%), followed by NOTCH4(52%), ARID1B (33%). please see table table1b.

Conclusion: Pencil beam scanning proton therapy re-irradiation is effective at achieving local control for recurrent head and neck cancer and is associated with a favorable toxicity profile. Distant metastases comprise the major failure pattern for this patient population and are associated with *TP53*, *NOTCH4*, and *ARID1B* somatic mutations. Validation of these findings may provide rationale for the inclusion of genomic alterations in the clinical decision process.

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Tumor Tissue Modified Viral HPV DNA Monitoring in Patients with Recurrent, Metastatic HPV-driven Oropharyngeal Cancer

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Purpose/Objective(s): Monitoring circulating tumor tissue modified viral (TTMV)-HPV DNA during post-treatment surveillance is a tool for detecting recurrence in patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). We investigated the utility of the assay to capture therapeutic response and predict survival outcomes in patients with recurrent, incurable or metastatic (R/M) disease.

Materials/Methods: This IRB-approved, retrospective observational cohort study included 82 patients across three U.S. centers who had R/M OPSCC and one or more TTMV-HPV DNA results (liquid biopsies) obtained during their disease course between 2020 and 2023. A baseline TTMV-HPV DNA test was not required, and HPV status was assessed by p16 and/or HPV PCR/ISH. Assay results were correlated with sequential imaging and treatment response parameters to assess disease status and survival.

Results: Median age was 64.5 (range: 41-83), with a cohort of mostly men (93%) that included smokers (57%) with half having received chemoradiation (50%) for their initial disease. Most had 0-2 distant metastatic (DM) sites (90%) and HPV subtype 16 was most common (87%) followed by HPV33 (5%). A subset of six patients (11%) recurred >5 years after the completion of initial treatment. Median follow-up time was 2.6 years (range, <1-9.8) and there was a median of 69 days between TTMV-HPV DNA tests (range, 5-503). Within this cohort, 52 patients had >1 test result in the R/M setting, with 19 (23%) having ≥4 tests following R/M diagnosis. TTMV-HPV DNA scores were more likely to resolve to not detectable (ND), indicative of a complete therapeutic response, when patients were on initial R/M treatment (15/24, 63%) compared to 2L+ (17/52, 33%), with no patient achieving resolution during or after completion of 3L treatment. The likelihood of achieving ND status was impacted by the number of DM sites: patients with 0-2 DM sites had a 59% chance of an ND test compared to 0% for patients with 3+ DM sites. Patients on immunotherapy tended to have more variable scores within the same treatment, whereas patients on other modalities tended to demonstrate a sharp change in scores. A

decline in TTMV-HPV DNA to ND significantly correlated with overall survival (OS) compared with patients whose last test was detectable (log-rank test, *P*=0.003). Among patients whose test value did not resolve, those with a ≥50% decrease in score showed improved OS (hazard ratio: 5.3; 95% CI: 1.5-19.3; *P*=0.046).

Conclusion: Our findings support the clinical value of monitoring circulating TTMV-HPV DNA in the R/M setting for patients with HPV-positive OPSCC. ND status was influenced by treatment stage and the number of DM sites, and correlated with patient survival. These results may inform clinical management decisions and improve prognostic risk stratification for R/M HPV-driven OPSCC.

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Re-irradiation After Osteocutaneous Free Flap Reconstruction for Locally Recurrent Head and Neck Cancer: A Case Series

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Purpose/Objective(s): Recurrent head and neck cancer (HNC) poses difficult management. Salvage surgery is often used in these situations. However, even after salvage surgery, many patients are still considered high-risk for further recurrence and benefit from re-irradiation. Free flaps not only enable reconstruction following salvage surgery, but there have also been limited studies suggesting free flap reconstruction may reduce the amount of re-irradiation complications. There are no studies to date specifically examining the effects of osteocutaneous free flap reconstruction upon re-irradiation toxicity. We hypothesize that the rate of local adverse events after re-irradiation is low in the setting of bony free flap reconstruction.

Materials/Methods: Patients with recurrent HNC that received salvage surgery with osteocutaneous flaps were identified. Those who had a history of HNC radiation prior to salvage surgery and then underwent adjuvant re-irradiation were included. Descriptive statistics was performed to assess outcomes.

Results: Six HNC patients met criteria for inclusion. The type of flap was fibula in five and osteocutaneous radial forearm in one. Within 90 days of re-irradiation, three (50%) had radiation ulcers and one (16.6%) had mucositis. No patients had xerostomia, dermatitis, new dysphagia, or thrush as acute radiation toxicities. 90 days after re-irradiation, no additional patients had these symptoms suggesting there were no chronic radiation toxicities. Wounds present following re-irradiation included plate exposure greater than 6 months after re-irradiation in one (16.6%) and surgical site infection greater than 6 months after surgery in one (16.6%). No patients had osteoradionecrosis following re-irradiation, fistula, plate removal, or plate fracture. Diet at 12 months post op was PO in two (33.3%), partial PEG-dependence in two (33.3%), and complete PEG-dependence in two (33.3%). Trach at 12 months post op was present in two (33.3%) patients. 4 (66%) had HNC recurrence median overall survival of 34.4 months.

Conclusion: In this cohort of patients undergoing re-irradiation after bone free flap reconstruction, most patients avoided local adverse events related to re-irradiation.

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Cemiplimab and Metronomic Chemotherapy in Recurrent/ Metastatic (R/M) Squamous Cell Carcinoma (SCC) of the Head and Neck (H&N): Trial in Progress.

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Purpose/Objective(s): The current first-line standard of care for recurrent/metastatic head and neck (H&N) squamous cell carcinoma (SCC) is anti-programmed death-ligand 1 (anti-PD-L1) immune checkpoint inhibition. Metronomic chemotherapy, low-dose high-frequency dosage aims to enhance immunomodulation, inhibit angiogenesis, and mitigate chemotherapy-related complications.

Materials/Methods: OSU-20258 (NCT04862650) is a Phase II, single-arm, open-label trial. Eligible subjects are those requiring first-line treatment for recurrent/metastatic head and neck squamous cell carcinoma. Ineligible subjects are patients with disease amenable to curative local treatment, recurrent nasopharyngeal carcinoma, salivary gland carcinoma and p16-negative cancer of unknown primary. Prior treatment with phosphoinositide 3-kinase inhibitors or monoclonal antibodies is also ineligible. The total study accrual target is 42 patients. This study employs a Simon two-stage optimal design, requiring 40% overall response rate (ORR) in the first stage to proceed. The trial treatment is Cemiplimab every three weeks (350mg, total 104 weeks) and low-dose Carboplatin and Paclitaxel (25mg/m^2 and AUC = 1mg/ml/min, respectively; administered weekly for a total of 24 weeks). Dose holds and consequent dose reductions of Carboplatin/ Paclitaxel are allowable in the case of treatment-related grade 2 toxicities. The primary endpoint is the ORR at 12 weeks, and secondary endpoints include toxicity assessment, progression-free survival, and overall survival (OS). A safety run-in phase was conducted for the first 10 patients. Exploratory objectives include the response assessment stratified by combined positive score <1%, >1% and >20%. Correlative samples aim to analyze phenotypic immune cell subsets, T cell functionality, cytokine production of T cells and T cell receptor sequencing to compare responders and non-responders. Clinical response evaluation is conducted per Response Evaluation Criteria in Solid Tumors version 1.1 at 12 weeks on treatment.

Results: Will be analyzed at the end of 12 weeks of treatment of the last accrued patient.

Conclusion: Study is actively accruing to Stage II of the study and we aim to complete accrual and overall response rate evaluation of Cemiplimab with metronomic chemotherapy in 2024.

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Mapping Key Clinical Trial Eligibility Criteria (EC) to Real-world Data (RWD): An Example Using KENYOTE-48

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Purpose/Objective(s): Extrapolating Randomized Clinical Trials (RCTs) evidence to the overall population is methodologically challenging. Here, we applied a novel methodology to map key EC from KEYNOTE-48 to patients initiating 1L pembrolizumab using RWD. Instead of filtering real-world patients based on EC which can rapidly shrink the sample size, we propose creating an augmented population to improve the power of RWD analyses.

Materials/Methods: A retrospective cohort study was conducted using the Flatiron Health Advanced Head and Neck database including adult recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) patients initiating pembrolizumab-based 1L treatment from 7/1/19 − 12/31/22. KEYNOTE-048 EC including patients > 18 years at initial diagnosis, histologically or cytologically confirmed, with primary tumor in oropharynx, oral cavity, hypopharynx, or larynx, ECOG 0-1 and PD-L1 test were used to the RWD to calculate the probabilities of each patient being eligible, ineligible (≥ 1 criterion not met), or unknown (≥ 1 criterion missing) using machine learning model approach. An augmented population was also formed, which combines the eligible and unknown groups through a propensity-based adjustment.

Results: Of the 945 patients initiating 1L pembrolizumab-based regimen, 290 (30.7%) would be eligible and 214 (22.6%) would be ineligible with 441 (46.7%) patients unknown. Unknown patients had high median (IQR) estimated probabilities of being eligible (0.85 (0.83-0.89)), suggesting these patients are highly likely to be eligible. Over 60% of the ineligible patients had ECOG 2+ and 30% of unknown patients had missing ECOG scores. Pembrolizumab alone was the most utilized 1L regimen in each group (65.9%, 75.7% and 65.1% for eligible, ineligible, and unknown respectively). The median rwOS (95% CI) of eligible, ineligible, and unknown patients that received pembrolizumab monotherapy was 17.0 (13.1, 21.7), 5.7 (4.5, 8.7) and 18.2 (15.5, 21.7), respectively. For patients that received pembrolizumab + platinum + 5-fluorouracil, the median rwOS (95% CI) of eligible, ineligible, and unknown was 14.7 (10.5, 22.1), 13.5 (7.2, 23.4) and 13.5 (11.3, 18.5), respectively. The augmented population (eligible + unknown) had a median rwOS of 17.4 (15.4, 20.8) for pembrolizumab alone and 14.3 (11.9, 17.8) for patients that received pembrolizumab + chemotherapy.

Conclusion: This study identified patients that are likely to be eligible for the trial and created an augmented population. Survival of patients who were eligible, with unknown eligibility, or the augmented group (eligible + unknown) was numerically better than that in the RCT. This could be applied as an exploratory post approval step to understand routine clinical practice and increase the power of RWD analysis.

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Health-Related Quality of Life (HRQoL) Data From KEYNOTE-412: Chemoradiotherapy (CRT) with or Without Pembrolizumab (pembro) in Patients (pts) with Locally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)

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Purpose/Objective(s): The phase 3 KEYNOTE-412 study (NCT03040999), pembro + CRT (pembro arm) showed a trend toward improved EFS vs placebo + CRT (pbo arm) in pts with LA HNSCC, although the difference was not statistically significant (HR, 0.83 [95% CI, 0.68-1.03]; P=0.0429 [superiority threshold, P=0.0242]). Prespecified HRQoL outcomes from KEYNOTE-412 are presented.

Materials/Methods: Pts aged ≥18 yrs with LA HNSCC were randomly assigned 1:1 to pembro 200 mg IV once Q3W or matching pbo + CRT. Pts received 1 priming dose of pembro/pbo 1 week before CRT followed by 2 doses of pembro/pbo during CRT and maintenance pembro/pbo for up to 14 doses. Prespecified secondary end points were mean change from baseline (BL) in EORTC QLQ-C30 global health status/quality of life (GHS/QoL) and physical functioning scores as well as EORTC QLQ-H&N35 pain, problems with swallowing, and speech scores. Prespecified exploratory end points included rate of improvement, stability, and deterioration, and mean change from BL in other prespecified scales of QLQ-C30, QLQ-H&N35, and EQ-5D VAS. Analysis population included pts who received ≥1 dose of treatment and completed ≥1 HRQoL assessment for a specific end point. Analysis was done at week 45 when respective completion and compliance rates of ≥60% and ≥80% were met per blinded data review. Treatment difference (least squares mean [LSM] change from BL) was estimated from a constrained longitudinal data analysis method.

Results: Completion and compliance rates were >95% at BL for all measures. Completion rates were >60% and compliance rates were >80% for all measures at week 45. LSM change from BL to week 45 for pembro vs pbo was 1.95 (95% CI, −0.10 to 4.00) vs 6.08 (95% CI, 4.02 to 8.13) for QLQ-C30 GHS/QoL (LSM difference: −4.13 [95% CI, −6.73 to −1.53]) and −5.54 (95% CI, −7.34 to −3.73) vs −3.46 (95% CI, −5.26 to −1.66) for QLQ-C30 physical functioning (LSM difference: −2.07 [95% CI: −4.51 to 0.36]). No meaningful differences in LSM change from BL to week 45 were observed between treatment arms for QLQ-H&N35 pain (1.44 [95% CI, −1.27 to 4.15]), problems with speech (−1.27 [95% CI, −4.60 to 2.07]), and swallowing (−0.31 [95% CI, −3.75 to 3.13]) scales or in EQ-5D VAS (−1.44 [95% CI, −3.74 to 0.85]). Similar percentages of pts for the pembro vs pbo arms had improved or stable scores for QLQ-C30 GHS/QoL (43.0% vs 47.6%) and QLQ-H&N35 pain (49.9% vs 50.3%), problems with speech (40.3% vs 41.4%), and swallowing (34.4% vs 34.3%) scales.

Conclusion: Patient-reported outcomes and disease symptom scores were generally similar between pembro and pbo arms, suggesting addition of pembro to CRT did not meaningfully impact HRQoL at week 45 in pts with LA HNSCC.

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Zanzalintinib Plus Pembrolizumab Versus Pembrolizumab Alone In Patients with PD-L1 Positive Metastatic Head And Neck Squamous Cell Carcinoma (STELLAR-305): A Double-Blind, Randomized, Placebo-Controlled, Phase 2/3 Study

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Purpose/Objective(s): Pembrolizumab as monotherapy or in combination with chemotherapy is a standard of care in patients (pts) with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) and PD-L1 CPS ≥1. While pembrolizumab monotherapy results in low response rates, the addition of 5FU/cisplatin adds significant toxicity for pts. Rational combinations which improve outcomes while avoiding cytotoxic chemotherapy are needed. HNSCC is associated with overexpression of VEGFR, MET, and AXL, and there are preclinical data supporting the antitumor effect of inhibition of these kinases through suppressing tumor growth and angiogenesis, and promoting an immune-permissive tumor microenvironment. In a phase 2 study, pembrolizumab plus the multikinase inhibitor cabozantinib demonstrated encouraging clinical activity and safety in pts with R/M HNSCC (Saba et al. *Nat Med* 2023), suggesting that targeting kinases including VEGFR, MET, and AXL has antitumor effect in this population and may enhance responses to immune checkpoint inhibitor (ICIs). Zanzalintinib (XL092) is a novel, multi-targeted kinase inhibitor that inhibits VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER). STELLAR-305 (NCT06082167) is a randomized, double-blind, phase 2/3 study that will evaluate the efficacy and safety of zanzalintinib plus pembrolizumab vs pembrolizumab plus placebo in pts with previously untreated, PD-L1-positive, R/M HNSCC.

Materials/Methods: Eligible pts are aged ≥18 years and have histologically or cytologically confirmed R/M HNSCC that is incurable with local therapy and has not been treated with systemic therapy, unless completed >6 months before randomization and given as part of multimodal treatment for locally advanced disease. Pts must have a primary tumor location of the oropharynx (HPV testing required), oral cavity, hypopharynx, or larynx; pts with nasopharynx, salivary gland, or occult primary sites are excluded. Other eligibility criteria include a PD-L1 CPS ≥1; measurable disease per RECIST v1.1; and an ECOG performance status of 0−1. Prior treatment with ICIs or zanzalintinib is not allowed. Patients will be randomized 1:1 to either zanzalintinib plus pembrolizumab or placebo plus pembrolizumab. The dual primary endpoints are PFS per RECIST v1.1 by blinded independent radiology committee and overall survival. Secondary endpoints include safety, PFS per RECIST v1.1 by investigator, objective response rate, and duration of response. If minimum efficacy requirements are met in phase 2, the study will proceed to phase 3. In total,

approximately 500 pts will be enrolled across phase 2 and 3. The study is ongoing with enrollment planned across sites in US, Europe, and the Asia-Pacific region.
Results: TBD
Conclusion: TBD

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Outcome of Cetuximab in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) Post-Immune Checkpoint Inhibitor (ICI) Treatment

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Purpose/Objective(s): Since the pivotal KN-048 study, pembrolizumab, with or without chemotherapy, has become the first-line therapy for R/M HNSCC. Cetuximab is often used in a second or later-line treatment after ICI. While novel EGFR-targeted agents and various cetuximab combination regimens are being tested in R/M HNSCC, there is no established efficacy benchmark for cetuximab in the post-ICI setting. This study examines the efficacy of cetuximab as a subsequent treatment.
Materials/Methods: We conducted a single-institution retrospective analysis of patients with R/M HNSCC who received cetuximab-based therapy after ICI, either with or without chemotherapy. Baseline demographic, clinicopathologic characteristics and treatment regimens were analyzed. The primary outcome measures were the duration of cetuximab therapy (DOT) and overall survival (OS) using multivariate Cox proportional hazard models.
Results: A total of 63 patients met the inclusion criteria. The median age was 77, 50 (79%) were male, and 27 (43%) had virus-mediated (25 HPV+ and 2 EBV+) SCC. The median interval from the last ICI therapy to cetuximab initiation was 5.7 weeks. Across all patients, median DOT was 7.9 weeks, and median OS was 6.2 months. DOT (12.1 vs. 5.1 weeks; HR 0.63, 95% CI 0.37-1.10) and OS (7.8 vs. 4.2 months; HR 0.49, 95% CI 0.28-0.84) were longer in patients with virus-negative HNSCC. Among all patients, 21% (N = 13) were treated with cetuximab for > 6 months. The proportion of patients on cetuximab for > 6 months was higher among patients with virus-negative (33%, N = 12) compared to patients with virus-positive HNSCC (3.7%, N = 1). In multivariate analyses, virus-negative disease was associated with increased DOT (HR 0.41, 95% CI 0.22-0.78), but the association with OS was not statistically significant (HR 0.63, 95% CI 0.31-1.25). Chemotherapy combinations, ICI-to-cetuximab interval, age at cetuximab start, sex, and smoking status were not associated with differences in DOT or OS.
Conclusion: Our analysis indicates that cetuximab is active in a minority of patients with R/M HNSCC previously treated with ICIs. Using DOT as a surrogate for progression-free survival, these data recapitulate trials evaluating cetuximab in heavily pre-treated patients in the pre-ICI era. These

findings reiterate the need for effective treatment in patients with R/M HNSCC who progress after ICI and suggest that cetuximab-based therapy may be a better option in virus-negative tumors.

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Weekly Paclitaxel, Carboplatin, and Cetuximab (PCC) as Treatment for Recurrent or Metastatic Head and Neck Squamous-cell Carcinoma (RM-HNSCC) that Progressed on Immune Checkpoint Inhibitors (ICI): A Retrospective Analysis

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Purpose/Objective(s): Data is lacking regarding the best treatment option for patients (pts) with RM-HNSCC after progression on ICI. Weekly PCC has reduced toxicity compared with triweekly PCC. We report the outcomes of pts treated with weekly PCC after progression on ICI.
Materials/Methods: We analyzed pts with RM-HNSCC who received weekly PCC (paclitaxel 45 mg/m^2, carboplatin area under the curve 1.5, cetuximab 400 mg/m^2 first week, and 250 mg/m^2 weekly thereafter) after progression on ICI between July 2016 and November 2022. We collected data on tumor site, P-16, combined positive score (CPS), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). PFS was defined as the time from PCC initiation and disease progression or death. OS was defined as the time from PCC initiation and death.
Results: Of the 44 pts available for analysis, 84% were male, and the median age was 60 yrs (IQR: 53, 68). The most common tumor site was oropharynx (48%), followed by oral cavity (27%) and others (25%). Nineteen pts (43%) were initially treated with ICI-chemotherapy and 25 (57%) with ICI alone. The median duration of treatment with ICI was 5.1 months (mo) (IQR: 2.7, 10.6). CPS values were available in 33 pts: 0% (8 pts), 1-20% (10 pts), and 21-100% (15 pts). The median follow-up time for PFS and OS was 4 mo (IQR: 2.8) and 8 mo (IQR: 3, 11), respectively. ORR were as follows: partial, 16 (36%); stable, 12 (27%); and progression, 16 (37%). Median survival time for PFS and OS was 3.8 mo (95% CI: 2.5,5.6) and 9.2 mo (95% CI: 7.8, 14.4), respectively. In overall survival analysis, after adjusting for age, sex, P-16 status, and lymphocyte count, increased duration of treatment on ICI was associated with better OS (HR: 0.96, 95% CI: 0.88, 1.05, p=0.4). A separate model including CPS showed that CPS values of 1-20% and 21-100% had reduced hazard compared to CPS of 0% (HR: 0.24, 95% CI: 0.05, 1.31; HR: 0.06, 95% CI: 0.01, 0.58; respectively, LRT p=0.006).
Conclusion: Weekly PCC is an active treatment for RM-HNSCC pts that progressed on ICI. There is an association between positive CPS, longer duration of treatment on ICI, and increased OS.

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Lenvatinib ± Pembrolizumab Versus Chemotherapy for Recurrent/Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC) That Progressed after Platinum and Immunotherapy: The Phase 2 LEAP-009 Study

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Purpose/Objective(s): Pembrolizumab monotherapy and pembrolizumab plus platinum-based chemotherapy are the standard of care for first-line treatment of R/M HNSCC. However, there is a growing unmet need for safe and efficacious treatment options for patients with R/M HNSCC whose disease progressed on or after platinum-based chemotherapy and immunotherapy. The randomized, open-label, phase 2 LEAP-009 (NCT04428151) study is being conducted to evaluate the safety and efficacy of lenvatinib plus pembrolizumab or lenvatinib monotherapy versus chemotherapy in patients with R/M HNSCC whose disease progressed after treatment with platinum-based therapy and a PD-1/L1 inhibitor.

Materials/Methods: Eligible patients have pathologically confirmed, locally incurable, histologically confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, and/or larynx, ECOG PS of 0/1, no ulceration and/or fungation of disease on skin, and disease progression on or after platinum-based therapy (with/without cetuximab) and PD-1/L1 inhibitor (progression must be <12 weeks from last dose, and patients must have received ≥2 doses). Patients will be randomly assigned 3:3:2 to receive oral lenvatinib 20 mg once daily plus pembrolizumab 200 mg IV every 3 weeks (≤35 pembrolizumab cycles), standard-of-care chemotherapy (investigator's choice of docetaxel, paclitaxel, cetuximab, or capecitabine), or oral lenvatinib monotherapy 24 mg once daily until centrally verified disease progression, unacceptable toxicity, or withdrawal. Patients with centrally confirmed disease progression in chemotherapy or lenvatinib monotherapy arms may transition to lenvatinib plus pembrolizumab at time of disease progression following consultation with the sponsor. Stratification factors are PD-L1 tumor proportion score (<50% vs ≥50%) and ECOG PS (0 vs 1). Imaging will be performed every 6 weeks through year 1 and every 9 weeks thereafter. Response will be assessed per RECIST v1.1 by blinded independent central review. Safety will be monitored throughout the study and for 30 days following treatment end (90 days for serious adverse events) and graded per NCI CTCAE v5.0. The primary end point is objective response rate; and secondary end points are progression-free survival, duration of response, overall survival, and safety.

Results: Approximately 400 patients will be enrolled, and recruitment is ongoing in Asia, Australia, Europe, and North America.

Conclusion: Results of LEAP-009 will offer insights into the efficacy and safety of lenvatinib with/without pembrolizumab versus chemotherapy for patients with R/M HNSCC whose disease progressed after platinum and immunotherapy.

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Olaparib, a poly (ADP-ribose) polymerase (PARP) Inhibitor, in Combination with Pembrolizumab and Carboplatin as First-Line Treatment of Recurrent or Metastatic Head and Neck Squamous-Cell Carcinoma (RM-HNSCC): A Single-Arm, Phase 2 Trial

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Purpose/Objective(s): The homologous recombination deficiency (HRD) phenotype is common in HNSCC and is due to mutation and promoter hypermethylation of DNA repair genes and *PTEN*. In pre-clinical models of HNSCC, HRD sensitizes tumors to PARP inhibition and to additive antitumor activity of PARP inhibition in combination with platinum agents. PARP inhibitors also activate the STING pathway and upregulate PD-L1 expression, resulting in synergistic antitumor activity when given with PD-1 inhibitors. Olaparib is a highly selective PARP inhibitor that has been safely combined with pembrolizumab and carboplatin. The primary hypothesis of this single-arm phase 2 trial of patients with RM-HNSCC was that first-line treatment with olaparib, pembrolizumab, and carboplatin would result in a higher objective response rate (ORR) than historically reported with 5-fluorouracil (5-fluorouracil), pembrolizumab and a platinum agent.

Materials/Methods: Patients with untreated RM-HNSCC who had adequate performance status and organ function received up to six 21-day cycles of olaparib (200 mg bid orally days 1-10), pembrolizumab (200 mg IV day 1), and carboplatin (AUC 5 IV day 1). This was followed by up to twenty-nine 21-day cycles of olaparib (300 mg bid orally days 1-21) and

pembrolizumab (200 mg day 1), or until discontinuation criteria were met. The primary endpoint was objective response, assessed by an independent radiologist using iRECIST. A Simon optimal two-stage design tested the null hypothesis (H_0:ORR≤36%) versus the alternative hypothesis (H_1: ORR=62%) at a type I error rate of 10% and 90% power. In the first stage, up to 13 patients would be accrued. If ≥6 responses occurred, 16 additional patients would be accrued. H_0 would be rejected if ≥14 responses were observed in these 29 patients. An interim analysis was performed after the first stage, to assess olaparib delivery during cycles 1 and 2 with the goal of 100% delivery in ≥ 80% of patients.

Results: Twenty-nine patients were enrolled, to date. Key characteristics included median age 65 years (range 38-83), tobacco history 54%, primary site (oropharynx 50%; oral cavity 36%; larynx 14%), HPV status (positive 46%; negative 54%) and PD-L1 CPS status (0: 4%; 1-19: 29%; ≥20: 64%; unknown: 3%). Twenty-eight patients were evaluable for response. Tumor response occurred in 14 patients, of which 13 were confirmed on subsequent imaging. Best tumor response included CR in 3 patients, PR in 11, SD in 10, and PD in 4. The ORR was 50.0% (95%CI 30.7-69.4%). Olaparib delivery during cycles 1 and 2 was 100% for all patients in the first-stage of the trial. No unexpected safety concerns occurred.

Conclusion: The primary hypothesis of the trial was met. Further studies of this combination are warranted.

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High Tumor Mutational Burden May Predict Improved Response to Immunotherapy in Head and Neck Cancer Patients

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Purpose/Objective(s): Tumor mutational burden (TMB) is an emerging biomarker utilized in some cancers as a predictive tool to determine benefit to immune checkpoint inhibitor therapy and high TMB alone is an indication for pembrolizumab monotherapy, tumor agnostic. For head and neck squamous cell carcinoma (HNSCC), there is limited data utilizing TMB as a biomarker to predict response to PD-L1 inhibitors. This study assesses TMB score and progression of disease in HNSCC patients treated with immunotherapy.

Materials/Methods: From an IRB-approved database, we retrospectively analyzed 51 patients treated between 2016 and 2023 with HNSCC who had at least one dose of pembrolizumab and known next generation sequencing (NGS). Patients were stratified between high TMB (≥10 mutations/Mb) and low (<10 mutations/Mb).

Results: Of the 51 patients, 40 (78%) had progression of disease while on pembrolizumab. The median TMB of those who progressed was 6.9 mutations/Mb. The median time to disease progression was 5.8 months.

There were 37 patients who were classified as low TMB with a median 5.0 mutations/Mb. Of these 37, 29 (78%) had progression while on pembrolizumab with a median time to progression of 3.5 months. For the 14 patients with high TMB scores, the median was 12.0 mutations/Mb. Of these 14, 11 (79%) had progression while on pembrolizumab with a median time to progression of 5.8 months. There was no statistical difference in time to progression between high and low TMB cohorts (p=0.3483).

Of the 11 (22%) without progression, all patients started pembrolizumab in the setting of recurrent HNSCC (7 metastatic, 4 locoregionally recurrent). The majority in this cohort are classified as having low TMB (n=8/11) with a median TMB of 5.0 mutations/Mb. Of the 10 patients who actively remain on pembrolizumab, they have been on pembrolizumab for a median of 14.7 months.

A multivariable analysis revealed that TMB as a continuous variable (i.e., increase in TMB mutations), the risk of progression decreased (p=0.0238, HR 0.940).

Conclusion: Although there was no statistical difference in time to progression between our high TMB and low TMB cohorts, a higher TMB score correlated with decreased risk of progression in our cohort of HNSCC patients. Further research is needed to better understand the utility of TMB as a biomarker in HNSCC.

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Randomized Phase 2 Trial of Stereotactic Body Radiation Therapy (SBRT) and Concurrent and Adjuvant Cetuximab vs Cetuximab and Docetaxel in Recurrent, Previously Irradiated Squamous Cell Carcinoma of the Head and Neck

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Purpose/Objective(s): The treatment of recurrent head and neck cancer presents a significant challenge in previously irradiated patients. Therapeutic options in this patient population tend to be limited and are often associated with severe toxicity and decreased efficacy compared with front line therapies. Stereotactic body radiation therapy (SBRT) is a salvage technique that provides highly conformal, ablative doses to tumor while minimizing exposure of the surrounding organs at risk. The precise role of concurrent systemic therapy with SBRT, though, remains unclear and is a topic of active investigation.

Materials/Methods: We conducted a randomized, phase 2 trial exploring the addition of docetaxel to concurrent and adjuvant cetuximab with head and neck SBRT in patients with recurrent or second primary head and neck cancers. Inclusion criteria included patients ages ≥18, ECOG 0-1 with squamous cell carcinoma of the head and neck arising within an area previously receiving a dose of at least 50 Gy. Patients were randomized to receive 44-50 Gy/5 fraction SBRT with concurrent and adjuvant cetuximab (control arm) vs the same regimen with the addition of concurrent and adjuvant docetaxel (experimental arm) and were stratified by prior cetuximab exposure. The primary objective was evaluation of 1-year locoregional progression-free survival (LRPFS) with secondary endpoints consisting of progression free survival (PFS), overall survival (OS) and toxicity assessment. The study was designed as a superiority trial to detect a 20% improvement in LRPFS in the experimental arm. Using a power of 85% at a significance level of 0.10, the estimated sample size was 92 patients randomized in a 1:1 manner.

Results: The trial was halted due to slow accrual after a total of 38 patients (19 in each arm) had been randomized. No difference was observed in 1-year LRPFS between the control and experimental arms (36% vs 37%, p=0.63). There were similar rates of 1-year PFS in both arms (36% vs 32%, p=0.92) with a non-significant difference in 1-year OS (46% vs 20%,

p=0.20) favoring the control arm. There was no difference in the rates of grade 3+ toxicity which was 84% in both arms (p=0.99) although there were twice as many grade 5 events in the docetaxel arm (n=4 vs 2).

Conclusion: Although underpowered, we did not observe an improvement in LRPFS, PFS or OS with the addition of docetaxel to concurrent and adjuvant cetuximab and SBRT for recurrent head and neck squamous cell carcinomas in previously irradiated patients. The relatively poor disease control and high degree of toxicity observed in both arms presents an ongoing challenge in the management of this patient population.

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A Pilot Clinical Trial of Sodium Thiosulfate (STS) for Prevention of Ototoxicity in Patients with Locally Advanced Squamous Cell Carcinoma of Head and Neck (SCCHN) Undergoing Concurrent Chemoradiation with Cisplatin

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Purpose/Objective(s): Ototoxicity is a well described side effect of cisplatin and up to 88% of SCCHN patients undergoing chemoradiation develop some degree of hearing loss. Clinical trials in pediatric cancer patients receiving high cumulative doses of cisplatin have demonstrated that use of STS infusion 4-8 hours after cisplatin administration led to a significantly lower likelihood of hearing loss. We therefore conducted a prospective pilot clinical trial to assess the feasibility and safety of intravenous STS after cisplatin in locally advanced SCCHN patients undergoing concurrent chemoradiation with cisplatin.

Materials/Methods: This was a pilot study to evaluate feasibility and safety of STS infusion in SCCHN patients, measured by successful completion of at least 200mg/m^2 cumulative dose of cisplatin without extended delay of more than 7 days. Assessment of ototoxicity was performed with pure tone audiometry by audiologic evaluation at baseline and at 3 months post-treatment. Intravenous STS of 20g/m^2 (for cisplatin 80-100mg/m^2) or 10g/m^2 (for cisplatin 40mg/m^2) was infused 4 hours after completion of cisplatin infusion through a central line over 1-2 hours.

Results: A total of 16 patients were enrolled. All were male (median age: 56 years) with HPV-positive oropharynx squamous cell carcinoma. Three (19%) received weekly cisplatin at 40mg/m2 and 13 (81%) received high dose cisplatin at 100mg/m2. Fifteen patients (94%) completed more than 200mg/m2 of cisplatin and 14 patients (88%) achieved complete metabolic response assessed by 3-month post-chemoradiation FDG PET/CT. No disease progression was detected at a median follow-up of 10.7 months. Ten (63%) patients completed all planned STS infusions, 4 (25%) attempted all planned infusions but had to stop infusion, and 2 (12%) refused to get the planned second dose due to grade 3 nausea. Four patients (25%) developed grade 3 infusion reaction with hypotension and 3 (19%) developed grade 3 nausea with STS infusion. Grade 2 or higher hearing impairment occurred in 3 (19%) patients all of whom received high dose cisplatin; however, 2 of them did not complete planned STS infusion for infusion related adverse events.

Conclusion: In this prospective pilot study, STS infusion after cisplatin did not interfere with delivery of target dose of cisplatin of 200mg/m^2. The rate of grade ≥2 hearing impairment at 3 months after chemoradiation seems to be favorable at 19%, but severe nausea and infusion reactions precluded completing planned STS infusion in 37% of patients. Further investigation with supportive management strategies to make STS infusion more tolerable would be desirable. Funding: This work was supported by pilot funds received from NRG Oncology (NCORP grant UG1CA189867).

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Safety of Planned Dental Extractions Immediately after Radiation Therapy: First Report of a Prospective Observational Study

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Purpose/Objective(s): Non-restorable teeth are recommended to be extracted prior to radiation therapy (RT). Occasionally, patients are unable or unwilling to complete the extractions, and RT delay can compromise survival. Some have proposed a safe "window" for extractions immediately post-RT which could improve time-to-treatment, but data is non-existent. We evaluated the feasibility and safety of dental extractions post-RT (D.E. Po.R.T.).

Materials/Methods: After IRB-approval we performed a single-arm, single-institution prospective observational study. Patients were eligible if dental evaluation prior to curative-intent RT recommended ≥1 extraction, and the patient was unable or unwilling to proceed for any reason. Patients were recommended DEPoRT within 4 months of RT.

The primary endpoint was the cumulative incidence of exposed alveolar bone. If exposed bone was noted by a non-dental provider (surgeon, radiation, or medical oncologist), dental referral was made for confirmation. Secondary objectives were to quantify the feasibility of DEPoRT, and to correlate outcomes with dosimetry and extraction timing. As a pilot study, no formal power calculation was performed; resources allowed for 50 evaluable patients. The actuarial cumulative incidence of exposed bone

(and confirmed osteoradionecrosis) was calculated using Gray's method with death as a competing risk. No hypothesis testing was pre-specified.

Results: From December 2019 to September 2022, 58 were screened and 50 enrolled. Cancers were 96% oral or laryngopharyngeal and 96% squamous cell. Treatment was non-operative for 32 and postoperative for 18. IMRT was delivered in all, and 86% were treated bilaterally. The median of the mean oral cavity dose was 39.8 Gy (range 10.1-64.8). 36 received chemotherapy.

Of the 50 patients, 20 declined DEPoRT and the remaining 30 underwent a median of 8.5 extractions (range 1-28) at a median of 64.5 days post-RT (range 13-152).

Five deaths occurred, 1 underwent DEPoRT and 4 did not. The median follow-up from the end of RT for survivors without exposed bone was 25 months (IQR 17-34).

The 2-year cumulative incidence of any exposed bone was 24% (95% CI 12-36%). The 2-year incidence of exposed bone for those who underwent DEPoRT was 40% (95% CI 22-58%) vs. 0% (95% CI NA) for those without DEPoRT. Of the 12 who developed exposed bone: 4 resolved, 1 was lost to follow-up and 7 were confirmed as osteoradionecrosis (ORN). Of the 7 with confirmed osteoradionecrosis, 2 died of cancer, 2 have been treated conservatively, 1 underwent surgery, 1 hyperbaric oxygen (HBO), and 1 both surgery and HBO.

Conclusion: Post-radiation dental extractions incur significant risk, even if performed within 4-months. Further follow-up is required to determine if any benefits exist as compared to observation without extraction.

Abstract 165 − Table 1

	2-yr Exposed Bone (95% CI)	2-yr ORN (95% CI)	Median F/U (Months, IQR)
All pts (N=50)	24% (12-36%)	15% (5-25%)	25 (17-34)
DEPoRT (N=30)	40% (22-58%)	26% (9-42%)	25 (23-35)
No DEPoRT (N=20)	0% (N/A)	0% (N/A)	23 (15-30)

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Subgroup Analysis of the Benefit of Avasopasem Manganese on the Incidence, Severity, Duration and Onset of Severe Oral Mucositis in ROMAN Phase 3 Trial

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Purpose/Objective(s): IMRT plus cisplatin is established treatment for LAHNC, but ∼70% of patients develop severe oral mucositis (SOM; WHO grade 3 or 4), limiting their ability to eat solids (gr 3) or liquids (gr 4), and often requiring feeding tube nutrition. Radiotherapy (RT)-induced bursts of superoxide initiate SOM (Sonis 2004). Avasopasem (AVA) is an investigational small molecule selective dismutase mimetic converting superoxide to hydrogen peroxide, which may protect normal cells from, and potentially sensitize cancer cells to, RT (Anderson 2019, Sishc 2021). Randomized, blinded, placebo (PBO)-controlled phase 3 was conducted and showed AVA significantly reduced SOM incidence and duration in ITT population, as well as reducing cisplatin kidney damage. The present analysis looks at reductions in SOM incidence, duration & severity, and delay in onset in key LAHNC subsets.

Materials/Methods: Patients with oral cavity (OC) or oropharynx (OP) LAHNC receiving 60-72 Gy of IMRT (≥50 Gy to ≥2 OM sites) plus cisplatin (weekly or q3 weeks) randomized 3:2 to IV AVA 90 mg vs PBO before each RT fraction. WHO scale OM was assessed by trained evaluators biweekly during RT & weekly for 2 weeks thereafter. Endpoints: SOM & gr 4 OM incidences through IMRT end; SOM duration through 2 weeks post-IMRT; time to SOM onset. Key subpopulations: Definitive vs Post-op; OC vs OP; HPV- vs HPV+; QW vs Q3W cisplatin.

Results: 80.8% (329/407) of patients were treated on study with definitive chemoradiation therapy between October 2018 and August 2021. In this group, SOM incidence was 51.2% in AVA arm vs. 66.5% in PBO arm (RR 0.77, p-value 0.0071), while gr 4 OM incidence was 23.0% for AVA vs. 35.2% for PBO (RR 0.65, p-value 0.0102, and median SOM duration was reduced by 12 days (8 days AVA vs. 20.5 days PBO; least square means 13.5 days AVA vs. 19.5 days PBO, p-value 0.0012). Median time of SOM onset was delayed by 14 days (Day 51 AVA vs. Day 37 PBO). Patients treated with postoperative chemoradiation therapy (19.2%) had no improvement in SOM incidence, severity, duration, or time to onset with AVA. Improvements in SOM incidence, severity, duration and onset with AVA did not vary significantly based on cisplatin schedule, HPV status or primary tumor type and were similar to ITT.

Conclusion: In this phase 3 randomized placebo-controlled trial, AVA markedly reduced SOM incidence, severity and duration, and delayed its onset, in patients treated definitively, but not postoperatively. Cisplatin schedule, HPV status and primary tumor type did not influence AVA benefit. Future trials of novel mucosal radioprotectant agents should consider that postoperative patients may experience SOM differently than definitive chemoradiation patients.

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A Pilot Study of HNC Patients Treated Daily with an Intraoral Photobiomodulation (PBM) Device While Undergoing IMRT Demonstrates Tolerability, Safety, and Preliminary Efficacy for Reducing the Impact of Oral Mucositis

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Purpose/Objective(s): Oral mucositis (OM) is a significant AE and can impact cancer treatment (interruptions and/or early termination), increase opioid usage, impact diet (dysgeusia, dysphagia, inadequate nutritional intake), instigate depression and cause sepsis and death. Pharmacological options are limited; however supportive care treatment guidelines (MASCC, WALT) recommend intraoral photobiomodulation therapy (IOPBMT) for the prevention/treatment of OM. Photobiomodulation (PBM) is the use of non-ionizing light in the visible and near-infrared light spectra to modulate biological processes, such as promoting wound healing. Current IOPBMT protocols for OM prevention involve laser-based treatments using spots that are technique sensitive and time consuming. The (Sponsor) Phototherapy System uses an LED-based intraoral mouthpiece to deliver a dosage of 6 J/cm^2 to the entire oral cavity, soft palate, uvula, retromolar trigone, and portions of the oropharynx in a daily 10-minute treatment. Per sponsor protocol, this medical device is used daily in the RT clinic without proximate physician supervision.

Materials/Methods: A pre-pivotal pilot study was performed at 7 centers (5 academic) to assess feasibility. HNC participants receiving CRT with IMRT (a minimum of 30Gy to >1 oral region) received a 10-min IOPBMT prior to daily RT. Pain medications and mouthwashes were permitted. IOPBMT was delivered at the radiation clinic throughout the entire duration of IMRT. Device safety (daily) and OM (weekly) evaluations were completed, and participant status was reviewed for primary and secondary outcomes at week six. OM was graded according to the Oral Mucositis Index (OMI), NCI, and RTOG scales.

Results: 40 patients were enrolled, 3 withdrew consent and 3 did not complete 80% of IOPBMT. 1227 of 1271 study treatments were completed in full and no device-related adverse events were reported. At week 6:

- Participants averaged 8.65/60 on the OMI
- NCI/RTOG grades ranged from 0-3
  - Grade distribution was 0 (1/1), 1 (5/5), 2 (9/8), 3 (19/20) respectively
- 52% of salivary flow was retained
- On average, participants reported they could swallow solids for 24.3/30 days of RT
  - 13/34 retained the ability to swallow solids throughout

Conclusion: IOPBMT has been recommended to prevent/treat OM; however, current options are technique sensitive and time consuming for physicians. The (Sponsor) Phototherapy System shows encouraging results in a pilot cohort, is well tolerated for daily treatments in a clinic setting and is safe without apparent device-related adverse events. This device presents a promising alternative for IOPBMT delivery and is currently being evaluated for safety and efficacy in a double-blind randomized clinical trial (NCT03972527).

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Developing Machine Learning Algorithms Incorporating Patient Reported Outcomes to Predict Disease Progression in Head and Neck Cancers

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Purpose/Objective(s): Patient reported outcome (PRO) is gaining traction for implementation into clinical practice within electronic medical record systems. Recent randomized controlled trials support standardized PRO-base monitoring in enhancing health-related quality of life, reducing emergency department use and improving overall survival. Here, we examined whether a validated head and neck cancer (HNC) specific PRO or general PRO can better predict disease progression using machine learning algorithms.

Materials/Methods: This was a retrospective analysis of a prospective observational study through the Comprehensive Translational Research Study of Head and Neck Tumors at our institution where baseline clinical, demographic and PROMs were collected between 2007 and 2018. Patients with a primary HNC, who had at least one MD Anderson Symptom Inventory (MDASI) or Edmonton Symptom Assessment Score (ESAS) questionnaire collected 3 months after curative intents treatment were included. Models were fit to predict disease progression three months following a post-treatment MDASI or ESAS questionnaire. Eight models were generated using supervised machine learning: least absolute shrinkage and selection operator (LASSO) logistic regression and random forest models. Predictive performances were assessed via area under the receiver-operating curve, computed with 10-fold cross-validation. Four of the models were based on first post-treatment PRO, while the others on change over time in PRO scores. Relative variable importance was computed with average decrease in out-of-bag prediction accuracy of each tree.

Results: We included 1302 HNC patients, of whom 527 (40%) were HPV-positive, and 556 (43%) were from oropharynx. Disease progression occurred in 123 (9.5%) of HNC patients. With baseline post-treatment MDASI, our best random forest model demonstrated an area under the curve (AUC) approximating 0.675. The top three variables were pain, speech and dry mouth. When comparing change in MDASI scores over time, random forest models again performed the best, with an AUC of 0.676. The top three variables were pain, choking and fatigue. Models incorporating MDASI were more predictive for disease progression than ESAS.

Conclusion: Machine-learning approaches on head and neck cancer specific patient reported outcomes can identify patients at high risk for disease progression with high sensitivity. Future work will involve evaluating whether implementing predictive models using MDASI with targeted clinical interventions can improve clinical outcomes.

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Ideal Reconstruction of Parotidectomy Defects with Parascapular Flaps: A Volumetric Analysis

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Purpose/Objective(s): Parotidectomy defects after oncologic surgery lead to significant soft tissue volume loss, resulting in unfavorable cosmetic outcomes and impaired quality of life. Free tissue transfer has become increasingly utilized for restoration of facial contours, although the optimal donor site requires a careful evaluation of patient preference and tissue volume. The purpose of this study was to compare free flap volumes to determine the optimal donor site for parotid defects.

Materials/Methods: A retrospective review was performed of patients who underwent PET-CT for a new cancer diagnosis and whole-body non-contrast enhanced CT imaging from January 2020 − December 2021. Patient demographics including age, sex, and BMI were recorded. Parotid tissue volume and the volume of parascapular, latissimus, rectus, anterolateral thigh, lateral arm, and radial forearm free flap donor sites were measured at standardized cross-sectional levels. An ideal donor site was defined as a match within $5mm^3$ of the reconstructed parotid defect volume.

Results: In review of 276 patients, 197 patients had at least one donor site that achieved an ideal volume match. This was most commonly the parascapular flap (58%), followed by the rectus (26.8%), latissimus (23.9%), ALT, (12.0%), and lateral arm (2.9%). When stratifying by age, sex, and BMI, the parascapular flap remained the best volume match across all groups. Rectus free flaps performed better in lower BMI patients, and female patients had an improved volume match with ALT flaps.

Conclusion: Ideal reconstruction of parotid tissue defects requires adequate volume to restore contour to the face in a cosmetically sensitive area. Our study presents the first objective measure of parotid defect volumes and supports the parascapular flap as an ideal choice across age, sex, and BMI.

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Non-HPV In-Field Second Primary Squamous Cell Cancers in the HPV De-Escalation Quarterback Trials

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Purpose/Objective(s): Clinical trials evaluating treatments for HPV oropharynx cancer select patients by p16 status rather than molecular identification of HPV and HPV genotype. It is unclear whether recurrences in these trials are tested for HPV either by p16 status or molecular HPV testing. Applying molecular diagnostics for HPV at diagnosis and relapse can avoid significant miss-assignment and inaccurate results. We reviewed and report results from the Quarterback Trials (QT) where we used molecular testing to assign HPV status to all patients at diagnosis and relapse.

Materials/Methods: Patients entered on the QT were required to have ≤ 20 py smoking history, not be active smokers, have nonmetastatic locally advanced disease, and have a molecularly identified HPV status including genotype (ISH or ISH and Sanger Sequencing). Subjects were treated with TPF chemotherapy for 3 cycles and patients with an adequate response were eligible for de-escalation of chemoradiotherapy (CRT) to 5600 cGy (RD). The first 20 patients were randomized to standard dose (SD) 7000 cGy (8) or RD (12). Patients were monitored for recurrent disease by routine surveillance with physical examination and PET scan. Recurrences were documented by FNA or core biopsy. We performed a retrospective analysis of 2nd in-field primaries (SP) and compared them to local regional recurrences (LRF).

Results: Ultimately, 64 patients were consented on to the QT. 4 patients failed screening and are not considered any further. 14 patients received 7000 cGy: 8/14 were randomized to SD, 5/14 had an inadequate response to TPF and 1/14 patient withdrew consent. One patient randomized to SD withdrew consent and stopped CRT at 5200 cGy. 45 patients received RD per protocol and a total of 46 patients received RD CRT. There were 7 HPV+ LRF: (1SD and 6 RD); and 4 molecularly documented in-field non-HPV SP squamous cell cancers: 2/14 SD (14%) and 2/46 RD (4%). 1 of 4 SP tumors was p16+; all were molecularly negative for HPV and had p53 mutations. Median time to LRF was 9 mo. (4-49) and 66 mo (35-84) for SP. Median survival after LRF is 18 (4-72+) and after SP 11+ (3-36+). 2/7 LRF occurred in p16+, non-16 genotypes. 1/4 SP was originally a non-16 genotype. 4/11 (36%) of post treatment local regional squamous cancer events were not HPV related.

Conclusion: Non-HPV SP SCC were not rare events in this documented HPV+ population. SP were more common in the SD then the RD treated patients suggesting an RT dose dependency and causality in this minimal smoking population although other biologic explanations are possible. We urge that entry into HPV de-escalation trials should be limited to patients with molecularly determined HPV status. Genotype determination would be desirable. We assert p16 is an inaccurate surrogate for determining HPV status at diagnosis and recurrence in HPV critical clinical trials and all In-field cancer events should be molecularly assessed to determine if they are LRF or SP.

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Aspiration Rates and Clinician-graded Dysphagia after Transoral Surgery (TOS): An Interim Analysis of Modified Barium Swallow (MBS) Studies (videofluoroscopy) from the PATHOS trial

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Purpose/Objective(s): PATHOS is an ongoing Phase II/III randomized trial examining risk-stratified de-escalated adjuvant therapy after transoral surgery (TOS) for human papillomavirus associated oropharyngeal cancer. While the goal of TOS is functional preservation, acute postsurgical dysphagia is expected with post-TOS aspiration prevalence (prior to adjuvant treatment) recently reported in 13% of patients from the E3311 trial. Our objective was to assess clinician-graded swallowing function per modified barium swallow (MBS, videofluoroscopy) in the PATHOS trial before and after TOS, prior to randomization for adjuvant therapy.

Materials/Methods: This is an interim analysis of the PATHOS trial. Standardized MBS were conducted and blind (to timepoint) graded using the Penetration-Aspiration Scale (PAS) and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST). Aspiration rates (per maximum PAS ≥6), any grade dysphagia (per DIGEST grade >0) and high-grade dysphagia (per DIGEST grade >1) were compared baseline to 4 weeks post-TOS in all patients using McNemar's test.

Results: 60 patients were included who underwent TOS between November 2015 and April 2021 in 15 UK centers and had both pre- and post-TOS MBS graded at the time of analysis. There was no aspiration at baseline; aspiration increased to 6/60 (10%) MBS after TOS (p = 0.014). Swallowing impairment was more prevalent using the DIGEST grade that accounts for both penetration/aspiration as well as residue as a marker of swallowing efficiency. Per DIGEST, any grade baseline dysphagia (DIGEST grade >0) was prevalent in 16/60 (27%) of baseline MBS increasing to 37/60 (62%) after TOS (p < 0.001), and high grade dysphagia (DIGEST grade >1) was prevalent in 1/60 (2%) of MBS at baseline increasing to 10/60 (17%) after TOS (p =0.007).

Conclusion: Aspiration rates were low overall, significantly increasing to 10% of MBS after TOS (before adjuvant therapy) in similar magnitude to rates observed in E3311. Preliminary results suggest that DIGEST grading may be more sensitive to detect changes on MBS that reflect potentially important functional changes beyond aspiration. By this measure, image-graded dysphagia was prevalent in more than half of patients prior to adjuvant therapy supporting an opportunity for post-surgical rehabilitation to optimize function in the interval prior to adjuvant therapy.

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The Impact of De-Escalated Radiotherapy on Carotid Stenosis Rates in Head and Neck Cancer Patients

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Purpose/Objective(s): Radiotherapy (RT) to the head and neck (H&N) often includes incidental dose to the carotid arteries, contributing to long-term development of carotid stenosis. While standard definitive and adjuvant (chemo)radiotherapy generally ranges from 60-70 Gy in 30-35 fractions, recent de-escalated approaches delivering total 30-36 Gy in 20-24 fractions have been developed. This project aims to evaluate whether de-escalated radiotherapy contributes to reduced carotid toxicity.

Materials/Methods: All patients with a head and neck cancer diagnosis who received radiotherapy from 2013 to present, who additionally received a carotid ultrasound at some point in their care, were identified. Ultrasound reads were used to determine date of development of carotid stenosis. Excluded patients were those with pre-radiotherapy carotid stenosis, multiple courses of head and neck radiotherapy, patients receiving a non-invasive stereotactic radiosurgery instrument to skull base lesions, and patients with multi-modality courses. Patients were censored at the earliest post-RT occurrence of carotid stenosis, or latest carotid ultrasound if stenosis did not occur.

Results: 304 patients met the above criteria. 83 (27%) experienced post-RT stenosis. No difference in stenosis occurrence was seen between proton and photon radiotherapy modalities (p=0.973). 30 and 36 Gy regimens included 28 and 38 patients, respectively; 50 to 66 Gy included 156 patients, and definitive regimens included 79 patients. The 30 and 36 dose levels demonstrated reduced risk of carotid stenosis (p < 0.001); 3-year and 5-year stenosis rates were 96.4% and 84.4% for 30 Gy, 97.2% and 87.4% for 36 Gy, 88.1% and 62.9% for 50-66 Gy, and 76.9% and 53.6% for definitive regiments, respectively.

Conclusion: De-escalated radiotherapy reduced the occurrence of carotid stenosis across a diverse H&N population on this retrospective review. Work to identify radiographic risk factors to enhance prognostication at time of treatment is underway.

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Characterizing Voice Changes and Primary Aberrant Features in Survivors of Locally Advanced Head and Neck Cancer Treated with Radiation Therapy

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Purpose/Objective(s): Voice changes are common in head and neck cancer (HNC) survivors who undergo radiation therapy (RT). Most studies have assessed changes with validated patient reported outcomes measures (PROMS). There is a need to combine PROMS with patient voice recordings. The purpose of this study was to characterize voice changes using a standardized protocol and describe primary aberrant features using expert listeners.

Materials/Methods: This study enrolled long-term survivors (>2 years) of locally advanced (T3+ or N+) HNC who received ≥60 Gy at a single academic center. Patients completed a standardized protocol of several vocal tasks. Recordings included a single reading of the first 4 sentences of the Rainbow Passage and sustained /a/ and /i/ edited to the first 3 seconds of each phoneme. Nine blinded speech language pathologists with voice specialization rated dysphonia using the CAPE-V visual analog scale. Scores ranged 1-100 with higher scores indicating greater dysphonia. Mean scores across the 9 listeners were calculated and severity of dysphonia was classified for this study as normal [0-12], mild [12-20], mild-moderate [20-30], moderate [30-45], moderate-severe [45-60], severe [60-85], and severe-profound [85-100]. A 10% repeat assessment was used for intra-rater reliability. Cronbach's alpha was calculated to assess inter-rater consistency. Primary aberrant features were roughness, breathiness, tremor, spasm, strain, and asthenia. Changes in voice resonance were indicated with a binary yes/no.

Results: Two hundred one patients were enrolled with 198 recordings available for analysis. Median time from completion of RT was 5.6 years (range 1.7-28.9 years). Most common primary disease sites were oropharynx (51%), larynx (12%), and oral cavity (11%). Seventy-two percent of patients were male. Surgery and systemic therapy were included in 58% and 63% of treatment courses, respectively. Mean CAPE-V score for all patients was 31.9 (IQR 19.9 − 38.1). Dysphonia was classified as normal in 6.6%, mild in 18.7%, mild-moderate in 28.8%, moderate in 27.2%, moderate-severe in 11.1%, severe in 7.1%, and severe-profound in 0.5% of patients. In the validation cohort, the median percent difference in CAPE-V scores between initial and repeat assessments was 5.5% (IQR 2.0-12.5%). Cronbach's alpha was 0.95. In 64.6% of patients, at least 50% of listeners reported voice roughness as the primary aberrant feature, while breathiness, tremor, spasm, strain, and asthenia were reported in 2%, 0.5%, 0%, 7.6%, and 1.5%, respectively. Resonance changes were noted in 20.7% of patients by over half of listeners.

Conclusion: Dysphonia was present in many long term HNC survivors following RT with 45% having at least moderate dysphonia. Voice roughness was the most common primary aberrant feature with many bearing changes in resonance. Further understanding of clinical factors predictive of vocal changes and treatment factors mediating changes is needed to develop strategies to mitigate this late toxicity.

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Pilot Randomized Clinical Trial of Geriatric Comanagement or Geriatric Guided Supportive Care for Older Patients with Head and Neck CancerReceiving Radiation and Chemotherapy

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Purpose/Objective(s): The standard of care for locally advanced head and neck cancer (HNC) includes radiation with concurrent chemotherapy due to superior disease control. Older adults with HNC experience higher rates of morbidity, treatment breaks, hospitalizations, and death. New strategies are needed to better support older adults with HNC through radiation and chemotherapy to minimize treatment morbidity. Geriatric assessment (GA) can be used to identify patient-specific deficits and facilitate interventions to improve patient outcomes. In this randomized pilot clinical trial (NCT05239000), we hypothesize that use of geriatric assessment with or without comanagement can reduce the risk of hospitalization for older adults with HNC.

Materials/Methods: Patients aged 65 and older with newly diagnosed or post-operative mucosal HNC with squamous cell histology are eligible for enrollment. All patients are planned for 6-7 weeks of radiation with concurrent chemotherapy. Enrolled patients complete an electronic GA before treatment, shortly following treatment, and 3-4 months after treatment. Patients are randomized between two groups: Arm 1 involves a geriatric consultation for management of geriatric-specific deficits; Arm 2 involves management of geriatric deficits by the radiation oncology team without geriatric consultation. All patients are seen twice weekly in radiation oncology clinic to enhance supportive care. Forty patients will be randomized equally between the two arms. The primary endpoint is the proportion of patients with unplanned hospitalization during the course of radiation therapy. The historic rate of hospitalization at Memorial Sloan Kettering Cancer Center is 44.6% for this cohort, and the study will be considered promising if there are 7 or fewer hospitalizations in either group. A secondary objective is to measure changes in GA before and after radiation and chemotherapy. The long term goal of this research is to identify new strategies that improve the care and outcomes of older adults with HNC receiving radiation and chemotherapy.

Results: TBD

Conclusion: TBD

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Prevalence and Impact of Frailty and Geriatric Assessment Identified Impairments among Older adults diagnosed with head and neck cancers

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Purpose/Objective(s): Nearly half of patients diagnosed with head and neck cancers are 65 years or older at the time of diagnosis. Older adults with cancer are at increased risk of treatment related toxicities and recent studies have suggested that geriatric assessment can be used to predict those at risk of excess toxicities. The objective of the current study was to study the prevalence of frailty and geriatric assessment impairments among older adults diagnosed with head and neck cancers.

Materials/Methods: Using data from the Cancer and Aging Resilience Evaluation (CARE) registry, a prospective cohort study of older adults (≥60y) diagnosed with cancer, we identified patients with biopsy proven head and neck cancers with an initial medical oncology visit at our institution between 3/2018 and 5/2021. All patients underwent a pragmatic multidimensional GA prior to their initial oncologist visit, as previously described (Williams et al J Geriatr Oncol 2019). Using deficit accumulation method, we constructed a 44-item frailty index (CARE-FI), categorizing patients as robust, pre-frail, and frail. Domain specific impairments were characterized using published cut points. Subsequently, we examined the prevalence of frailty and GA domain impairments and the association between pre-treatment frailty and overall survival in multivariable time to event (Cox) models adjusted for age, sex, race/ethnicity, cancer stage and time from diagnosis. All statistical tests were two sided and the level of significance was chosen as 0.05.

Results: A total of 94 patients were identified with a mean age of 70 ± 7y, 79% males and 87% non-Hispanic Whites. Majority of patients had stage III (20%) or IV cancers (52%; 27% with distant metastasis) treated with radiation therapy (76%), chemotherapy (64%) and/or surgery (46%). Overall, 23% and 30% respectively were identified as pre-frail or frail respectively. GA impairments were prevalent: 19% reported ≥1 falls in past 6 months, 17% reported dependence in activities of daily living (ADL), 53% reported dependence in Instrumental ADL, 43% had malnutrition, 72% reported polypharmacy (≥4 medications) and 40% had ≥3 comorbidities. As compared to robust patients, frailty was associated with significantly increased risk of all-cause mortality in unadjusted (HR 2.74; 95% CI 1.19-6.35; p=0.02) and adjusted (HR 2.37; 1.03-6.08; p=0.04) models.

Conclusion: Frailty and GA impairments are common among older adults with head and neck cancers and appear to have prognostic relevance. Future studies should explore how GA can inform treatment decision making and guide interventions to improve treatment outcomes in this population.

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Assessing Feasibility and Acceptability of a Computerized Food Frequency Questionnaire (FFQ) Intervention to Determine Dietary Patterns in Head and Neck Cancer (HNC) Survivors

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Purpose/Objective(s): There is no systematic approach to diet assessment in HNC survivors. We piloted a novel computerized FFQ (VioScreen) that provides nutrition-specific feedback on diet quality with suggested dietary improvements in HNC survivors to assess feasibility and acceptability of the FFQ, explore associations between diet quality, QOL, and patient/treatment characteristics, and assess longitudinal changes in diet quality.

Materials/Methods: HNC patients at least 6-month post curative-intent treatment (radiation (RT), chemoradiation (CRT), surgery/RT, or surgery/

CRT) were eligible. Patients were excluded due to feeding tube or recurrent/metastatic disease. The study included two intervention cohorts: 1) a cross sectional study of 50 patients completing the FFQ intervention, and 2) a longitudinal cohort of 10 patients completing the FFQ and meeting with a Registered Dietitian to review results at baseline and 3 months. Dietary assessment was conducted using the FFQ, dietary quality was defined by Healthy Eating Index (HEI), and QOL by EORTC QLQ-C30 and H&N35. All participants received an automated feedback report after completing the FFQ. An acceptability questionnaire was given 3-8 weeks post FFQ for cohort 1 and post 2nd dietician visit for cohort 2.

Results: 50 patients consented to cohort 1 and 34 (68%) completed all initial surveys. Mean HEI score was 63.2 (SD 11.3). 26/34 completed acceptability; of those, 16 (61%) agreed/strongly agreed the FFQ was useful, 9 (38%) agreed/strongly agreed they made diet changes, and 18 (69%) agreed/strongly agreed they would recommend to others. Patients with worse swallowing on H&N35 were less likely to find the FFQ useful (P = 0.046). 10 patients enrolled on cohort 2; 9 completed all baseline surveys and dietitian visits and 8 completed 3-month follow-up surveys and visits. Baseline mean HEI score was 61.74 (SD 15.7) and increased to a mean of 64.5 (SD 13.9) at 3 months. Of the 9 participants, 6 had improved HEI scores with the intervention (range 3.6-20). Of the 8 who completed acceptability, the majority agreed/strongly agreed that the FFQ was useful (7; 87.5%), made diet changes (4; 50%), and would recommend the FFQ (8; 100%). 7 (87.5%) agreed/strongly agreed meeting with the dietitian was helpful to interpret the FFQ feedback. There were no significant differences between cohort responses.

Conclusion: For HNC survivors, the FFQ intervention was acceptable to patients with or without meeting with a dietitian. Patients that met with a dietitian were numerically more likely to endorse dietary changes and recommend the FFQ, and all believed the dietitian helped to interpret the recommendations. Given the pilot results, a study in a larger cohort of HNC survivors is warranted to determine the impact of the FFQ intervention with dietitian consultation on longitudinal outcomes.

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Prospective Study of Plasma Biomarker-Guided Surveillance of HPV-positive Oropharynx Cancer Using TTMV-HPV DNA: The SPHERE Study

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Purpose/Objective(s): Previous observational studies suggest that circulating tumor HPV DNA may facilitate early detection of recurrent HPV-positive oropharynx cancer (OPC). This is the first prospective cohort study to investigate whether biomarker-guided surveillance detects recurrent disease sooner than standard of care.

Materials/Methods: We enrolled adult patients evaluated for HPV-positive OPC at a single center 11/2020-4/2023 and treated with curative intent.

Pretreatment plasma and/or tumor tissue were tested for tumor tissue-modified viral (TTMV) HPV DNA from subtypes 16/18/31/33/35 using a commercial assay. Patients were excluded if they had undetectable TTMV DNA in both pretreatment plasma and tumor tissue. Post-treatment plasma TTMV DNA (cTTMV) was assessed every 3 months. Positive or indeterminate tests were repeated in 4 weeks. Two serial positive/indeterminate results prompted imaging. Negative imaging was repeated every 8 weeks while cTTMV was positive, up to 6 months. The primary outcome was the proportion of recurrences first detected by cTTMV testing. NCT04965792

Results: The study cohort comprised 150 OPC patients, 80% male with median age 64 years (IQR 58-69). cTTMV was positive pretreatment in 125 (86%), indeterminate in 3 (2%), and negative in 18 (12%); 4 patients enrolled after treatment with unknown pretreatment status. Median follow-up was 18 months (range 5-34 months). Patients had a median of 6 post-treatment tests (range 1-12). Fourteen patients (9%) developed recurrent or persistent disease. Among these, 6 patients (43%, 95%CI 17-69%) had positive surveillance cTTMV as the first sign of disease that prompted the imaging that ultimately detected recurrence. Time from first positive cTTMV test to diagnosis of recurrence was median 132 days or 4 months (range, 47-280 days). Another 4 patients (29%, 95%CI 5-52%) had positive cTTMV corroborate persistent disease detected on standard 3 months post-treatment surveillance imaging. The final 4 patients (29%, 95%CI 5-52%) with recurrence did not have positive surveillance cTTMV (1 had a single transient elevation to indeterminate). Pre-treatment cTTMV was positive for 2 of these, negative for 1, and unknown for 1. Among the 136 patients who remained clinically disease-free, cTTMV was positive or indeterminate for 6 (4%). Two have had low levels of cTTMV for >6 months with no evidence of disease on serial imaging and exams. Four others had temporary 'spikes': 3 had a single indeterminate test; 1 had low level positive tests for 4 months that returned to negative.

Conclusion: Nearly one-half (43%) of patients with recurrence had positive cTTMV results that prompted a search for disease. The remaining patients with recurrence either had positive cTTMV results that confirmed suspicious findings on standard imaging (29%), or had negative cTTMV results despite clinical disease (29%). Biomarker-guided surveillance for HPV-positive OPC likely benefits a subset of patients, and further study of its impact on outcomes is warranted.

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Observations on Carotid Artery Stenosis Following Neck Irradiation

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Purpose/Objective(s): Carotid artery stenosis (CAS) is a known potential late effect of neck radiation. There are varying estimates of its incidence and mixed consensus on whether screening for this late effect standard practice should be. As treatment techniques have evolved and the presence of HPV has increased, the impact on the future trajectory of this problem is unclear.

Materials/Methods: A sample of head and neck cancer (HNC) patients treated from 1997 through 2022 who underwent carotid ultrasound (US) at any time after receiving radiation therapy to the neck were identified from an IRB-approved, single institution database. Patient treatment characteristics including radiation laterality, co-morbidities at consult, and smoking history were coded in addition to carotid US dates and results. CAS was defined as >40% stenosis of either side of the vessel, which prompted a vascular surgery consult.

Results: A total of 308 patients were included in this study with an average follow up of 70 months (range: 3.3-255.9 months). All included patients received bilateral neck radiation and had no evidence of disease at their last follow up. Most patients received definitive, concurrent chemoradiation (96.4%), were male (85.1%) and had a primary oropharyngeal tumor (64%). The most common co-morbidity at time of consult was hypertension (HTN, 45.8%). Median time to CAS was 10.7 years. The five- and ten-year rates of CAS were 15.4% and 39.6%, respectively. On Cox regression univariate analysis age at consult (HR=1.054, 95% CI= 0.649-1.941, p<0.001), having known HTN (HR=2.551, 95% CI=1.610-4.032, p<0.0001), hyperlipidemia (HR=1.658, 95% CI= 1.066-2.584, p=0.0248), diabetes (HR=2.398, 95% CI=1.397-4.115, p=0.0015), or cardiac disease (HR=2.283, 95% CI=1.333-3.922, p=0.0026) at time of consult, and being an ever smoker (HR=2.336, 95% CI=1.403-3.891, p=0.0011) were statistically predictive of CAS. On multivariate analysis, patients who were older (HR=1.037, 95% CI=1.008-1.068, p=0.0122), were an ever smoker (HR=2.375, 95% CI=1.425-3.968, p=0.0009), and having known hypertension (HR=2.037, 95% CI=1.235-3.356, 0.0053) at consult were at highest risk for CAS.

Conclusion: CAS was frequently detected five and ten years after head and neck radiation. Carotid artery US screening should be strongly considered in these patients, especially older patients with a history of smoking and/or HTN. Future prospective studies are warranted to verify this finding.

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Health Care Utilization and Opioid Use in Patients Receiving an Integrated Palliative Care Intervention for Treatment of Head and Neck Cancer Compared to a Historical Control

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Purpose/Objective(s): Patients receiving chemoradiation therapy (CRT) for head and neck cancer (HNC) can develop significant symptomology (odynophagia, malnutrition) resulting in frequent hospitalizations and decreased quality of life (QOL) and continue to have chronic symptoms such as dysphagia and/or pain. The integration of a palliative care (PC) team during CRT has the potential to address the high symptom burden and improve QOL.

Materials/Methods: We performed a prospective single arm study of 20 patients with HNC who received an integrated PC intervention during curative-intent CRT that consisted of visits with a PC team focused on symptomology alongside oncology visits. To compare to a control cohort, we performed a retrospective review of patients who received curative-intent CRT for HNC from 1/2008 to 1/2019 at our institution. Data included: demographics, comorbidities, human papilloma virus status, inpatient admissions, feeding tube and opioid usage. Groups were compared by Fisher's exact test.

Results: 20 patients received CRT with an integrated PC intervention; the mean age was 59.5, 12 had p16+ oropharynx cancer (60%), and 16 received definitive CRT (80%). 332 patients were included in the control cohort; mean age was 61.4, 146 (44%) had p16+ oropharynx, and 262 (82%) received definitive CRT. In the integrated PC pilot cohort, at the start of treatment, 12 patients (60%) were on opioids for pain and only 1 patient (6%) remained on opioids 6 months after CRT ended, compared to the control group where 108 (38%) (p=0.53) were on opioids at treatment start and 91 (29%) six months after CRT (p=0.05). In the integrated PC pilot compared to control, 7 patients had a feeding tube (35%) vs 144 (44%) (p=0.50) and 5 were admitted to the hospital (25%) vs 150 (45%) (p=0.10). Patients who received the integrated PC intervention required proportionally fewer feeding tubes, had fewer hospitalizations during treatment and required fewer long-term opioids to control pain when compared to a historical control, but only decreased long-term opioid use was statistically significant (p=0.048).

Conclusion: While the cohort who received integrated PC is small, the integration of PC in treatment shows potential to reduce health care utilization and long term opioid use; further evaluation of this integrated PC intervention during CRT is warranted in a large, randomized study.

Abstract 179 — Table 1

	Retrospective cohort (N= 332)	Prospective cohort who received integrated PC (N=20)	p-value
Age - Mean (SD)	61.4 (7.30)	59.5 (9.85)	0.30
P16 status - oropharynx			
Positive	146 (79.3%)	12 (60%)	0.01
Negative	26 (14.1%)	8 (40%)	
Unknown	12 (6.5%)	0	
Inpatient admission within 3 months of CRT			
Yes	150 (45.1%)	5 (25%)	0.10
No	182 (54.8%)	15 (75%)	
Feeding Tube during CRT			
Yes	144 (43.3%)	7 (35%)	0.50
No	188 (56.6%)	13 (65%)	
Opiate Use 6 months post CRT			
Yes	97 (29.2%)	1 (6.25%)	0.048
No	235 (70.7%)	15 (93.75)	

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Oral Cavity Obliteration is a Novel Predictor of Functional Outcomes after Glossectomy Reconstruction

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Purpose/Objective(s): The primary goal for reconstruction of oral tongue defects is to improve speech and swallowing. We hypothesize that degree of oral cavity obliteration will correlate to a specific functional outcome. The purpose of this study is to present a new reconstructive metric that uses volume displacement to measure oral cavity obliteration and correlate this metric to outcomes of speech and swallowing.

Materials/Methods: 33 patients (23m:10f, 51.mean age) underwent resection and template based free-tissue reconstruction of oral tongue defects based on the principle of maintaining oral cavity obliteration. All patients were followed for greater than 12 months postoperatively. Oral cavity obliteration was measured by using a novel oral volume assessment test (OVAT). Briefly, by placing a latex balloon filled with dyed pudding on the patient's tongue and then patients performed mouth closure to expel the pudding. The residual volume represented dead space in the oral cavity and was measured by water displacement. These results were correlated with the Speech and Swallowing Assessment and Assessment of Intelligibility of Dysarthric Speech (A.I.D.S.) instruments.

Results: The mean residual volume on OVAT was 7.4 cc (range 3 − 20cc; sd 4.5cc). The mean AIDS efficiency ratio was 0.6055 (range 0.31 - 0.92; sd 0.16) and mean AIDS % sentence intelligibility was 96% (range 64.1 − 100; sd 8.0). There was a correlation with lower residual volumes (better obliteration) with increasing AIDS efficiency ratio (R = 0.72, p < 0.001). A receiver operator curve was used to identify 10 cc of residual volume as the curve where the inflection defines better versus worse outcomes. Using this cut point, binary logistic regression showed that residual volume significantly predicts normal nutritional mode (p<0.001), ability to tolerate all liquids (=0.007), range of solids (p=0.004), eating in public (p=0.007), understandability (p<0.001), and speaking in public (p=0.01).

Conclusion: Oral volume assessment test (OVAT) is a novel measure of residual volume (obliteration) that correlates with improved speech efficiency, intelligibility, speaking in public and swallowing outcomes.

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Patient-Reported and Dosimetric Determinants of Trismus after Chemoradiation for Nasopharyngeal Carcinoma: A Prospective Study

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Purpose/Objective(s): Trismus is a common side effect following radiation therapy for head and neck cancer and may be most severe for patients with nasopharyngeal carcinoma. To date, prospective efforts investigating patient reported outcomes combined with dosimetric predictors are lacking.

Materials/Methods: We conducted a prospective, phase II clinical trial of adult patients with biopsy proven, stage IIB-IVB nasopharyngeal cancer treated with concurrent proton-based chemoradiotherapy (cisplatin 100 mg/m2 q3week), followed by adjuvant cisplatin and 5-fluorouracil. Trismus was assessed in a multifactorial fashion. Objective trismus was defined as a decrease in maximal inter-incisal distance (MID) of >20%, relative to baseline. Patient-reported trismus was assessed using trismus domain of the EORTC QLQ H&N35 questionnaire. The relationship between radiation dose to the muscles of mastication / temporomandibular joint (TMJ) and the development of trismus was evaluated using Cox regression.

Results: Between 2006-2011, 24 patients were enrolled. Median age was 48 years old. Median follow-up was 3.0 years. 63% of patients had stage III/IV disease. The mean doses to the lateral pterygoids, medial pterygoids, suprahyoids, infrahyoids, masseters, temporalis, and TMJs was 54, 51, 16, 46, 14, 12, and 32 Gy RBE, respectively. Eleven patients developed objective trismus. The median decrease in MID at 24 months was 6mm (range 1-19mm, IQR 5-11mm). Nine patients developed patient-reported trismus. Association of presence vs absence of patient-reported trismus and decline in 2y MID was seen (median 10mm vs 5mm, p=.03). Dose (per Gy increase) to the lateral pterygoids was associated with patient-reported trismus (HR 1.16, 95% CI 1.01-1.33, p=.04) and magnitude of decline in 2y MID (β=0.48mm, 95% CI 0.01-0.96mm, p=.045) but not objective trismus (HR 1.07, 95% CI 0.96-1.19, p=.25). Dose (per Gy increase) to TMJs was associated with patient-reported trismus (HR 1.14, 95% CI 1.02-1.26, p=.02), objective trismus (HR 1.12, 95% CI 1.01-1.25, p=.04) magnitude of decline in 2y MID (β =0.53mm, 95% CI 0.12-0.95mm, p=.01). Patients with patient-reported trismus had higher mean dose to TMJ (36 vs 30 Gy, p=0.01) and lateral pterygoids (57 vs 52 Gy, p=0.03) than those who did not.

Conclusion: In this prospective study incorporating a homogeneous patient population and treatment regimen, the development of patient-reported trismus after chemoradiation with proton beam was associated with increase in mean dose to the lateral pterygoids and TMJ and decline in 2y MID. Delineation and avoidance of these structures seems prudent.

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Testing and Validation of a Custom Trained Large Language Model for HN Patients with Guardrails

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Purpose/Objective(s): The goal is to custom-train an advanced large language model (LLM) chatbot utilizing data approved by qualified medical professionals (Physicians and Nurses), for a patient-focused platform for head and neck (HN) cancer patient survivorship and overall well-being.

Materials/Methods: Seventy unique sets of questions and answers on oropharyngeal cancer patient survivors were collected from institutional records (2021-2022). Additionally, frequently asked questions related to the 40 most common Grade 1+ head and neck (H&N) toxicities observed within our practice were collected. All questions were redacted to protect patient privacy and were then re-entered within the framework of OpenAI's Turbo 4.0 platform. The model was trained on those collected questions and other peer-reviewed literature relevant to the studied diagnosis, with an effort to establish guardrails and refine the model's responses. The questions chosen for training covered various subjects, including pre-operative preparations, post-radiation symptoms, medications, COVID vaccinations, relevant side effects, and pain management. The temperature (a hyperparameter of any LLM) was set to 0.2 in order to reduce the randomness of its responses and leaving the output more focused and deterministic. The model was tested using an independent set of questions, including those outside the training scope. Model accuracy and relevance,

as well as failure rates, were assessed by three experienced HN Radiation Oncologists.

Results: An interactive chatbot using LLM was developed, complemented with an intuitive frontend interface. The mean response time was less than 2 seconds. The chatbot accurately addressed 10 specific questions related to radiation-induced toxicities. The scores of each response remained acceptable for the testing questions, showcasing an overarching comprehension of the posed questions with varied phrasing. However, for questions outside its training scope, fine optimization was needed to reduce instances of model misinterpretation.

Conclusion: This customized chatbot constitutes a substantial advancement in addressing the pertinent challenge of accessing contemporaneous and medically relevant information within the purview of head and neck (HN) cancer survivorship. The chatbot displays a broad understanding, effectively addressing varied phrasings of the same query. The preliminary validation of this model shows significant potential in offering health assistance to HN patients and professional staff. The model still required fine optimization in order to enforce stricter guardrails as for the mix of questions that remained outside the scope of training documents.

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Early Treatment With Mesenchymal Stromal Cells Prevents Development of Long-term Radiation Induced Salivary Dysfunction

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Purpose/Objective(s): There is a critical need for a treatment that will safely and effectively prevent the development of radiation-induced xerostomia (RIX) or salivary dysfunction. We preformed preclinical studies to test the ability of IFN-γ stimulated marrow-derived mesenchymal stromal cells (MSC(M)) to prevent the development of long-term salivary dysfunction in a mouse model.

Materials/Methods: MSC(M) were established from C57Bl/6 mice, expanded in culture, had identity confirmed by flow cytometry, were stimulated with IFN-γ, and cryopreserved. Thawed MSC(M) were injected into the submandibular glands of mice 24 h after delivery of a 15 Gy dose of radiation. Saliva was assessed at baseline, 1 week, and 3 months after radiation. Tissues were harvested and analyzed by histology for acinar density (H&E), fibrosis (Masson's Trichrome), and the presence of salivary gland stem cells (MIST1).

Results: MSC(M) were isolated from mice. MSC identity was confirmed via flow cytometry for CD105, CD73 and CD90. Radiation resulted in a significant decrease in salivary production as measured both 1 week (50%) and 3 months (20%) following radiation. Injection of MSCs maintained salivary production at 1 week (100%) and 3 months (45%) following radiation. Histologic analysis demonstrated improved salivary structure including retained acini, decreased fibrosis, and increased salivary stem cells.

Conclusion: Injection of MSC(M) immediately following radiation can prevent the development of radiation induced salivary dysfunction in mice. These data support the development of translational studies focused on moving this cellular therapy approach into clinical testing using autologous MSC(M).

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Incidence of Flap Failure Following Sinonasal Surgery, Flap Reconstruction and Postoperative Proton Radiation Therapy

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Purpose/Objective(s): Following sinonasal surgery, orofacial reconstruction often requires the use of tissue flaps (1). Currently, there is a paucity of data addressing the incidence of flap complications following postoperative radiation using proton therapy.

Materials/Methods: From our patient database at the ProCure Proton Therapy Center (New Jersey) and the New York Proton Center (New York), we identified patients treated between 2013 and 2023 who had sinonasal surgery with flap reconstruction and postoperative proton therapy. Eligible surgical techniques included anterior craniofacial resection or maxillectomy with or without palatectomy. Flap reconstruction techniques included free flaps, rotational flaps, and obturators. We aimed to quantify the rate of flap failure in this patient population.

Results: From 2013-2023, we identified 17 patients who were treated with the combination of sinonasal surgery with flap reconstruction and postoperative proton therapy. Tumor histologies included adenoid cystic carcinoma (23.5%), squamous cell carcinoma (17.6%), adenocarcinoma (17.6%), sarcoma (17.6%), esthesioneuroblastoma (5.9%), melanoma (5.9%), and sarcomatoid carcinoma (5.9%). Fibular (29.4%), Radial forearm (23.5%), and anterolateral thigh (17.6%) free flaps were most commonly used for reconstruction. Postoperative proton therapy doses ranged from 34 CGE to 76 CGE, with a median of 66 CGE. 3 patients (17.6%) were treated with intensity-modulated radiation therapy (IMRT) followed by proton therapy boost. Overall, 4 patients (23.5%) experienced flap complications, including 3 patients with complete soft tissue flap failure, and 1 patient with partial bone flap loss. All 4 patients had reconstruction with free flaps from various donor sites. One patient received a total of 66 CGE. Two patients received 60-66 CGE to the entire postoperative bed with areas suspicious for potential residual gross disease boosted to 70 CGE. The last patient received 50 Gy IMRT followed by 20 CGE small field boost to a region of potential gross disease.

Conclusion: Patients who had sinonasal surgery, flap reconstruction, and postoperative proton radiation therapy may be at risk for flap failure.

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A Randomized, Double-blinded Pivotal Study of the Safety and Efficacy of a Novel Intraoral Photobiomodulation Device in Head and Neck Cancer Patients Undergoing Radiation Therapy With or Without Vhemotherapy

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Purpose/Objective(s): Oral mucositis (OM) is a significant adverse event (AE) that affects over 90% of head and neck cancer (HNC) patients undergoing radiation (RT) with chemotherapy (CT). OM is characterized by

ulceration, erythema, and edema of the oral tissues and can result in interruptions in and/or early termination of cancer treatment, increased opioid usage, and decreased alimentation and quality of life. Pharmacological interventions for OM are limited; however supportive care treatment guidelines (MASCC, WALT) recommend photobiomodulation (PBM) therapy for the prevention/treatment of OM. PBM is the use of non-ionizing light in the visible and near-infrared light spectra to modulate biological processes, such as promoting wound healing. However, current recommended PBM protocols are technique sensitive and time consuming. We present an ongoing randomized, controlled clinical trial to evaluate whether an intraoral PBM device can improve HNC patient outcomes without proximate physician supervision in a daily 10-minute therapy.

Materials/Methods: The (Sponsor) Phototherapy System uses two LED-based, intraoral mouthpieces that can repeatedly deliver a dosage of 6 J/cm^2 to the entire oral cavity and part of the oropharynx in 10-minutes prior to daily IMRT. To be eligible, patients must have oral and/or oropharyngeal squamous cell carcinoma and receive IMRT +/- CT with ≥ 2 oral sites receiving >50 Gy. The primary effectiveness endpoint is OM severity according to the Oral Mucositis Index (OMI); a quantitative assessment of OM at 9 oral mucosa locations. Additional endpoints include OM scales (WHO, NCI), functional changes in body weight and salivary flow, and patient-reported outcomes on quality of life, pain, opioid usage, taste changes and swallowing ability using validated scales (OMWQ-HN and UW-QoL). Requirements for nutritional support (PEG, IV Hydration) and cancer treatment interruptions are recorded. Assessments are completed daily and weekly, and endpoints are assessed after 6 weeks of treatment (50-66 Gy). Device-safety and tolerability of treatment is captured daily. A two-week post-RT assessment is completed. A minimum of 82 patients are planned to be enrolled in this study. The total sample size results in a minimum statistical power of 91.3% to detect significance when using Welch's 2-sample t-test ($\alpha = 0.05$). A fixed-sequence fallback procedure will be utilized to assess secondary endpoints at an overall significance level of $\alpha = 0.05$.

Results: A double-blind randomized study (NCT03972527) is being conducted at 12 centers (8 academic). Results are pending.

Conclusion: Safety and efficacy of an LED-based intraoral PBM device intended to reduce OM severity is currently being assessed. Endpoints selected reflect objective, functional, and patient-reported outcomes related to the signs and symptoms of OM.

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Characteristics and Management of Post Treatment Pharyngeal Ulceration in Oropharyngeal Squamous Cell Carcinoma Patients Treated with Definitive Radiation/Chemoradiation

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Purpose/Objective(s): Treatment of oropharyngeal cancer with definitive radiation/chemoradiation (RT/CRT) is an effective treatment and rapid regression of tumor can occur. Following treatment some patients will develop a pharyngeal ulcer which may or may not be associated with disease persistence. Data for the management of ulcers could improve post radiation care.

Materials/Methods: From an IRB approved database of head and neck cancer cases at a tertiary care center, we reviewed patients with non-metastatic squamous cell carcinoma of the oropharynx treated curatively in non-operative fashion with RT/CRT between 1/1/2011 and 1/1/2022. Patients were reviewed for clinical, radiographic and laryngoscopic evidence of pharyngeal ulcer development following completion of radiation. Pharyngeal ulcer patients were evaluated for management strategy of the ulcer and associated complications and association with recurrence.

Results: A total of 45 patients with a pharyngeal ulceration following RT/CRT with a median follow up of 30.8 months were identified. The median age of patients was 60 (range 35-82) years, 80% of patients were caucasian, 82% were male, and 42% of patients were active smokers at the time of RT/CRT. 75% of patients had p16/HPV+ disease with T stages of T1/2, T3 and T4 of 44, 20 and 36% respectively. 93% of patients were treated with concurrent chemotherapy (74% cisplatin) to a median dose of 70 Gy (range 60-74 Gy). The median time to development of ulcer was 3.1 months (range 0.2-31.4 months). 19 patients (42%) underwent biopsy of their ulcer of whom 9 (47%) where found to have disease persistence. Ultimately thirteen patients (29%) had associated tumor persistence. Among the 32 patients with ulcer not associated with recurrence, 28 (87.5%) were p16/HPV+ and 90.6% has received chemotherapy. 3 ulcers (9.4%) were associated with exposed bone. Treatment of ulcers revealed 15 (46%) received antibiotics, 23 (72%) needed narcotics and 5 (16%) required feeding tube placement for pharyngeal rest. Three patients (9.4%) required surgical reconstruction to facilitate resolution. Overall, at time of last follow up 28 (88%) of ulcers not associated cancer had resolved with a median time to resolution of 3.6 months (range 1.3-75.2) months. The overall survival of the non-malignant ulcer group was 83% at 3 years compared to 28% in the patients with ulcers associated with persistent cancer.

Conclusion: Pharyngeal ulceration is a significant potential complication of RT/CRT in oropharyngeal cancer. Ulceration is frequently identified around 3 months post treatment and when not associated with disease persistence has a high rate of resolution with conservative measures including antibiotics and pain control. Severe case may necessitate feeding tube and rarely surgical reconstruction.

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Opioid and Adjunctive Medication Prescriptions in Curative-Intent Radiation Therapy for Head and Neck Cancer (HNC)

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Purpose/Objective(s): Managing pain during curative-intent radiation therapy for head and neck cancer (HNC) is crucial, yet little is known about opioid prescription trends and long-term use in these patients. For this patient population we sought to quantify opioid and adjunctive pain

medications, as well as characterize HNC radiotherapy patients. Identifying individuals with higher opioid needs can inform targeted interventions to reduce overall opioid usage.

Materials/Methods: In this retrospective observational study, we explored electronic medical record (EMR) data encompassing 10,755 HNC and 15,664 breast cancer (BC) patients, for comparative purposes, diagnosed between 2008 and 2022 at our institution. Our analysis focused on 894 HNC and 1100 BC patients who underwent 4-6 weeks of definitive or adjuvant radiation therapy. Utilizing multivariate logistic regression and adjusting for patient demographics, including age, gender, race, ethnicity, insurance type, and substance use history, we estimated the odds ratios pertaining to prescriptions for opioids and adjunctive medication, like gabapentin.

Results: Among HNC patients, 774 out of 894 were prescribed opioids. Opioid prescriptions were most common in the 30 days before and during radiation, decreasing by over 80% within six months of radiation initiation. Fentanyl and oxycodone were the most frequently prescribed opioids, while morphine and hydromorphone were less common. Gabapentin was concurrently prescribed to over 80% of HNC patients receiving opioids. In comparison to BC radiation patients, HNC patients had significantly higher odds of receiving opioid and adjunctive medication prescriptions (p < 0.01). Patient characteristics of HNC radiation patients described that 69% were male, 66% were white, and the median age was 65.9 years. Nearly half had a history of smoking, and 2% reported heavy drinking. Age, race, ethnicity, and prior smoking history did not significantly influence prescription patterns, but males had lower odds of being prescribed opioids (p < 0.01).

Conclusion: Patients undergoing curative-intent radiation for HNC frequently receive opioid prescriptions. These opioid prescriptions peak during the period preceding and encompassing radiation therapy, and subsequently diminish by more than 80% within six months of radiation initiation. A noteworthy 6% of HNC patients require continued opioid prescriptions beyond this six-month threshold. Moreover, HNC patients receive opioids and adjunctive medications at a notably higher frequency compared to their BC counterparts undergoing similar radiation therapy. These findings underscore the significance of optimizing opioid prescription practices within the context of curative-intent radiation therapy for HNC, ensuring judicious and tailored pain management while mitigating the protracted use of opioids.

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Mitigating Oral Mucositis in Proton Therapy with Advanced Dose-, LET- and Organ Volume-based Constraints

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Purpose/Objective(s): Oral mucositis is one of the most frequent and impairing acute adverse effects of radiotherapy for head and neck malignancies, occurring in almost 100% of patients. Although proton therapy provides a superior sparing of the oral cavity compared to photon therapy, up to 70% of patients still experience oral mucositis. Currently, the only countermeasure for mitigating this sequela is to set dose limits in the oral cavity, whose values have been derived from photon therapy data using the Relative Biological Effectiveness (RBE) as a scaling factor. In this work, we provide a comprehensive analysis of oral mucositis in H&N patients. Our objectives are to identify dose and radiation quality constraints on the oral cavity and build a Normal Tissue Complication Probability (NTCP) model of oral mucositis specific for proton therapy.

Materials/Methods: Our study involved 62 patients treated with Intensity-Modulated Proton Therapy (IMPT), and 124 treated with Volumetric Modulated Arc Therapy (VMAT) at one institution. Toxicity grades were scored according to the Common Terminology Criteria for Adverse Events (CTCAE) scale v5.0. To compare the dosimetric differences between IMPT

and VMAT plans, we calculate the equivalent uniform dose received by the oral cavity per fraction and cumulatively up to the fraction where oral mucositis was observed. Using the Monte Carlo software TOPAS MC, we calculated the radiation quality inside the oral cavity using the Linear Energy Transfer (LET) for all IMPT patients.

Results: Salivary gland tumor patients showed significant benefits with IMPT, as none developed severe (grade >1) mucositis, compared to 34% of VMAT patients. Oropharyngeal tumors are the worst scenario, with 74% severe cases for IMPT versus 90% for VMAT. Severe mucositis induced by IMPT occurred at lower doses than VMAT, both per treatment fraction (1.0 vs. 1.5 Gy/fx, p<0.05) and cumulatively (22 vs. 30 Gy, p<0.05). Our findings for IMPT confirm that absorbed dose plays a central role in developing mucositis, with the more severe cases occurring at higher doses. Data also suggest a relation between grade, LET, and organ volume irradiated. Mild mucositis occurred with 10% of the organ volume receiving 1 Gy/fx and LET of 4 keV/micron, whereas the same dose and LET led to severe mucositis when 30% of the oral cavity received it. At a cumulative dose of 25 Gy, severe cases exhibited higher radiation quality than mild cases, independently of the oral cavity volume considered.

Conclusion: Clinical RBE underestimates the biological effectiveness of protons to induce oral mucositis. This outcome is a consequence of the complex interplay between dose, radiation quality, and organ volume effects. Our NTCP model incorporating dose-, LET- and organ volume-based constraints can be used for advanced treatment plan optimization to mitigate toxicity.

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Twelve Month Follow Up on MARSH: A Pilot, First in Human Study of Autologous IFN-gamma Stimulated Mesenchymal Stromal Cells for Treatment of Radiation-induced Xerostomia

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Purpose/Objective(s): There are no existing effective treatments for radiation-induced xerostomia (RIX), a common side effect of head and neck radiation. Mesenchymal stromal cells (MSCs) exhibit regenerative effects in multiple tissues and may represent an effective cell therapy for the treatment of RIX. Here we present the updated primary safety and secondary efficacy endpoints of a first-in-human pilot study of IFNγ-stimulated autologous bone marrow- derived MSCs [MSC(M)] for the treatment of RIX.

Materials/Methods: We conducted a single-center clinical trial investigating the safety and tolerability of autologous IFNγ-stimulated MSC(M). The study was conducted under an FDA-IND and approved by the local IRB. Patients underwent bone marrow aspiration, MSC(M) were then cultured, stimulated with IFNγ, and cryopreserved. Banked IFNγ-stimulated MSC (M) were thawed, allowed to recover, and then 10×10^6 MSC(M) were injected into one submandibular gland. The primary objective was safety and tolerability determined by dose-limiting toxicity (DLT) defined as submandibular pain > 5 on a standard 10-point pain scale or any serious adverse event (SAE) within one month after injection. Secondary objectives included analysis of efficacy as measured by salivary quantification, salivary protein quantification, and saliva extensional viscosity and using 3 validated quality of life instruments. Quantitative results are reported as mean and standard deviation (SD).

Results: Six radiation-induced xerostomia patients who had completed radiation at least 2 years earlier were enrolled. The median age was 71 (61-74), 5 (83%) patients were male and all patients had a KPS of 100. Five patients (83%) were treated with chemoradiation and one patient (17%) with radiation alone. The average dose of radiation to the injected submandibular gland was 59.9 Gy (range 37.7 Gy − 68.2 Gy). Three patients (50%) reported a pain score of 1 after submandibular gland injection, all pain resolved within 4 days. No SAEs or other DLTs were reported up to 12 months after injection. The analysis of secondary endpoints demonstrated a trend of increased salivary production. Quality of life surveys also showed a trend towards improvement. Updated salivary quantification data through 12 months of follow up will be presented.

Conclusion: Injection of autologous IFNγ-stimulated MSC(M) into the submandibular gland of patients with RIX is safe and well tolerated. A trend towards an improvement in secondary endpoints of salivary quantity and quality of life was observed with 12 months of follow up. This first-in-human pilot study provides support for further investigation into IFNγ-stimulated MSC(M) as an innovative, potentially curative, remedy to treat RIX and restore quality of life. A phase I dose-escalation study injecting into bilateral submandibular glands has begun accrual in fall of 2023.

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Phase II Trial of Quality-of-Life Outcomes after Proton Beam for Nasopharyngeal Carcinoma

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Purpose/Objective(s): Radiotherapy is a primary treatment modality for nasopharyngeal cancer (NPC). Advances in radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) have shown less detriment in quality of life (QOL). Proton beam therapy (PBT) has potential to further reduce detriment in QOL due to reduced exposure of normal tissues to low-dose radiation. The purpose of this study was to assess patient-reported QOL outcomes after PBT.

Materials/Methods: Twenty-five patients with biopsy-confirmed stage IIB-IVB nasopharyngeal carcinoma were enrolled on a prospective, phase II, NCI-funded study. The primary endpoint was patient-reported QOL outcomes. Patients were treated with concurrent PBT/cisplatin and adjuvant cisplatin/5-fluorouracil. EORTC-HN35 was performed before PBT and at 1.5, 3, 6, 12, and 24 months following completion of CRT. Wilcoxon signed ranks test were performed to compare difference in means at each time point to baseline. Mann-Whitney test was performed to assess differences in distribution for pooled 12- and 24-month chronic phase data compared to baseline.

Results: Twenty-three patients had complete baseline and QOL follow-up data at 24 months. The Global Health Status QOL metric at 12 and 24 months was not significantly different from baseline (p=0.39 and p=0.62, respectively). At 12 months the only four domains had a statistically significant decrease from baseline: Head and Neck Pain (baseline mean: 6.5 vs 16.7, p=0.02), Swallowing (mean: 4.3 vs 8.7, p=0.004), Dry Mouth (mean: 18.8 vs 58.3, p=0.001), and Sticky Saliva (mean: 11.6 vs 40.0, p=0.006). At 24 months, the only three domains demonstrated statistically significant decrease from baseline: Swallowing (mean: 4.3 vs 8.3, p=0.033), Dry mouth (mean: 18.8 vs 42.4, p=0.017), and Mouth Opening (mean: 5.8 vs 21.2,

p=0.015). For the chronic phase of 12-24 months, Swallowing (p=0.003), Dry mouth (p=0.001), Sticky Saliva (p=0.005), and Mouth Opening (p=0.009) were the only domains different from baseline. In the chronic phase, 43% had responses of "Quite a bit" or "Very Much" to Dry Mouth, 26% to Sticky Saliva, 16% to Mouth Opening, and only 3% to Swallowing.

Conclusion: This study marks the first study prospectively assessing the QOL outcomes of nasopharyngeal cancer patients treated with PBT. Compared to historical controls, fewer domains were adversely affected at the 12- and 24-month time points. This study demonstrates that with proton beam radiation therapy, the long-term quality of life detriment is minimized. These data provide a foundation for further studies phase III involving proton beam therapy and quality of life.

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Unraveling the Psychological Burden and Stress Faced by Caregivers of Head and Neck Cancer Patients: A systematic review

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Purpose/Objective(s): Head and neck cancer is a multifaceted and physically debilitating illness, with consequences that reach beyond the patients themselves, affecting those responsible for their care. The objective of this review is to systematically gather and analyze existing literature, seeking to comprehend the difficulties faced by caregivers, identify the factors that contribute to their psychological burden, and examine the resultant impact on their well-being.

Materials/Methods: A comprehensive literature search was conducted in PubMed and Embase, covering publications from their inception to October 2023. This systematic review adhered to the 2020 PRISMA guidelines. Inclusion criteria involved full-text articles published in the English language, focusing on the examination of psychological distress and challenges encountered by caregivers of head and neck cancer (HNC) patients. The quality of included studies was evaluated using a modified version of the Newcastle-Ottawa Scale (NOS). Eligible studies underwent evaluation using the Covidence data screening and extraction tool, with information pertaining to general study details and article characteristics being collected via a data collection web application.

Results: Among 536 initially identified articles, 8 met the inclusion criteria, comprising primarily descriptive surveys (n = 5; 62.5%), cross-sectional studies (n = 2; 25%), and retrospective chart reviews (n = 1; 12.5%), encompassing a total of 851 caregivers for analysis. The caregiver demographic breakdown revealed a predominance of females (n: 548, 64.4%) with low socioeconomic and education levels. Psychological impacts of caregiving for head and neck cancer patients included depression, anxiety, and stress linked to the fear of cancer recurrence and loneliness. Four studies indicated an increased caregiver burden contributing to heightened psychological stress, while three studies found age to be inversely correlated with caregiver psychological stress. Notably, one study explored the relationship between caregivers' physical activity levels and their reported mental distress, revealing that those engaging in physical activity three or more days per week reported lower levels of depressive symptoms and anxiety compared to those who did not.

Conclusion: Caregivers are the primary support for patients and often bear a substantial psychological burden. Acknowledging the pivotal role caregivers play in the care and recovery of head and neck cancer patients, this systematic review aims to offer insights to healthcare professionals, policymakers, and researchers to improve support systems and resources for caregivers. Ultimately, this enhanced understanding of caregivers' psychological burden will lead to improved care and outcomes for head and neck cancer patients.

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Association Between Frailty and Adverse In-hospital Outcomes after Head and Neck Cancer Surgery Among US Older Adults

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Purpose/Objective(s): Nearly half of patients diagnosed with head and neck cancers are 65 years or older at the time of diagnosis. While surgery remains an important curative modality, older adults with cancer are at increased risk of immediate post-operative complications. Emerging studies indicate the role of pre-operative frailty assessment in predicting adverse outcomes after cancer therapy. The objective of this study was to study the association between frailty and in-hospital complications in a cohort of older adults undergoing head and neck cancer surgery.

Materials/Methods: Using discharge level data from the National Inpatient Sample (NIS), we identified a cohort of older adults ($\geq$65y) who underwent an ablative procedure for a malignant oral cavity, oropharyngeal, hypopharyngeal or laryngeal neoplasm at US community hospitals in 2020. Frailty was defined using diagnosis codes corresponding to the Johns Hopkins Adjusted Clinical Groups frailty indicator. Multivariable regression was used to study the impact of frailty on in-hospital mortality, length of stay non-home discharge and cost of hospitalization, taking into account the complex survey design of NIS.

Results: A total of 3586 (weighted 17,929) US hospitalizations were identified among older adults ($\geq$65y) undergoing head and neck cancer surgery. The overall mean age was 74y$\pm$6 years, with 60% males and 78% non-hispanic Whites. The overall in-hospital mortality was low (0.8%), with a median length of stay of 3 days (Interquartile range, IQR 1-8 days). Overall 36% had discharge disposition other than home and the median hospital charge was $80872 (IQR 46443-157127). Overall, 10.4% patients were identified to be frail. In multivariable models, frailty was associated with a significantly increased risk of adverse outcomes including higher in-hospital mortality (Odds Ratio, OR 4.95; 95% CI 2.01-12.18, p value <0.01), longer hospitalization days (β 6.76; 95% CI 5.21-8.32; p value <0.01), non-home discharge (OR 4.50; 95%CI 3.40-5.95; p value <0.01) and increased cost of hospitalization (β 88670; 95% CI 65523-112917; p value <0.01).

Conclusion: Frailty assessment prior to head and neck cancer surgery may help identify patients at risk of adverse outcomes. Future studies should investigate how to incorporate frailty assessment in daily clinical practice as well as how to use frailty information to guide interventions to minimize post-operative complications as well as choosing alternative therapies (such as definitive radiation therapy)

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Brachial Plexus Tolerance To Standard Fractionation Re-irradiation

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Purpose/Objective(s): Head and neck re-irradiation treatment approach can lead to various side effects like radiation induced brachial plexopathy (RIBP). Factors contributing to brachial plexus injury in the re-irradiation setting need further assessment. We aim to identify these factors to help tailor treatment management.

Materials/Methods: 71 BP sites with 48 patients (pts), treated with re-irradiation between 2015 and 2022 for recurrent head and neck cancer, were assessed. Reverse Kaplan-Meier and logistic regression were used to test the correlation between variables and outcomes. Common terminology criteria of adverse events (CTCAE v5.0) was used to define brachial plexus injury.

Results: The median age of pts was 65 (range, 29-79), 65% of pts were males, and 88% had ECOG performance status of 0-1. All pts received 1.64-2.12 Gy per fraction with one fraction per day and 5 fractions per week via VMAT. 15% additionally received IORT during salvage treatment ranging from 10-15Gy. 27% of patients in the first course and 88% in the second course of pts had surgery, with RT delivered in the adjuvant setting; the remainder had definitive-intent radiation without surgery. Concurrent chemotherapy was delivered to 67% of pts in the first course (Cisplatin 40%, Cetuximab 17%, Carboplatin +/- Paclitaxel 10%) and 62% in the second course (Carboplatin/Paclitaxel 38%, Cisplatin 16%, Cetuximab 6%, Nivolumab 2%). The median duration between RT courses was 34 months (4.6-216). With a median follow-up of 20.1 months, the cumulative incidence of RIBP at 1- and 2- year for the whole cohort was 9% and 17%, respectively. The cumulative incidence of RIBP was lower in pts with a cumulative Dmax of less than 116Gy, (1-year: 2% vs 22%, p <.001), Dmean of less than 70Gy, (1-year: 4% vs 18%, p .003). When V80 less than 1.9cc, V90 less than 1.5cc and V100 less than 1.3cc, the 1-year cumulative incidence of RIBP was 3% vs 18% p .004, 2% vs 20% p 0.001, and 6% vs 18% p .023, respectively. The 1- year cumulative incidence of RIBP in correlation with concurrent cisplatin was 62% vs 3%, p <.001. 1- year cumulative incidence of RIBP with age less than 65 was 18% vs 2%, p .002. 1-year cumulative incidence of RIBP with positive neck lymph node was 22% vs 3% p <.001. On multivariate analysis, age below 65 (HR 9.7 [CI 1.7-57], p .012), Dmax above 116Gy (HR 23 [CI 2.2-245], p .009) and positive neck lymph node during second radiation (HR 6.1 [CI 1.1-33], p .039] continued to show increasing risk of RIBP.

Conclusion: RIBP was higher in younger pts, pts received concurrent cisplatin during the 2nd course, positive neck lymph node, cumulative Dmax 116Gy, mean 70Gy, V80 1.9cc, V90 1.5cc and V100 1.3cc. We identified 10 cases with brachial plexopathy. six pts had grade I, 3 pts had grade II and one pt had grade III brachial plexopathy. Median time to develop RIBP was 9.5 months (range, 1-17.1). Prospective study, longer follow up, and higher numbers are warranted.

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Utility of a Focused Patient Reported Outcome Assessment in a Head and Neck Cancer Radiation Oncology Clinic

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Purpose/Objective(s): Head and neck (HN) radiotherapy (RT) is associated with a substantial acute and late toxicity burden. Patient-reported outcomes (PROs) are critical in understanding the patient's perception of RT toxicity and may provide valuable data points in both clinical trials and the clinic. We sought to evaluate the concordance between clinician rated CTCAE and PRO-CTCAE in HN cancer patients treated with RT.

Materials/Methods: From 10/2020 to 02/2023 all new and returning patients to our HN RT clinic received a focused, HN-specific PRO-CTCAE toxicity assessment. The 11-question form contained 10 modified PRO-CTCAE items - HN pain, dry mouth, taste changes, difficulty swallowing, voice quality changes, hoarseness, fatigue, and a self-report swallowing item using the Functional Oral Intake Scale (FOIS). At each visit,

corresponding CTCAE measures were also collected. Encounters containing CTCAE and PRO-CTCAE data were eligible for analysis. The percent agreement between CTCAE and PRO-CTCAE was quantified using thresholds of 0 and 1 point, and strength of association was examined using Spearman's correlation. Statistical significance was defined as P<0.05.

Results: A total of 407 encounters for 197 consecutive patients were available for analysis: most assessments were collected at baseline (25%) or within 3 months of completing RT (33%). Among the included patients, the most frequent primary site was oropharynx (36%) and the majority had locally advanced disease (64%), were treated with curative intent (59%), or received concurrent chemotherapy (59%). When the threshold for agreement was 0 (perfect agreement), concordance between clinician and patient reported symptoms ranged from 49.1% to 71.2% (Table). When the threshold for agreement was set to +/-1 point, concordance increased to 81.3% to 92.3%. At both thresholds, agreement between clinician and patient assessment were strongest for swallowing function (FIOS) and weakest for dry mouth. For all symptoms, correlation between CTCAE and PRO-CTCAE were statistically significant (P<0.001).

Conclusion: In the setting of RT for HN cancer, we demonstrate significant associations between clinician and patient rating of symptoms using the CTCAE scale. Clinician and patient ratings were most strongly in agreement for swallowing function, suggesting that physicians can incorporate FIOS into baseline and follow-up assessment of patients receiving RT for HN cancers.

Abstract 194 – Table 1

Symptom	Spearman's Rho	Agreement	
		Threshold = 0	*Threshold = 1*
Pain	0.608*	49.1%	85.1%
Dry Mouth	0.526*	42.5%	81.3%
Problems with Taste	0.634*	51.3%	86.2%
Difficulty swallowing	0.498*	51.5%	83.5%
Voice changes	0.376*	61.9%	87.9%
FOIS	0.709*	71.2%	92.3%

*p<0.001 Spearman's Rho: values 0.01-0.10 indicate no relationship, 0.20–0.29 a weak relationship, 0.30–0.39 a moderate relationship, 0.40– 0.69 a strong relationship, and ≥0.70 a very strong relationship.

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Internal Lymphedema Response to A Single Session of External Advanced Pneumatic Compression in Head and Neck Cancer Survivors

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Purpose/Objective(s): Dysphagia is one of the most significant quality-of-life toxicities reported by individuals with head and neck cancer (HNC) and is ranked as the highest cited reason for decisional regret regarding cancer treatment. Head and neck cancer related lymphedema (HNCRL), both external (subcutaneous) and internal (submucosal), is a common consequence of surgical and non-surgical HNC treatments and has been reported in up to 90% of HNC survivors. Despite this, HNCRL remains significantly underrecognized and undertreated. Recent studies have better elucidated the relationship between internal lymphedema and swallowing safety and efficiency (Jeans et al., 2021). Untreated lymphedema results in fibrosis, which is a precipitating and exacerbating factor for worsened swallowing function. Evidenced-based HNCRL treatments involve drainage, either manually or via advanced pneumatic compression. While reduction in external lymphedema after a single treatment session have been reported, reduction in internal lymphedema after a single treatment session has not been assessed.

Materials/Methods: 14 HNC survivors ranging from 3 months to 10 years post radiation underwent a single treatment of advanced pneumatic compression (Flexitouch-Plus, Tactile Medical) in a videofluoroscopic imaging suite. Both external and internal measures were obtained before and after a single 32-minute pneumatic compression treatment session. Internal measures were obtained using pixel based TIMS Software from a videofluoroscopic swallowing study scout image. Internal sites measured were as follows: the width of the velum, posterior pharyngeal wall at C2, C3, and C4 levels, and the width of the epiglottis. External sites measured were as follows: shortest distance from the skin to the mandibular symphysis, inferior hyoid bone, and thyroid cartilage.

Results: All 14 patients had reduction in multiple internal measures after a single 32-minute treatment with pneumatic compression. Specifically, 43% (6/14) had reduction across 100% of measures; 43% (6/14) had a reduction across 60-88% of measures; 14% (2/14) had a reduction across 44-50% of measures.

Conclusion: Head and neck cancer-related lymphedema occurs both externally and internally, while treatments such as manual lymphatic drainage and pneumatic compression are inexorably limited to the external surfaces of the head and neck. However, the impact of external neck treatment on internal pharyngeal lymphedema response has not been elucidated. This dataset demonstrates that a single 32-minute treatment with external pneumatic compression reliably impacts the extent of edema in the pharynx. These findings suggest a direct correlation between internal lymphedema and external treatment, and further supports the contention that lymphedema treatment is an important element in swallow recovery after head and neck cancer treatment.

Author Disclosure: J. Gregor: None.

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A National Comparison of Postoperative Head and Neck Reconstructive Surgery Outcomes in Patients with and Without Immunosuppression

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Purpose/Objective(s): To characterize and assess the effects of immunosuppression on non–head-and-neck-specific postoperative complications following head and neck free flap reconstructive surgery.

Materials/Methods: A 2005-2016 retrospective analysis of adults undergoing head and neck reconstructive procedures was performed using the National Surgical Quality Improvement Program (NSQIP) database. Patients with immunosuppression (n=3,222) were compared with patients with no immunosuppression (n=130). Immunosuppression was defined as steroid use for a chronic condition. Categorical variables were assessed with Fisher's exact test and continuous variables were assessed with Student's t-test. Primary outcomes were 30-day postoperative variables, including return to the operating room, re-intubation, surgical site infection (SSI), and readmission. Multivariable logistic regression analysis was used to evaluate preoperative factors that were noted to be significantly associated with the primary outcomes of interest on univariate analysis. Significance was set at alpha <0.05.

Results: Patients on immunosuppression were more likely to be older, have higher American Society of Anesthesiology (ASA) class, have worse functional status, and have higher rates of hypertension. The 30-day mortality rate was 2.3% for immunosuppressed patients and 0.9% for non-immunosuppressed patients (P > 0.05). Overall, immunosuppressed patients were more likely to experience at least 1 complication (53.8% vs 32.9%, P < 0.001) and almost twice as likely to have a postoperative surgical complication (50.0% vs 28.1%, P < 0.001). The immunosuppressed cohort had higher rates of superficial SSI (11.5% vs 5.9%, P = 0.014) and organ space SSI (4.6% vs 1.7%, P = 0.029). On multivariable analysis,

immunosuppression was not associated with increased risk of return to the operating room within 30 days. However, ASA class 3 or 4, dependent functional status, hypertension, inpatient status, and malignant final pathology were all risk factors for re-operation (P < 0.05). Patients with a BMI > 30 were significantly less likely to return to the operating room (OR, 0.726; 95% CI, 0.569, 0.926; P = 0.010).

Conclusion: National data suggest that head and neck reconstructive procedures in both immunosuppressed and non-immunosuppressed populations are relatively safe. However, immunosuppression is associated with higher rates of postoperative complications and postoperative surgical complications, with superficial and organ space surgical site infections being the largest contributors. These findings may play a role in determining treatment plans for patients and optimizing risk reduction.

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A Pilot Study of Carotid Ultrasound to Identify Head and Neck Cancer Survivors with High Cardiovascular Risk after Radiation Therapy

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Purpose/Objective(s): Radiotherapy (RT) for head and neck cancer (HNC) is associated with multiple late toxicities and may be a potential driver of accelerated atherosclerosis and a higher risk of carotid artery stenosis (CAS), cerebrovascular and cardiovascular diseases. To date, feasibility, acceptability, and clinical utility of carotid artery ultrasound (CUS) imaging as a part of HNC survivorship has not been studied prospectively.

Materials/Methods: In this study (NCT05490875), 60 patients who completed RT for HNC at least 2 years prior with no evidence of disease will be enrolled. Patients with a history of CAS, stroke, transient ischemic attack, carotid endarterectomy, carotid stent, prior CUS, recurrent HNC, re-irradiation, or ECOG 2+ will be excluded. Eligible patients will undergo a CUS with assessment of peak systolic velocity, measurement of bilateral carotid intima-media thickness (IMT), and evaluation for luminal diameter narrowing/occlusion and/or carotid plaque. An IMT-based relative risk of cardiovascular disease will be calculated. After the CUS, surveys assessing the acceptability of/barriers to CUS, as well as perceived stroke risk will be obtained. At 3- and 6-months after CUS, patients will be contacted to determine if any changes to their medical care have occurred since the CUS. Lipid profiling and high-sensitivity C-reactive protein (CRP) will be performed. The results of the CUS will be made available to the patient, their primary care provider, and their HNC physicians; if any abnormality (including clinically significant CAS) is detected, a referral for formal evaluation will be made.

Results: The study opened in October 2022 and has accrued 22/60 patients. The primary objective is to determine the proportion of patients with clinically significant CAS in HNC survivors treated with RT. Secondary objectives include: measure bilateral carotid IMT, determine the risk of CAS based on baseline clinical/treatment factors, and obtain preliminary data on feasibility, acceptability, barriers to care, and perceptions of stroke risk. We will also determine the proportion of patients with high cardiovascular risk based on IMT and plaque presence. Exploratory objectives include determining the proportion of patients with abnormal CUS findings with actionable interventions (e.g., consultations, medications, procedures) and correlating carotid IMT measurements with RT dose to the carotid artery. Planned translational analyses include correlation of CUS findings with CT-based measurements of carotid calcification, peripheral blood mononuclear cell bioenergetics, metabolomic/lipidomic signatures, and serum cytokine profiles.

Conclusion: This study will provide preliminary data on the feasibility, acceptability and expected proportion of clinically actionable findings in patients who undergo screening CUS in survivorship after RT for HNC.

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Dosimetric Predictors of Clinician-rated and Patient-reported Radiation Dermatitis in Head and Neck Cancer: Exploratory Analysis of a Prospective Pilot Study

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Purpose/Objective(s): There are no well-established dosimetric predictors of clinician-rated acute radiation dermatitis (ARD) in head and neck (HN) radiotherapy (RT). Data regarding the dosimetric associations with patient-reported outcome (PRO) measures of RD are even more scarce.

Materials/Methods: In this secondary analysis of a pilot study (NCT04173247) in which 24 patients were treated with at least 60 Gy, we examined dosimetric predictors of ARD. Dermatitis assessments were performed at baseline, weekly during RT, and at 1-month post-RT using clinician-rated (CTCAE v5.0) and patient-reported outcome measures (PRO-CTCAE v1.0 and Dermatologic Life Quality Index [DLQI]). The skin was defined as a ring-like structure comprising the inner 5 mm of the external contour generated by the treatment planning system, excluding bolus (if applicable). The volume of skin (cm^3) receiving a specified dose (V[x] Gy) was calculated in 5-Gy increments between V30-V70 Gy. For each parameter, the volume of skin was compared between patients who did and did not develop each RD outcome: CTCAE G2+ RD, PRO-CTCAE G2+ radiation skin reaction (RSR), or clinically significant 4-point increase from baseline DLQI score (DLQI4+).

Results: Median RT dose was 68 Gy (range 60-70) in 28-35 fractions with the target including the bilateral neck (n=19), unilateral neck (n=2), or primary site alone (n=3). Treatment was definitive in 16 patients and postoperative in 8; concurrent chemotherapy was delivered in 18 patients. CTCAE G2+ ARD was observed in 16/24 patients, PRO-CTCAE G2+ RSR in 18/24, and DLQI4+ in 13/24. Skin V40-V55 were associated with DLQI4+, and multiple skin dose parameters were identified to be associated with ARD at varying significance levels (Table 1). Skin dose was significantly associated with stage (I-II v. III-IV), nodal classification, extent of neck target, and concurrent chemotherapy. Skin dose-volume metrics were not associated with treatment group, intent (definitive v postoperative), age 65+, BMI category, diabetes, tumor classification, or primary site.

Conclusion: Multiple skin dose-volume parameters were associated with clinician-rated and PRO measures of ARD during HN RT. When feasible, the skin should be included as an organ at risk and avoided to limit the risk of moderate to severe ARD. These hypothesis-generating findings warrant further validation and may be helpful in identifying patients at high risk of ARD for inclusion in future ARD studies.

Abstract 198 — Table 1

	CTCAE G2+		PRO-CTCAE G2+		DLQI4+	
	No	Yes	No	Yes	No	Yes
V30	187.4	267.8*	180.9	261.1*	202.5	273.6*
V35	158.8	226.8*	148.9	222.5*	168.4	234.4*
V40	134.9	193.4*	122.5	191.0*	139.4	203.1**
V45	112.1	162.2*	98.3	161.2**	113.0	173.0**
V50	90.6	130.0	76.4	130.3*	88.0	141.2**
V55	64.7	91.9	53.1	92.7*	59.5	102.5**
V60	36.2	44.5	28.5	46.1	30.2	51.4
V65	10.8	14.5	8.7	14.8	9.1	16.8
V70	1.8	2.7	0.9	3.0	1.0	3.7
Mean (SD) volume in cm^3 *P <0.10; **P <0.05						

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Association of Radiation Dose to Pharynx with Long-term Quality of Life in Patients with Head and Neck Cancer

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Purpose/Objective(s): Radiation therapy (RT) is often the primary curative treatment modality for head and neck cancer (HNC). Patients receiving definitive RT for HNC are at high risk for long-term toxicity, including dry mouth, swallowing difficulties, and speech difficulties. Previous studies have suggested structure sparing during RT planning may reduce treatment toxicity as a way to mitigate these long-term effects. The purpose of this study was to evaluate the association of RT dose to the pharynx, larynx, and esophagus with long-term patient-reported quality of life (QOL) in the domains of xerostomia, dysphagia, and dysarthria. We hypothesized that RT dose is associated with QOL metrics.

Materials/Methods: A single-institutional retrospective review of patients with primary HNC undergoing definitive RT or concurrent chemoradiation (CRT) between January 2015 and July 2022 was performed. Patient-reported QOL was assessed on the first day of RT, last day of RT, and every subsequent follow up visit with the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and Head and Neck Cancer Module (EORTC QLQ-H&N35). For each patient, the dose mean (D_{mean}) and dose max (D_{max}) for the pharyngeal constrictor muscles (PC), supraglottic larynx (SGL), and esophagus were calculated. The PC were further subdivided into superior pharyngeal constrictors (SPC), middle pharyngeal constrictors (MPC), and inferior pharyngeal constrictors (IPC). Pearson correlation coefficients were calculated comparing RT dose to these structures to QOL outcomes at 1 and 3 years following completion of RT.

Results: Among 213 eligible patients, the median age was 61.3 years (interquartile range [IQR], 55.8-67.4) and 176 (83%) patients were male. The median follow up was 24.0 months (IQR, 12.5-40.4). PC D_{mean} significantly correlated with xerostomia (r=0.21, 95% confidence interval [CI], 0.08-0.33; p=0.002), dysphagia (r=0.30, 95% CI, 0.17-0.42; p<0.001), and dysarthria (r=0.31, 95% CI, 0.19-0.43; p<0.001) at 1 year and with xerostomia (r=0.31, 95% CI, 0.10-0.49; p=0.004), dysphagia (r=0.28, 95% CI, 0.07-0.47; p<0.001), and dysarthria (r=0.28, 95% CI, 0.07-0.47; p=0.009) at 3 years. Among the PC subsites, IPC D_{mean} correlated the strongest with 3-year xerostomia (r=0.30, 95% CI, 0.09-0.48; p=0.006), dysphagia (r=0.25, 95% CI 0.03-0.44; p=0.02), and dysarthria (r=0.28, 95% CI 0.07-0.47; p=0.009).

Conclusion: RT dose to the PC weakly correlated with development of long-term patient-reported toxicity (r~0.3). Efforts should be made to reduce dose to these structures when clinically feasible during treatment planning without compromising target coverage. RT to the IPC showed the greatest correlation with development of dysphagia, dysarthria, and xerostomia. Continued research on novel factors leading to poor outcomes following HNC CRT is needed.

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Carotid Blowout after Standard Fractionation Re-irradiation: The Ohio State University Experience

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Purpose/Objective(s): Carotid blowout (CB) is a rare but devastating risk for patients (pts) with head and neck cancer. Here, we examined risk of CB among pts treated with conventional fractionation re-irradiation at a single institution.

Materials/Methods: We identified 70 carotid sites among 41 pts treated with conventionally fractionated re-irradiation between 2015 and 2022 for recurrent or second primary head and neck cancer. Reverse Kaplan-Meier analysis was used to assess correlation between clinicopathologic variables and CB outcome. CB outcomes was classified as threatened (type I), impending (type II), or acute (type III).

Results: The median age at the time of re-irradiation was 65 (29-78). 71% of pts were males and 86% had ECOG performance status of 0-1. Median prescription dose was 70Gy (60-70) for the first radiation course and 66Gy (44-70Gy) for the second course. All pts received conventionally fractionated RT at 1.64-2.12Gy per daily fraction. 13% additionally received intraoperative radiotherapy (IORT) during salvage surgery. Overall, 18% of pts in the first course and 76% in the second course of pts had surgery. Concurrent chemotherapy was delivered to 81% of pts in the first course and 65% in the second course. The median interval between RT courses was 28 mo (8-217). The median follow-up after the second RT course was 27 mo (3-71.5). Across both courses of radiation, the median cumulative Dmax (0.03cc) to the carotid artery was 130Gy (76-146). The median V60, V70, V80, V90, and V100 were 5.8cc (1.8-16.59), 4.9cc (1.1-13.3), 4.3cc (0-13.2), 3.7cc (0-13.2), and 3.1cc (0-12.4), respectively. Two pts developed CB, one at 3 months and the other at 5 months after completing re-irradiation. Both pts also had further disease recurrence at the time of CB. One pt had grade II CB that was initially controlled with a covered stent and dual antiplatelet therapy. Rebleeding subsequently developed and was temporarily controlled with embolization, but 7 days later bleeding recurred and led to death. The other pt had grade II CB controlled with endovascular embolization and aspirin; no further bleeding occurred. At 2-year, the cumulative incidence of CB was 3% for the whole cohort. In our cohort, there was no correlation between carotid dosimetry, history of surgery, or systemic therapy utilization and the incidence of CB. The cumulative incidence of CB was higher in patients with LR (9% vs 0%, p=0.048). The 1-year OS was 75% and LRC was 65%.

Conclusion: Among 41 pts with 70 carotid sites treated with conventionally fractionated re-irradiation, the 2-year incidence of CB was 3% at a median follow up of 27 months. We observed no correlation between carotid dosimetry metrics and CB incidence. However, local recurrence was significantly associated with CB incidence. Further study is warranted to identify any additional factors that may modify the risk of this rare but potentially devastating outcome.

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A Review of the Evolution of Quality of Life Measures in Head and Neck Cancer Clinical Trials

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Purpose/Objective(s): To best study the complex toxicity profiles experienced by patients treated with radiotherapy (RT) for head and neck (HN) cancer, a greater focus on quantifiable, reproducible quality of life (QOL) measures is needed. Both clinician-rated outcomes (CRO) and patient-reported outcome (PRO) measures of toxicity and QOL have been collected in HN clinical trials for over two decades. A clear understanding of existing PRO practices in these studies may inform future study design and spark innovative QOL-focused hypothesis-generating research.

Materials/Methods: The protocol documents for HN-specific clinical trials activated within the National Cancer Institute (NCI) National Clinical Trials Network cooperative groups since 2002 were reviewed. Both active and closed trials were included, regardless of publication status. Phase I trials and those that were terminated without enrolling patients were excluded. All protocol specified QOL measures (CRO, PRO, and/or functional assessments [FA]) and the time points of these measurements were abstracted from the protocols, as were basic trial details. Data collection was performed between May 26 and October 12, 2023. Descriptive statistics were performed.

Results: A total of 30 trials including 76 QOL (66 PRO, 10 CRO) and 10 FA measures were included. These trials were activated between 2002-2023; 13 were phase II, 9 phase II/III, and 8 phase III. The most common disease process studied was squamous cell carcinoma of the HN (n=12), oropharynx (n=6), and nasopharynx (n=5). Most studies enrolled patients treated with curative intent (n=20), while 10 enrolled patients with recurrent/metastatic disease. The most frequent study interventions were systemic (n=14) and RT (n=13). Across all studies, 27 distinct PRO measures were utilized, and the most frequent measures were EuroQol-5D (12 trials), FACT-HN (8), PRO-CTCAE (6), MDADI (6), and EORTC-QLQ-C30 (4). The most frequent CRO measure was PSS-HN (7); the most common functional assessment was audiogram (7) followed by modified barium swallow (n=2) and objective salivary flow (n=1). The median number of PRO measures per trial was 2 (range, 0-8) and the median number of data points was 11 (range, 0-35). In trials activated prior to 2012, 17 of 24 (71%) QOL measures (not including FA) were PROs compared to 49 of 52 (94%) measures in trials activated on or after 2012 (p=0.009).

Conclusion: Over time, the use of patient-reported measures of QOL in HN cancer cooperative group clinical trials has increased. This reflects patients' increasing prioritization of QOL as well as requirements by the NCI for increased standardization and quantitation of these impacts on patients in clinical trials. This dataset may inform future study of QOL in patients with HN cancer through a better understanding of specific PRO data that has been or will be collected within current and future NCI-supported clinical trials.

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Interrogating Frailty as a Predictor of Mortality and Treatment Complications in Older Adults with Oropharyngeal Squamous Cell Carcinoma

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Purpose/Objective(s): As the population continues to age, there will be an increase in human papilloma virus (HPV) associated oropharyngeal carcinomas (OPSCC) in older adults. Frailty is a risk factor for worse disease and survival outcomes in the geriatric population. Biomarkers and frailty indices have been used to quantify and predict survival outcomes and complications. We seek to develop a frailty index using lab abnormalities and comorbidities to predict of mortality and morbidity in older adults with OPSCC.

Materials/Methods: Study participants were identified from a retrospective database of head and neck squamous cell carcinoma patients consecutively treated from 2007 to 2020 at our institution's cancer center. Patients aged $\geq$65 with newly diagnosed, nonrecurrent, nonmetastatic, curatively treated OPSCC, with a minimum follow-up of 1 month, were included in this study. Approval for this study was obtained from the IRB at our institution and informed consent was waived given the retrospective nature of the study. Pre-treatment lab values (basic metabolic panel) were used to extract data on albumin levels. The modified frailty index (mFi-5) was also calculated — it is a 5-item score validated from the NSQIP dataset that calculates frailty based on comorbidities including hypertension (on medications), diabetes mellitus, CHF, COPD/pneumonia, and functional status. Outcome measures included disease specific survival (DSS), treatment interruptions, prophylactic PEG tube placement, and overall survival. Subsequently, univariate analyses were adjusted for stage and Charlson Comorbidity Index. DSS, treatment interruptions, and prophylactic PEG tube placement were compared across frailty markers using the χ^2 test and Fisher's exact test. Overall survival was analyzed using ANOVA.

Results: 146 patients with OPSCC were identified with a median age of 71.5 (IQR: 67.9-76.1). The majority of patients were male (83%), white (63%), former/active smokers (90.4%), and HPV+ (68.6%). There was no association between mFI-5 score and any of the outcome measures. Low albumin levels at diagnosis (<3.5 g/dL) were associated with lower DSS (p=0.023) as with higher rates of prophylactic PEG tube placement (p=0.028). There was an association between albumin levels and acute mucositis (3 months after RT) (p=0.008). The relationship of albumin and prophylactic PEG tube placement remained significant after adjusting for comorbidities and stage.

Conclusion: This is one of the first studies to investigate the indexes of frailty (albumin and mFI-5) on DSS, PEG-tube placement, and treatment complications in older adults with OPSCC. Preliminary analysis shows that low albumin levels are associated with worse disease specific survival, higher rates of prophylactic PEG tube placement, and acute mucositis.

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Functional Outcomes from a Phase II Trial of Adaptive Deescalation of Radiation Therapy Dose in p16+ Oropharyngeal Cancer Patients Demonstrating Favorable Mid-treatment Nodal Response

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Purpose/Objective(s): Chemoradiation therapy (CRT) for p16+ oropharyngeal cancer (OPC) can result in excellent overall prognosis but have adverse effects on swallowing and salivary function. We report outcomes of patients (pts) with favorable risk p16+ OPC who received deescalated CRT based on mid-treatment (tx) response with rapid mid-tx nodal shrinkage (RMNS) at week 4.

Materials/Methods: Inclusion criteria were as follows: T0-3, N1, M0 (AJCC 8th edition) p16+ OPC with <10 pack-year smoking history. All pts were initially planned for standard dose CRT (70 Gy) and weekly cisplatin. Pts were evaluated for RMNS at week 4 for RMNS (>40% nodal volumetric reduction from baseline). If RMNS was achieved, pts proceeded to deescalated CRT (60 Gy). If not, pts received standard CRT (ClinicalTrials.gov: NCT03215719). Post-RT swallowing outcomes were evaluated with the MD Anderson Dysphagia Inventory (MDADI) and Saxon test for salivary secretion, before tx and at 1, 3, 6, 12, and 24 months (mos) post-tx. Mean MDADI composite scores and salivary secretion were compared using two-sample t-test without adjustments or one-way ANOVA pairwise T-testing with holm-sidak correction (significance determined at p<0.05). Pearson correlation coefficients were calculated.

Results: 39 pts were enrolled: median age: 60 years, 82% male; 36% (n=14) base of tongue (BOT), 54% tonsil (n=21), 10% both (n=4); 67% (n=26) had RMNS and received deescalated CRT while the remaining proceeded to standard CRT. Pts receiving standard dosing show minimal clinically important decrease (MCID) of 10 MDADI composite points at 1, 3, 6 and 12 mos post-tx, while deescalated pts only show MCID at 1 mo post-tx. Mean MDADI composite score difference between deescalated and standard pts at 1, 6 and 12 mos were 12.37 (95% CI: -1.3-26.0, p=0.072), 13.81 (95% CI: -3.2-24.4, p=0.014), and 15.66 (95% CI: -3.0-28.3, p=0.021), and 3.473 (95% CI: -8.4-15.4, p=0.521) at 24 mos. Despite all pts meeting standard dose constraints for constrictor tolerance, significant correlation between mean dosage to superior constrictor muscles (SCM) and magnitude of change in MDADI composite score are noted at 1, 3, 6, and 12 mos (r=-0.45, p=0.014; r=-0.5, p=0.002; r=-0.43, p=0.02; r=-0.58, p=-0.58, respectively). In BOT and tonsil pts, there was significant change in salivary secretion compared to baseline at 1 and 3 mos post-tx (p=0.0008 and 0.0014), with persistent salivary changes in BOT pts up to 12 mos (p=0.0036).

Conclusion: This study demonstrated intermediate term swallowing function benefit with deescalated CRT. Even under standard dose tolerance, RT to the SCM significantly impacted MDADI scores. Salivary flow was suppressed in the first 6 mos, but returned to baseline more quickly in tonsil pts. Our findings suggest there may be further functional benefit with greater dose deescalation.

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CLIA Validation of a New High Performance HPV ctDNA Assay Covering Multiple High Risk HPV Types

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Purpose/Objective(s): To develop and CLIA validate a droplet digital PCR (ddPCR) assay capable of enhancing the detection of multiple high-risk types of human papillomavirus (hrHPV) circulating tumor DNA (ctDNA) in plasma from patients with HPV-associated oropharyngeal squamous cell carcinoma (HPV+ OPSCC).

Materials/Methods: We advanced our previously developed HPV16 probes, and newly developed hrHPV probes designed to detect HPV-18, HPV-31, HPV-33, HPV-35 and HPV-39 (total 26 primers and 13 probes) as a new high-performance assay for validation in our CLIA certified laboratory using Clinical and Laboratory Standards Institute (CLSI) guidelines. Analytical control and plasma samples from HPV+ OPSCC patients were used to characterize and validate the performance as a lab developed test (LDT).

Results: The assay demonstrated analytical accuracy and precision during in depth evaluation consistent with requirements for clinical use. For HPV16, the assay had a limit of the blank (LOB) of 0 copies/μL, a limit of detection (LOD) of 0.53 copies/μL, and a limit of quantification (LOQ) ranging from 1.29 - 4.36 copies/μL. For detection of other hrHPV types, the assay had a LOB of 0 copies/μL, a LOD of 0.77 copies/μL, and a LOQ ranging from 1.72 − 14.0 copies/μL. Regression of the observed copy number versus measured concentration of HPV DNA, and the observed versus expected copy number had excellent correlation in the linear range of the assays (R^2 = 0.99 for each). For HPV16, the assay had a linear range from 0.53 to 9384 copies/μL. For other hrHPV types, the assay had a linear range from 0.77 to 6000 copies/μL. Above the linear range of each assay, the analyte was detected resulting in a positive test, but recovery was <90%. Testing of blanks following known positive samples did not find any substantial carry over. Testing of analytes over a 96-hour period showed appropriate stability of the analyte (both primary and processed) and assay over time. Cross-reactivity was assessed using each assay (alone and in combination) to evaluate contrived samples of HPV16, HPV18, HPV31, HPV33, HPV35, and HPV39 (individually and in combination) and found that there was no substantial cross-reactivity between the assays or HPV types, confirming the high specificity of the assay for HPV type.

Conclusion: These results confirm this assay has both high analytical sensitivity and specificity for detection of multiple hrHPV types and is capable of detecting low levels of HPV ctDNA from clinical plasma samples.

Abstract 204 − Table 1: Characteristics of Novel Assay for Detecting HPV16 and high-risk HPV

Assay Target	LOB (copies per μL)	LOD (copies per μL)	LOQ (copies per μL)
HPV16	0	0.53	1.29
hrHPV	0	0.77	1.72

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A Silicone-based Film-forming Gel Wound Dressing for the Prevention of Radiation Dermatitis in Head and Neck Cancer Patients: A Retrospective Cohort Analysis Using Clinical Informatics

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Purpose/Objective(s): Patients undergoing radiation treatment for head and neck cancers often experience radiation dermatitis, a breakdown of skin that can limit the ability to deliver optimal doses of radiation. To address this, patients typically use topical moisturizers to help prevent or ameliorate these symptoms, with mixed efficacy. A novel silicone-based polymer film, StrataXRT, has been developed to provide barrier protection against radiation-induced effects, in addition to possessing integrated antibacterial properties. We adopted the routine use of StrataXRT in our clinical practice in 2020. We sought to retrospectively determine the efficacy of this cream compared to standardly utilized moisturizers in reducing the incidence of severe radiation dermatitis in patients treated for a wide spectrum of head and neck malignancies.

Materials/Methods: We used a clinical informatics approach to conduct a large retrospective analysis of all patients treated with StrataXRT compared to historic controls using conventional moisturizers (mostly Aquaphor at our institution). We analyzed the endpoint of grade 2+ radiation dermatitis measured by CTCAE in 172 patients treated with StrataXRT compared with 172 propensity score-matched patients treated with traditional moisturizers. Patients were matched such that maximum skin doses were within 10 Gy to control for skin dose, a confounder. We then ran a multivariate Cox regression to compare StrataXRT versus moisturizer, adjusting for age, gender, use of surgery, use of chemotherapy, and p16 status.

Results: We found an absolute risk reduction of grade 2 or higher radiation dermatitis of 14.5%, which translated to a number needed to treat of 7 patients to prevent one occurrence of grade 2+ radiation dermatitis. In the multivariate Cox regression, the hazard ratio was 0.59 (95% CI [0.37,0.95], p=0.031) favoring StrataXRT.

Conclusion: We demonstrated the feasibility of running retrospective virtual trials using a clinical informatics approach with automated extraction of patient data from electronic health records. Using this data-driven method, we showed that patients benefited from StrataXRT by significantly decreasing the incidence of radiation dermatitis throughout the course of radiation therapy. This study thus introduces and supports the routine use of a novel topical agent providing barrier protection to reduce the toxicity of head and neck cancer treatments.

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Voice Related Quality of Life (qol) in Volumetric Modulated Arc Therapy (vmat) for Non-laryngeal Head and Neck Malignancies

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Purpose/Objective(s): To assess the Voice Quality of life in non-laryngeal carcinoma who undergo VMAT. Primary objective:

1.   Subjective assessment of the Voice related QOL in patients undergoing radiation therapy with VMAT technique for non-laryngeal head and neck malignancy using Voice Handicap Index.

2.   Objective assessment of the Voice related QOL in patients undergoing radiation therapy with VMAT technique for non-laryngeal head and neck malignancy using Video-stroboscopy and voice analysis.

Secondary objective:

1. To assess the correlation between Voice related QOL and dose-volume parameters of radiation therapy.

Materials/Methods: INCLUSION CRITERIA

1.   Patients undergoing loco regional radical radiotherapy or chemo radiotherapy with VMAT for non-laryngeal head and neck malignancies.

EXCLUSION CRITERIA

1.   Any tumor primarily involving the larynx or extending from other sub sites.

2.   Any history of benign laryngeal pathology or surgical interventions in neck or larynx. IRB approval obtained,16 patients with non-laryngeal carcinoma planned for VMAT and at baseline, completion and 3 month follow up three assessments done. 1. Subjective assessment done using Voice handicap index (VHI) 2.Objective assessment done using Video-stroboscopy and voice analysis 3.Dose volume histogram acquired using Treatment planning system (TPS)

Results: Mean age of patients is 45 years and most of the patients had oral cavities as a primary. Subjective analysis with VHI showed statistically significant change in the Physical domain at post radiation assessment which became insignificant after 3 months. There is meaningful change in the VHI total score at the end of RT compared to the baseline and after 3 months of radiation therapy, though statistically not significant. Baseline VHI total scores were higher in oral cavity patients. Objective assessments done with video-stroboscopy showed there is a significant change in vocal cord closure patterns at the end of radiation therapy (p=0.02) but became insignificant post 3 months of radiation therapy. Other significant finding found in the objective assessment is vocal edema significantly seen after radiation therapy and 3 months post-radiation therapy. Objective assessments done with Voice analysis couldn't find any significant change in the voice after radiation or post 3 months of radiation therapy. DVH analysis done showed correlation between the laryngeal dose and edema.

Conclusion:

- Volumetric modulated arc therapy (VMAT) minimizes the voice related QOL changes in non-laryngeal cancers. There was strong correlation between higher mean laryngeal dose and laryngeal edema, but it did not affect the Voice related QOL in our study may be due to smaller sample size.

Abstract 206 − Table 1

DVH parameter	Edema patient			Non edema patient		
	Mean	Min	Max	Mean	Min	Max
Mean	48.95 Gy	39.11 Gy	69 Gy	39.35 Gy	21.07 Gy	45 Gy
D Max	63.15 Gy	54.08 Gy	74.23 Gy	58.58 Gy	51.53 Gy	64 .32 Gy
V50	36.79 %	1.676 %	100 %	15.71 %	0.049 %	47.04 %

Mean laryngeal dose in our study is 42.95 Gy and V50 is 23.62%

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Imaging-based Prognostic Artificial Intelligence Model for Oropharyngeal Carcinoma after Radiation Therapy

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Purpose/Objective(s): Predicting treatment prognosis for oropharyngeal carcinoma (OPC) remains a significant challenge. This study hypothesizes that pre-treatment CT imaging holds important prognostic information. We developed an artificial intelligence (AI) model to predict locoregional recurrence (LRR) post-radiation therapy (RT) for OPC.

Materials/Methods: In an IRB-approved study, we collected imaging and outcome data from 1095 patients newly diagnosed with oropharyngeal carcinoma. They were treated with RT with curative intent, with or without chemotherapy, and none underwent surgery. Data originated from multiple institutions: 124 from ours and 971 from The Cancer Imaging Archive, contributed by four institutions in the US, Canada, and Europe. We excluded patients with a follow-up duration of less than 2 years unless they experienced LRR within this period. Each patient's pre-treatment CT images, along with segmentations for the gross tumor volume of the primary tumor and lymph nodes (if present), served as model input. We clipped the Hounsfield values of CT images within the range [-200, 200]. A 3D convolutional neural network, adapted from the ConvNeXt architecture, was employed as the deep learning model. The primary endpoint was the risk of 2-year LRR. The training used a weighted binary cross-entropy loss function, and we developed the model through five-fold cross-validation on 730 cases. For inference, the ensemble model provided a risk score between 0 and 1, indicating the probability of 2-year LRR on the 365 patients in the test cohort.

Results: On the independent test set, the model attained a Harrel's concordance index of 0.72 for predicting 2-year LRR. Using 0.5 as a threshold to classify the test cohort into low- and high-risk groups, the log-rank test highlighted a significant difference in LRR risk between the two groups (p=3.6 × 10^-7).

Conclusion: Our study demonstrates the potential of an imaging-based AI model for predicting OPC prognosis. However, further research is required to validate this model and integrate more clinical parameters as inputs.

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Metabolics Underlying Dynamic Optical Contrast Imaging for Head & Neck Cancer Margin Determination

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Purpose/Objective(s): To describe the metabolics underlying cancer and cancer margin detection of lifetime fluorescence in Dynamic Optical Contrast Imaging (DOCI).

Materials/Methods: Cell lines Tu686, OKF, FADU, and RH2 were cultured in and sequentially treated with mitochondrial poisons oligomycin, FCCP, then rotenone + antimycin A. Treated cells, untreated cells, and vehicle control were plated with powdered magnesium at 50,000 cell density and imaged with the DOCI machine. These same cell lines then were plated in a 96 well culture microplate with the same mitochondrial poisons as above, and analysis was run via a Seahorse XF96 assay, yielding in vitro metabolic data. Redox ratio was calculated for the cell lines after mitochondrial poisons were treated, and were compared to data from the Seahorse assay.

Results: Redox ratio as measured from the DOCI machine correlate with changes in the oxygen consumption rate of the cell, as measured via Seahorse, after administration of oligomycin, FCCP, and rotenone with antimycin A. In both DOCI and Seahorse assay, average values decreased after administration of oligomycin, increased after adding FCCP, and again decreased when adding rotenone + antimycin A.

Conclusion: DOCI has been utilized for cancer margin detection, and this in vitro study demonstrates the underlying mechanism of detecting specific metabolic shifts, by comparing DOCI redox ratios to Seahorse assay metabolic data.

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Enhancing Oral Cancer Diagnosis: A Deep Learning-Based Approach for Malignant Tongue Tumors

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Purpose/Objective(s): Oral cancer, while relatively rare in Korea, is characterized by rapid metastasis and frequent recurrence, making early detection crucial for patient survival and quality of life. If diagnosed late, extensive surgical resection of the malignant tumor can lead to permanent damage throughout the head and neck, severely impacting the patient's quality of life. Consequently, early detection is vital. However, due to its rarity, misdiagnoses are common in general hospitals, potentially leading to treatment delays. Recognizing the need for tools to aid in the early detection of oral cancer, this study aims to propose a deep learning-based classification model for malignant tongue tumors, focusing on the tongue − the site with the highest single-point incidence rate among oral cancers

Materials/Methods: We developed a binary classification model for malignant tumors using 5,224 tongue endoscopic images from five major comprehensive hospitals, which include normal, benign, and malignant tumors. Utilizing MONAI's pre-trained 20 CNN models (VGGNet 16, 19, ResNet 101, 152, etc.) as the backbone, we selected our model based on a cross-comparison of the F1-score, which indicates malignant tumor

prediction, and the AUROC, which shows the model's overall classification performance (Internal validation). Subsequently, we evaluated the expected performance of the model using data from a specific hospital that was excluded during training (Hold-Out) (External validation). This study emphasized image standardization and augmentation. To mitigate variance in endoscopic images due to differences in hospitals and equipment, we removed unnecessary features. Considering the image's technical statistics such as brightness, contrast, and shadow, we augmented the data within an arbitrary range. Additionally, to compensate for the insufficient performance of the CNN model's DropOut layer, we applied CutOut.

Results: The model that exhibited the highest inference performance was EfficientNet-b2, with metrics demonstrating its malignant tumor inference capability in Internal validation (External validation) as follows: Sensitivity 0.904 (0.771), Precision 0.892 (0.841), F1-score 0.898 (0.804), and AUPRC 0.982 (0.940). The model's overall inference performance was reflected in an Accuracy of 0.928 (0.859) and AUROC 0.974 (0.920).

Conclusion: Based on the results, the tongue cancer binary classification model proposed in this study demonstrated its classification performance in both Internal and External validations. Notably, in the medical field where minimizing beta errors is essential, the model achieved an F1-score of over 0.8. These outcomes suggest that the model developed in this study has potential as a tool to assist medical professionals in clinical settings.

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Head and Neck Contour Peer Review Ensures Quality of Radiation Targets

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Purpose/Objective(s): Head and neck (HN) radiotherapy contour quality can directly impact local control (LC) and survival. However, few departments peer review (PR) contours prior to radiotherapy planning (RP). In an effort to improve radiotherapy quality at our institution, we implemented a formal HN contour PR process; this series reports the outcomes of this quality project.

Materials/Methods: A formal HN contour PR process was implemented within our department in 2018. Contours were reviewed by HN radiation oncologists (RO) and revised prior to RP. A PR task item was built into the care path of the electronic medical record (EMR) to track the PR process. All HN RO participated in PR. Together, the RO evaluated factors pertinent to contours including imaging, physical examination photographs, flexible scope examination, operative notes and surgical pathology. Contours were assessed by the RO HN team, and feedback was provided to the treating physician if contour revision was recommended. Contour revisions were graded by the HN RO team as follows: R0 (no change), R1 (minor revision, not high risk) or R2 (major revision, deemed high risk to negatively impact LC). The PR task was completed and contour grade recorded in the EMR. The Cochran-armitage trend test was performed to determine if contour grade trend was significant over time.

Results: The pilot PR process was performed across a 7 month period in 2018. 88 patients had contour grade recorded. Four RO participated in the first 3 months and 3 RO participated all 7 months of the pilot. Contours were graded as follows: R0 (N=50), R1 (N=20) and R2 (N=18). Over time the number of major revisions (R2) decreased (p=0.0001); month 1 (N=7) month 2 (N=3), month 3 (N=5) month 4 (N=2) and months 5-7 (N=0). Each individual RO who participated the entire time demonstrated reduction in R2 revisions; Oncologist A: month 1 (N=2), month 2 (N=1), month 3 (N=2), month 4 (N=1) and month 5-7 (N=0). Oncologist B: month 1 (N=2), months 2-4 (N=1) and months 5-7 (N=0). Oncologist C: month 1 and 3 (N=1) and months 2, 4-7 (N=0). The total number of R0 revisions improved over time (p=0.0203); month 1 (N=5), months 2-3 (N=9), month

4 (N=5) month 5 (N=8), month 6 (N=12) and month 7 (N=3). Upon completion of the pilot phase in 2018, the PR process continued into a maintenance phase from 2019 through August 2023. 692 patients had contour grades recorder; 493 patients are included in this analysis of the maintenance phase for attending RO evaluation. 199 contours were excluded due to grades representing resident physician scores. Within the maintenance phase, all 3 RO had low rates of R2 revision of less than 3 cases per year and this rate remained stable for each RO from 2019-2023.

Conclusion: HN contour PR can be implemented into routine clinical workflow. The collective experience of multiple high volume RO led to improved contour quality in the pilot phase for each RO and continued to ensure high quality in the maintenance phase of this project.

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Deep Learning Based Recurrence Prediction in Head and Neck Cancers after Radiotherapy

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Purpose/Objective(s): Nearly half of patients with head and neck (H&N) cancers experience recurrence, yet the challenge of prognosticating high-risk individuals for intensified radiotherapy persists. Here we aimed to develop a deep learning (DL) model for predicting H&N cancer recurrence based on clinical and radiomic features (texture, shape, intensity) from radiation planning CT simulation scans.

Materials/Methods: We analyzed contrast enhanced CT scans of 249 patients with H&N cancers from The Cancer Imaging Archive (TCIA). This dataset included patients with known recurrence status, defined as a locoregional recurrence or distant metastasis. Radiation treatment clinical target volume (CTV) contours from the CT scans were extracted, z-score normalized, and resized to $128 \times 128 \times 128$ volumes before analyzing radiomic features. For the recurrence prediction task, we utilized a modified 3D variant of Resnet50, with patients randomly assigned to training (n=199) or test (n=50) sets. ROC, AUC, sensitivity, and specificity were reported across 5-fold cross validation.

Results: The majority of patient in the study involved oropharyngeal cancer (68%) with a median age of 63 years and follow up of 42.9 months. In total, 26.5% of patients experienced a recurrence in a median time of 14.9 months. The combined clinical-radiomic DL model achieved an AUC of 0.75 with an accuracy of 0.71. When considering only the highest-performing clinical features (TNM stage, treatment modality, HPV status, and sex), the model yielded an AUC of 0.6 and an accuracy of 0.61. Finally, utilizing only the top 5 out of 1218 radiomic features in the model resulted in an AUC of 0.64 with an accuracy of 0.47.

Conclusion: This study underscores the potential of DL models in predicting H&N cancer recurrence by combining clinical and radiomic features from CT scans. The promising results of our integrated model suggest its role in identifying high-risk individuals who could benefit from intensified treatments, ultimately improving the management and outcomes for patients with H&N cancers. Even when using clinical and radiomic features separately, valuable insights into patient risk stratification were obtained. Further refinement and validation of these models have the potential to pave the way for more precise and personalized treatment strategies.

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3D Surface Scanning for Virtual CT-Based Electron Beam Treatment Planning in Skin Malignancies of the Head and Neck

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Purpose/Objective(s): Radiation therapy is an important treatment option for skin cancers of the head and neck. Electron beam therapy is a common radiation modality for skin cancer due to its suitability for treating superficial tumors. CT simulation is the gold standard for modeling the 3D characteristics of a patient in electron beam treatment planning. High-resolution 3D surfacing imaging has recently become available for general use. We propose that 3D surface images can be used to generate virtual CT patient models for electron therapy treatment planning. We present the results of a clinical trial evaluating spatial and dosimetric accuracy of 3D surface scans used to produce virtual CTs for electron therapy treatment planning.

Materials/Methods: Ten head and neck skin cancer patients receiving electron therapy were prospectively enrolled in this study, with a diversity of tumor types and locations. For each patient, a 3D scan was acquired using a hand-held high resolution 3D scanner immediately following CT acquisition during simulation. Patients were then planned and treated according to department standard protocol using the planning CT. To evaluate spatial accuracy of the 3D scans compared to the planning CTs, the external contour from the planning CT was exported from the treatment planning system as a 3D mesh and then rigidly registered to the 3D surface scan mesh using the iterative closest point (ICP) algorithm. The ICP registration was used to calculate distances between the mesh points from the planning CT and 3D scan. The 3D scan mesh was further processed to a DICOM-compliant virtual CT. This virtual CT was imported into the treatment planning system and a copy of the clinical treatment plan was applied to the virtual CT. Absorbed dose was calculated on the virtual CT assuming all tissue being water-equivalent. Dosimetric accuracy was evaluated by dose volume histogram (DVH) metrics of the clinical target volume (CTV).

Results: For spatial accuracy of the 3D scans, mean distance and standard deviation between points were less than 1 mm for all patients. Individual points exceeding 1 mm distance were primarily localized to regions where the 3D scan included patient hair, tape, and wire stickers. For dosimetric accuracy of the virtual CT, Wilcoxon signed rank test for the CTV D95% (p>0.5) and V100% (p>0.5) DVH metrics showed no significant difference between the dose distributions of the CTVs.

Conclusion: This study shows that 3D surface scans can be used for treatment planning of skin cancers of the head and neck with no appreciable loss of accuracy in most cases. This has several potential benefits, including reducing patient appointment loading on the CT simulator. Some caveats apply to the use of 3D scans for treatment planning, including when the surface has significant hair or tape used to wire the target.

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Radiomic features associated with recurrence in a case: control cohort of surgically treated HPV+ OPSCC

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Purpose/Objective(s): Despite the more favorable prognosis of HPV-associated OPSCC, a subset of these patients are not cured by initial therapy. At presentation, conventional staging and smoking history have poor ability to predict recurrence and survival of the HPV+ OPSCCs undergoing transoral robotic surgery (TORS) followed by pathology-guided adjuvant therapy. In order to enhance prediction of oncologic outcomes under this treatment paradigm, we evaluated a machine learning approach to identify radiomic characteristics that distinguish the patients who subsequently recurred.

Materials/Methods: From a single-institution cohort of patients undergoing TORS for HPV+ OPSCC from 2007 through 2017, we identified 42 patients who experienced disease recurrence within the radiation field (n=7), at distant sites (n=29), or both (n=6). These patients were matched on several characteristics (8th edition AJCC pathologic T and N stage, smoking history, adjuvant radiation, and adjuvant chemotherapy) to 42 patients from the same cohort who did not recur with minimum follow up beyond the latest recurrence. Using baseline diagnostic CT images (n=51) or low-dose CT images from PET/CT (n=33), primary tumor sites, contralateral non-tumor sites, and ipsilateral and contralateral oropharyngeal soft tissues were manually segmented on axial CT images using CAVASS software. Morphologic, intensity-based, and texture-based features (680 in total) were then extracted for each tissue and compared for discriminative capability between the two patient cohorts using unpaired t testing with p<0.01 considered as significant.

Results: 69 (out of 680) radiomic features on baseline CT scans were significantly different between patients with recurrence vs. without recurrence after TORS. Volume of oropharyngeal tissue was greater in patients who experienced recurrence, on both tumor (ipsilateral, 36.22 ± 9.28cc vs. 25.39 ± 11.43cc, p<0.0001) and non-tumor (contralateral, 33.62 ± 7.24cc vs. 24.73 ± 11.83cc, p<0.0001) sides. Additionally, the mean CT intensity value of ipsilateral oropharyngeal tissue in the recurrence group was significantly higher than that in the control group (47 ± 16 vs. 34 ± 26 Hounsfield units, p <0.01). Several texture-based features also differed between the groups.

Conclusion: Radiomic features can distinguish between HPV+ OPSCCs that do and do not recur after TORS. Oropharyngeal tissue volume seems to be greater in patients with recurrence. Further analysis and validation on external cohorts are needed to establish clinical utility.

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ICG Functionalized Gold Nano Stars Allow for Delivery of Therapeutics and Deep Tumor Imaging Intraoperatively

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Purpose/Objective(s): The primary management of head and neck squamous cell carcinoma relies on complete surgical resection of the tumor, as positive margins are associated with decreased survival. The advantages of radiotherapeutic (RT) dose de-escalation and less aggressive treatments provide better patient quality of life, assuming complete tumor control can still be achieved. The use of gold nanostars (GNS) to accumulate in cancerous tissues via the enhanced permeability and retention (EPR) effect can be employed to localize and treat cancer, offering the potential for enhanced margin delineation and RT dose reduction while still maintaining tumor control. Indocyanine green (ICG), a fluorescent dye utilized in various intraoperative imaging modalities, can be conjugated to GNS forming ICG-GNS, enabling intraoperative fluorescence-based imaging for real-time evaluation of deep tumor margins.

Materials/Methods: Forty male HeJ mice were subcutaneously injected with 400k SSC7 (mouse squamous cell carcinoma) cells in the rear

hindquarter. Once the tumors reached 1cm in size, mice underwent surgery to debulk the tumor by 50%. Subsequently, mice were randomly assigned to receive one of the following treatments: dissolvable polymer laced with ICG-GNS implanted onto the remaining tumor, ICG-GNS injected into the tumor, ICG-GNS injected via tail vein, and polymer vehicle control or injection vehicle control groups. Mice were further stratified based on whether they received 4×2Gy, 4×4Gy, or no fractionated RT post-surgery in conjunction with ICG-GNS/control delivery.

Results: GNS in all treatment regimens demonstrated significantly improved tumor control compared to 4×4Gy RT alone. Additionally, GNS localization was visualized using conventional CT imaging: GNS tail vein-injected mice exhibited GNS accumulation around the periphery of the tumor; intratumorally injected GNS displayed hotspots of GNS concentration at the injection site; while polymer-administered GNS exhibited strong intensity at the polymer location. Secondary sites of ICG-GNS accumulation were the liver and spleen. Fluorescence based imaging also demonstrated that ICG conjugated to GNS could be visualized from intraoperative deep tumor margin delineation.

Conclusion: This study underscores the promising potential of GNS in reducing tumor burden while enhancing patient quality of life through dose de-escalation strategies while providing intraoperative imaging capabilities of deep tumor margins .

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Improving Treatment Plan Robustness at Internal Tissue-Air Interfaces in Head and Neck Radiotherapy

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Purpose/Objective(s): Volumetric Modulated Arc Therapy (VMAT) has become a staple of modern head and neck (HN) radiation planning, but there may exist unexpected failure modes in which VMAT plans are less robust than typically expected. We identify and characterize one such potential instability (to our knowledge not previously described) that can occur at the interface between target volume (e.g. a mucosal primary tumor) and internal air (e.g. pharyngeal lumen, sinuses, nasal cavity, etc.), where the lack of a sufficient region for full dose buildup can lead to development of unexpected hotspots with even minor variations in target geometry.

Materials/Methods: Plans for ten HN patients treated with curative-intent VMAT radiation therapy (RT) at our institution in 2023 were reviewed. All patients received 60-69.96 Gy in 30-33 daily fractions with 6MV photons, with plans created in a technology company treatment planning system and calculated with an advanced dose calculation algorithm (version 16.1). To model the effect of swelling or tumor growth at the internal air/tumor interface, verification plans were run in which internal air within 3 mm of the planning target volume (PTV) was overridden to soft tissue density (Hounsfield Unit [HU] = 0), and resulting hotspots were assessed. A modified planning technique was employed to increase robustness, wherein the plan was initially optimized with the luminal air density on CT overridden to HU = -300, before being re-calculated and re-normalized with the original CT HU values. Finally, the modified plan was then assessed for robustness in the event of tissue filling by again overriding luminal air to HU = 0.

Results: Although hotspots were well controlled in clinically treated plans at baseline (median 110%, range 109%-114%), relatively minor changes at the tumor-air interface (within 3 mm of PTV) resulted in development of significant unexpected hotspots (median 131%, range 115%-155%). With the proposed robust planning technique, plans were similar at baseline (median hotspot 110%, range 108%-114%, p=0.275 relative to original plan), but significantly more robust in the event of changes at the internal air-tumor interface (median hotspot 110%, range 108%-114%, p=0.001

relative to non-robust plan) while maintaining stable target coverage (D95% of 99.1% to 100.2%).

Conclusion: In cases requiring full dose to the interface between target volume and luminal air, standard VMAT plans can exhibit unstable behavior due to insufficient region for dose buildup, resulting in clinically unacceptable hotspots with even minor variations in target geometry—variations that are well under thresholds that would conventionally trigger replanning. A density override planning technique can mitigate this effect, creating VMAT plans that differ minimally at baseline but are substantially more robust against the development of unexpected hotspots. This technique is worthy of further consideration, particularly for HN plans with high dose regions abutting luminal air.

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Patterns of Discordance Between Clinical and Pathologic Stage in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): Like other malignancies, treatment and prognosis of head and neck squamous cell carcinoma is highly dependent on TNM staging. Clinical TN staging (cTN), which is established during the primary workup, helps guide initial treatment but is limited by the quality of physical examination and imaging studies. Pathologic TN staging (pTN) is determined from collected specimens if surgical resection occurs and is considered the gold standard for staging. Previous studies have shown discordance between cTN and pTN, likely due to the limitations of clinical staging. The aim of this study is to define patterns of discordance between clinical and pathological T staging in multiple subsites of head and neck cancer.

Materials/Methods: A retrospective cohort of 580 surgically treated head and neck squamous cell carcinoma patients from a single institution is presented. cTN and pTN were compared in the overall cohort and at specific anatomical subsites, including the oral cavity, oropharynx, and larynx. Cohen's kappa (κ) statistic was used to assess the "inter-rater reliability" between cTN and pTN.

Results: Nearly 1/3 of cases had staging discordance. Cohen's kappa coefficient for the entire cohort was κ =0.55, indicating moderate agreement. Highly discordant stages/subsites with κ <0.45 included T2 oral cavity, T2 oropharynx, T3 larynx, and N1 neck. Oral cavity lesions T2-4 were often overstaged, and more than 1/3 of T3 larynx cancers were understaged. Highly concordant stages/subsites with κ >0.65 included T1 larynx, T4 oropharynx, N0 neck, and N3 neck.In general, there was higher concordance between cTN and pTN at the extremes of the staging systems (i.e. T1/N0 and T4/N3) while intermediate stages had higher discordance. Distribution of our cohort across each stage and Cohen's kappa coefficient for overall T and N stage are presented in the table. Groups with concordant clinical and pathologic stages are highlighted in blue. Highly discordant κ values (<0.45) are indicated by an asterisk, while highly concordant values (>0.65) are indicated by two asterisks.

Conclusion: Our results provide data on specific TN stages and anatomic sites where discordance is more likely to occur. Patients with discordant staging may initially receive inadequate counseling or inappropriate treatment. For example, since T3 larynx cancer was often understaged, less aggressive treatment may incorrectly be selected in this setting. The

opposite may be true in T2-4 oral cancer, which was often overstaged. Further investigation is warranted to improve clinical staging accuracy in the areas of highest discordance.

Abstract 216 − Table 1

Overall T stage	pT1	pT2	pT3	pT4	Total	% of total	κ
cT1	123	26	2	3	154	26.6	0.63
cT2	52	123	23	12	210	36.2	0.43*
cT3	4	14	49	17	84	14.5	0.50
cT4	2	23	12	95	132	22.8	0.66**
Overall N stage	pN0	pN1	pN2	pN3	Total	% of total	κ
cN0	130	19	23	0	172	57.0	0.66**
cN1	4	27	18	0	49	16.2	0.44*
cN2	5	6	63	3	77	25.5	0.57
cN3	0	0	0	4	4	1.3	0.72**

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Characterization of Heterotopic and Orthotopic Syngeneic MOC1 and MOC2 Tumor Models

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Purpose/Objective(s): MOC1 and MOC2 represent two human papillomavirus (HPV)-negative mouse oral carcinoma (MOC) models commonly used for preclinical studies of head and neck squamous cell carcinoma (HNSCC). While most publications employ subcutaneous heterotopic implantation of these cell lines, orthotopic models are increasingly being used to better recapitulate the tumor microenvironment of human HNSCC. However, the behavior of these tumor models based on location has not been well characterized. Here we present a comparison of time to tumor onset, tumor penetrance, and metastatic potential for MOC1 and MOC2 tumor models in heterotopic (subcutaneous vs intramuscular) or orthotopic (buccal) locations.

Materials/Methods: MOC1 or MOC2 cells in PBS were implanted heterotopically (MOC1: 1×10^6 cells, MOC2: 1×10^5 cells) in the subcutaneous (SC) flank (MOC1: n=20, MOC2: n=11), intramuscular (IM) hind limb (MOC1: n=29, MOC2: n=29) or orthotopically (MOC1: 3×10^6 cells, MOC2: 3×10^4 cells) in the buccal mucosa (MOC1: n=23, MOC2: n=29) of C57BL/6J mice. Mice were monitored and tumors measured ≥3x/week. Time-to-tumor onset and penetrance were estimated by Kaplan-Meier method and compared by log-rank test. Tumor growth curves were compared by 2-way ANOVA with Tukey's Post Hoc test. H&E-stained slides of lungs were analyzed by a veterinary pathologist blinded to tumor model.

Results: MOC2 had a shorter time-to-tumor onset compared to MOC1 in all models. In the buccal model, median time to tumor onset was 7.7 wks with 74% penetrance for MOC1 versus 2.1 wks with 97% penetrance for MOC2. In the SC model, tumor onset and penetrance were 6.4 wks and 55% for MOC1 and 1.4 wks and 100% for MOC2. In the IM model, tumor onset and penetrance were 13.7 wks and 52% for MOC1 and 1.1 wks and 97% for MOC2. Tumor growth curves showed a similar trend with MOC2 being more aggressive than MOC1 across all models. In the buccal model, MOC2 tumors grew significantly faster than MOC1 (p<0.0001), where MOC2 tumors were >2.5x the size of MOC1 tumors by Day 7 post-initial measurement. The SC and IM models showed similar differences with MOC2 growing significantly faster compared to MOC1 (p<0.0001 for SC, p=0.009 for IM). The MOC2 SC model grew the fastest with most tumors reaching volumetric endpoint (2000 mm^3) at least one week before any other heterotopic model. Lung metastases were observed in all three MOC2

models (25% buccal, 60% IM, 75% SC), as well as both heterotopic MOC1 models (50% IM, 12.5% SC), which has not been reported in the literature.

Conclusion: We demonstrate significant intra-model differences for MOC1 and MOC2 models based on location, indicating the importance of microenvironment on tumor behavior. Importantly, we found that MOC1 tumors, normally considered non-metastatic, can spread to the lungs in heterotopic models.

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Patient-specific 3D CT Images Reconstruction from 2D KV Images

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Purpose/Objective(s): In some proton therapy facilities, patient alignment relies on two 2D orthogonal kV images, taken at fixed, oblique angles, as no 3D on-the-board-imaging is available. The visibility of the tumor in kV images is limited since the patient's 3D anatomy is projected onto a 2D plane, especially when the tumor is behind high-density structures such as bones. This can lead to large patient setup errors. A solution to this problem is to reconstruct the 3D CT image from the kV images obtained at the treatment position.

Materials/Methods: An asymmetric autoencoder-like network built with vision-transformer blocks was developed. We trained a primary and a secondary model focusing on the reconstruction of the whole CT and head region, respectively. The following data was collected from head and neck cancer patients: 3 pairs of orthogonal kV images and the corresponding 3D CT-on-the-rails (CToRs) (i.e., the ground truth CT (gCT)) from different fractions. We introduced a data augmentation strategy termed as geometry property-reserved shifting to create more data samples, where the kV and gCT were simultaneously and arbitrarily shifted within mm. Moreover, the kV and gCT were geometry property-reserved resampled to small-size data pairs. For the secondary model, the gCT was cropped to focus on the head region before the resampling. Finally, the full-size synthetic CT (sCT) was formed by concatenating the outputs from two models based on their spatial relationship. The image quality of the sCT was evaluated using mean absolute error (MAE) and per voxel absolute CT number difference volume histogram (CDVH). 3D Gamma analysis of the CT numbers comparing the sCT to the gCT was done. Forward dose calculation was performed on the sCT and gCT using the same plan and compared using 3D Gamma analysis as well. Dose volume histogram indices of targets were compared as well. The robustness of the sCT against random shifts was tested through simulations mimicking patient alignment during treatment, where the model predicted the shifted sCTs given manually shifted kVs as input. The predicted shifted sCTs were compared with all the gCTs with known shifts and the one with the minimum MAE was considered as the closest matched CT (mCT). The difference of the associated shifts between the mCT and gCT was calculated as the shift error (SE).

Results: The model achieved a MAE of <30HU and the CDVH showed that <5% of the voxels had a per voxel absolute CT number difference larger than 128HU. 3D Gamma passing rates of 0.999 and 0.998 with

criteria of 3%/3mm and 2%/2mm were obtained in the CT number comparisons, respectively. We achieved 3D Gamma passing rates of 0.999 and 0.986 with criteria of 3%/3mm and 2%/2mm in the dose comparisons, respectively. The difference of CTV D$_{95}$ between the *sCT* and *gCT* was only 90 cGy[RBE]. The model yielded a mean SE of only 0.2 mm in the *sCT* robustness test.

Conclusion: A patient specific vision transformer-based network was developed and shown to be accurate and efficient to reconstruct 3D CT images from kV images.

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Do Spatial-Radiomics Improve Prediction of Locoregional Recurrence Following Radiotherapy for HNSCC?

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Purpose/Objective(s): Definitive chemoradiation for HNSCC has improved significantly with modern planning techniques and supportive care. However the locoregional recurrence risk (LR) persists and can range up to 30% depending on patient-specific factors. Prior research has used machine learning on radiomic features (or quantitative, sub-visual cues) from diagnostic imaging to predict LR with some success. In this study, we attempt to improve on these models by introducing 2 key innovations. First we identify "supervoxels," or sub-regions near but outside of the gross tumor volume (GTV), from which to extract radiomic features. Second we create a radiomic graph model where the supervoxels are prioritized based on their similarity to the GTV. We hypothesize that this spatial, graph-based approach can better identify regions suspicious for microscopic tumor involvement, which in turn would better predict clinical outcomes.

Materials/Methods: We identified the RADCURE (D1) and Head-Neck-Radiomics-HN1 (D2) datasets containing 2,611 patient CTs and RT structures from The Cancer Imaging Archive. D1 was divided into training, validation, and testing splits whereas D2 was used only for testing. For each patient CT, we identified 100 supervoxels within 10 voxels of the GTV. Texture-based radiomic features were then extracted from each supervoxel, and the top 20 with feature expression most similar (via Euclidean distance) to the GTV used to create a graph model. The nodes of this graph represent feature expression within the supervoxels and the edges the correlation to the GTV. Clinical features including age, sex, ECOG, chemotherapy use, tumor stage, size, and HPV status were used as a model parameter and baseline comparison. A graph attention neural network (GAT) was trained using these graphs for the LR prediction task. Comparisons were made with a traditional radiomic model and clinical features alone. Following prediction, model attention weights were extracted and used to identify which CT supervoxels were most informative to the model.

Results: Graph radiomics with clinical features resulted in AUCs of 0.834 and 0.806 for D1 and D2, respectively. Traditional radiomics with clinical features resulted in AUCs of 0.819 and 0.784 compared to clinical features alone achieving AUCs of 0.808 and 0.784. Qualitative examination of attention heatmaps revealed that our spatial radiomic model attention was heavily concentrated along cervical lymph node chains.

Conclusion: Spatial radiomics utilizing supervoxels from peritumoral areas were able to predict LR for HNSCC in large, multi-institutional datasets, outperforming other previously studied methods. It is notable that our model's performance did indeed improve on an already robust baseline for an independent test dataset, suggesting there is additional utility in our graph-based approach. Our attention maps further suggest that disease-relevant regions outside of the GTV can be identified in an unsupervised manner.

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Radiographic Predictors of Extranodal Extension on Preoperative Contrast-enhanced CT in Patients with Oropharyngeal Squamous Cell Carcinoma

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Purpose/Objective(s): Upfront treatment options for patients with oropharyngeal squamous cell carcinoma (OPSCC) include surgical resection or radiotherapy (RT). In surgically managed patients, extranodal extension (ENE) is an accepted indication for adjuvant chemoRT. Reliable methods to predict ENE using preoperative contrast-enhanced computed tomography (CECT) are needed to better select the initial treatment approach and avoid trimodality therapy.

Materials/Methods: Consecutive patients treated with surgical resection and neck dissection (ND) for OPSCC between 10/2012-10/2020 were identified. Exclusion criteria were recurrent/second primary disease, lack of preoperative CECT. Four fellowship-trained neuroradiologists reviewed preoperative CECTs and assessed the dissected neck side(s), blinded to the pathologic outcomes. Patients with bilateral ND had both sides of the neck evaluated individually. Each radiologist measured the following factors: axial and coronal/sagittal short/long axis, central necrosis, perinodal stranding, matted nodes, spiculation/irregular margins, absence of perinodal fat plane, infiltration of adjacent structures. ENE presence was based on the pathology report. Each factor was tested for association with pathologically confirmed ENE using univariate and multivariate models.

Results: In total, 162 patients with 206 neck sides were included in the analysis, 44 of which had ENE. Most patients had HPV-associated disease (90%) and tonsil/base of tongue tumors (98%). 4 neuroradiologists performed 824 individual neck assessments, 176 of which harbored ENE. On univariate analysis, all factors were significantly and consistently associated with ENE for all 4 radiologists. Various multivariate models were evaluated to best predict the risk of ENE based on these factors. The presence of matted nodes (odds ratio [OR] 6.45, p<0.0001) and spiculated/irregular nodal margins (OR 8.62, p<0.0001) were consistently associated with ENE on multiple models. After controlling for within-patient correlation, matted nodes and absence of perinodal fat plane were included in the model (p<0.03), as was infiltration of adjacent structures (p=0.08).

Conclusion: Multiple CECT nodal features associated with ENE are consistently identified by multiple radiologists. Matted nodes and spiculated/irregular nodal margins were found to be most strongly associated with ENE. These findings will guide the development of an accessible, clinically facile scoring system to predict the risk of ENE on preoperative CECT in the clinic or multidisciplinary tumor board.

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Detection of Minimal Residual Disease in Post-surgical Drain Fluid Synergizes with Pathology to Predict Recurrence in HPV-negative Head and Neck Cancer Patients

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Purpose/Objective(s): Locoregional cancer relapse remains a major cause of failure in head and neck squamous cell carcinoma (HNSCC), particularly for HPV-negative patients whose 3-year locoregional failure rate is 32.5%. There is major unmet need for an accurate diagnostic test that predicts risk of locoregional recurrence prior to adjuvant therapy selection. We present a novel proximal assay for minimal residual disease (MRD) profiled in lymphatic exudate collected via surgical drains ("lymph").

Materials/Methods: Lymph, plasma, and blood were collected from 46 HPV-negative HNSCC patients postoperatively at 24 hours along with resected tumor. Cell-free DNA was extracted from lymph and plasma and sequenced using the TruSeq Oncology 500 panel to a depth of >100 million reads. Somatic mutations were identified by exome sequencing (200x) tumor and blood. Nine patients had <2 somatic mutations in tumor and were excluded. Two patients were censored due to lack of clinical data, yielding 16 patients with disease recurrence (REC) and 19 with no evidence of disease (NED) with >1 year of follow-up. Two plasma samples were not available. Tumor-specific variants were force-called in lymph and plasma using a custom pipeline. Patients were considered MRD positive if the mean variant allele fraction (mVAF) was greater than 0.02% (the estimated limit of detection). Mann-Whitney U test was used for group comparisons. The Kaplan-Meier (KM) estimator with log-rank test and Cox proportional-hazards model were used for survival analyses. Logistic regression models were performed with 5-fold cross-validation.

Results: ctDNA levels were significantly higher in the lymph of REC patients compared to NED (median mVAF: REC = 0.041% ± 0.034%; NED = 0.013% ± 0.064%. p = 0.036), but not plasma (REC = 0.01% ± 0.15%; NED = 0% ± 0.02%. p = 0.53). KM survival analyses showed lymph accurately predicts recurrence (sensitivity (SN) = 81%, specificity (SP) = 63%; p = 0.004, Hazard ratio (HR) = 5.6). Performance was enhanced when the cohort was limited to locoregional relapse (SN = 91%, SP = 63%; p = 0.003, HR = 11.6. N=30). Lymph outperformed pathology features (extranodal extension, perineural invasion, lymphovascular invasion, and nodal disease status) as well as a logistic regression model of all 4 (SN = 62%, SP = 63%; p = 0.19, HR = 2.0). A model incorporating lymph MRD plus the 4 high-risk pathology features showed superior performance over either lymph alone or pathology alone (SN = 88%, SP = 68%; p = 0.001, HR = 8.3).

Conclusion: Postoperative ctDNA analysis of lymph from surgical drains represents a novel MRD approach in HPV-negative HNSCC. Lymph significantly outperforms plasma or a multi-feature pathology model for prediction of recurrence, particularly in patients with locoregional relapse. The observed synergy between lymph MRD testing and traditional pathology suggests that

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Investigating NRF2-Mediated Radioresistance in HPV-Negative Head and Neck Squamous Cell Carcinoma Preclinical Models

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Purpose/Objective(s): Head and neck squamous cell carcinomas (HNSCC) that are not driven by human papillomavirus (HPV) are associated with a higher likelihood of treatment resistance and recurrence compared to HPV-positive HNSCC. There are currently no genomic-guided treatments for HPV-negative HNSCC, meaning that patients do not benefit from precision medicine approaches. Thus, it is critical to understand the mechanisms underlying HNSCC progression to identify molecular targets and better stratify therapeutic options for patients. NFE2L2 encodes for nuclear erythroid 2-related factor 2 (NRF2), a transcription factor that plays a crucial role in responding to oxidative stress by regulating the expression of genes associated with cellular defense mechanisms. Mutations in NFE2L2 and its negative regulator, KEAP1, make up 25% of HPV-negative HNSCCs. Additionally, constitutive activation of NRF2 confers a growth advantage and causes resistance to chemo- and radio-therapy. We will elucidate the role of NRF2, identifying novel radiosensitizers to better guide therapeutic strategies for HPV-negative HNSCC patients.

Materials/Methods: Using clonogenic and long-term viability assays measuring radiation response, we identified radioresistant and radiosensitive cells in a panel of 19 HPV-negative SCC cell lines. An area-under-the-curve (AUC) metric was used to measure cellular response to multiple doses of ionizing radiation. Reactive oxygen species (ROS) and DNA double strand breaks (DSBs) were quantified using DCFDA and γH2AX assays, respectively. Radiosensitization was measured using the ΔAUC of varying drug doses of NRF2 inhibitor, ML385. NFE2L2 and KEAP1 were knocked down using RNA interference in radioresistant and radiosensitive cells, respectively.

Results: We identified 13 radiosensitive and 6 radioresistant cell lines out of the 19 HPV-negative SCC cell lines. There was a strong correlation between AUCs of the clonogenic and long-term viability assays (Pearson r=0.74, p=3.0×10^{-4}). Six cell lines were consistently radioresistant (AUC>3.5) in both assays. None of the cell lines contained mutations in the NRF2 pathway, and only 1/6 were radiosensitized by ML385 (ΔAUC=2); this effect was not correlated with ROS or DSBs, yet was abrogated by NFE2L2 knockdown. KEAP1 knockdown cell lines were generated for ongoing functional characterization and for genetic screens to identify radiosensitizers in HPV-negative HNSCC.

Conclusion: We aim to identify the role of NRF2 in the treatment response of HPV-negative HNSCC. Although NRF2 is an important pathway in driving a radioresistant phenotype, the majority of radioresistant cell lines were not sensitized by NRF2 inhibition. Therefore, elucidating the molecular underpinnings of NRF2-mediated therapeutic resistance will be critical to identifying novel radiosensitizers with activity in HPV-negative HNSCC.

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Imatinib plus Cetuximab as a Window of Opportunity Clinical Trial in Head and Neck Cancer

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Purpose/Objective(s): Cetuximab, an approved anti-EGFR receptor monoclonal antibody, is used for the treatment of metastatic cancer, often in conjunction with cytotoxic chemotherapy. It is also employed as a radiosensitizer in the context of definitive radiation therapy for locally advanced cases. However, overcoming resistance to cetuximab, whether intrinsic or acquired, represents a significant challenge in clinical practice. In preclinical studies, the identification of tyrosine 821 (Y821) on the C-terminal of AXL has been linked to resistance to both cetuximab and radiation therapy via signaling through the tyrosine kinase c-Abl. Blocking c-Abl signaling with the tyrosine kinase inhibitor imatinib restored sensitivity to cetuximab and radiotherapy, ultimately resulting in complete tumor regression without recurrence in models of head and neck cancer. In this clinical trial, we aim to translate these promising preclinical findings into clinical practice through a window-of-opportunity trial that evaluates the effects of combining cetuximab with imatinib in head and neck cancer patients.

Materials/Methods: This is a window-of-opportunity study conducted at a single center, involving patients diagnosed with head and neck squamous cell carcinoma who are undergoing treatment with surgery, radiation, or chemoradiation. A total of 15 patients will be recruited for this study. Participants will initially undergo a medical history review and physical examination and provide written informed consent. To be eligible, subjects must have sufficient tumor volume to allow for a minimum of two core research biopsies. The first research biopsy will be performed at baseline prior to therapy to analyze Ki67 and potential markers of sensitivity to cetuximab and imatinib. Simultaneously with the first research biopsy, research-related blood samples will be collected to assess circulating tumor cells through the course of the trial. Subjects will receive two doses of cetuximab as follows: a loading dose of 400 mg/m2 on Day 1 and 250 mg/m2 on Day 8. In addition, they will take 400 mg of imatinib orally daily for a period ranging from a minimum of 8 days to a maximum of 14 days before undergoing definitive surgery or definitive radiation/chemoradiation. Following the combined treatment with imatinib and cetuximab, subjects will undergo a second research blood draw and a research biopsy. The administration of imatinib will be discontinued 1-3 days prior to the second research biopsy. For patients undergoing surgical resection, this second research biopsy will be obtained during the surgical procedure. Patients will return for follow-up visits at 1, 3, and 12 months after completing definitive therapy to assess toxicities, monitor adverse events, and collect blood samples. Enrollment in the study is ongoing. NCT05816785

Results: TBD

Conclusion: TBD

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High Expression of Sphingosine-1-Phosphate Phosphatase 1 Inversely Correlates with p16 Expression and Is Associated with Poor Prognosis in Laryngeal Cancer Patients

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Purpose/Objective(s): While high protein expression of p16 is associated with better clinical outcomes and a less aggressive phenotype in larynx cancers, the molecular mechanisms underlying the association of p16 over-expression and improved survival in larynx cancer remain to be defined. We hypothesized that p16 protein expression levels are associated with distinct cellular pathways and clinical outcomes in larynx cancer.

Materials/Methods: Clinical data and mRNA expression levels of The Cancer Genome Atlas (TCGA) patients with larynx cancer were downloaded from CBioPortal. We divided the patients into p16 low, medium, and high cohorts based on mRNA expression level. We performed differential gene analysis using DESeq2 with an adjusted p-value of 0.05. Differentially expressed genes from the p16 low and high groups were imported and analyzed by the open-source, open-access pathway database REACTOME. Kaplan-Meier estimates were used to determine the impact of individual genes from REACTOME-defined pathways on clinical outcomes. Chi-square was used to compare the clinical characteristics of patient cohorts.

Results: We identified 209 differentially expressed genes using p16 low and high cohorts. REACTOME analysis demonstrated an association of lipid metabolism as defined by the genes ACER3, SGPP1, ELOVL3, ARSI, and CIDEA with the p16 low cohort. Median progression-free survival was 2.4 years in the SGPP1 high cohort and not reached in the SGPP1 low cohort (p<0.01). Median overall survival was 2.3 years in the SGPP1 high cohort and 6.3 years in the SGPP1 low cohort (p=0.09). The SGPP1 high cohort was more likely to exhibit extranodal extension (52%) compared to the SGPP1 low cohort (26%, p<0.05).

Conclusion: High expression of p16 by larynx cancers, commonly associated with better clinical outcomes, may be related to the differential expression of lipid metabolism genes, such as SGPP1, which is inversely correlated with p16 expression and survival. Indeed, over-expression of SGPP1 is associated with worse clinical outcomes and a more aggressive phenotype in larynx cancers. External validation of these findings is warranted to define further the role of SGPP1 in larynx cancer development, progression, and treatment response.

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Histone/Lysine Acetylation as a Target for Sensitization in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): CREBBP and EP300, encoding for CBP and p300 respectively, are highly homologous multifunctional histone/lysine acetyl-transferases (HATs or KATs) that are mutated in ~15% of Head and Neck Squamous Cell Carcinoma (HNSCC) and these mutations are associated with clinical recurrence and poorer survival following radiation. We found that some of these mutations demonstrate gain-of-function (GOF) related to increased HR-mediated DNA damage repair (DDR). We hypothesize that targeting GOF mutations in HATs/KATs sensitizes HNSCC through induction of a BRCA-like phenotype with decreased DNA repair, increased sensitivity to PARP inhibition, and enhanced immunogenic cell death through a synthetic lethal interaction. .

Materials/Methods: UM-SCC-22A (CREBBP GOF mt), HN31 (CREBBP wt) cells, and HN31 cells with CRISPR knock-in CREBBP GOF mts were used to perform Proximity Ligation Assays (PLA), immunoprecipitation, immunofluorescence staining for DNA damage foci, direct HR and NEHJ assays, TUNEL staining, and calreticulin (CRT) translocation FACS analysis. For in vivo studies, UMSCC22A cells were injected subcutaneously on the flank of Nu/Nu mice and treated with 8 fractions of 2 Gy +/- 100 mg/kg/d of a HAT/KAT inhibitor specific for CREBBP/EP300 (A-485) in development for clinical use.

Results: The combination of HAT/KAT inhibition and conventionally fractionated radiation (conRT) in a GOF mt CREBBP HNSCC model led to a profound tumor growth delay. A-485 had no effect on its own, but when delivered concurrently with conRT it led to a 40-50% reduction in tumor volume at Day 10 post-completion of treatment versus vehicle (p=3.9e-5) and either A485 (p=3.35e-5) or conRT (p=1.6e-3) alone. Separately, in vitro analysis revealed that mutant CREBBP directly interacts with BRCA1 in a radiation-dependent fashion, with this interaction significantly greater than that observed in wild-type CREBBP, leading to increased BRCA1 acetylation. Forced expression of GOF CREBBP mutant(s) in wild type HN31 cells increased HR activity, BRCA1 acetylation and radiation-associated foci, which was abrogated by HAT/KAT inhibition. The potential BRCA-ness of this phenotype was evaluated via apoptosis assays which found a synergistic effect of A-485 and Olaparib in CREBBP GOF mt cells not observed in wt cells. Additional studies found that the combination of radiation and A-485 enhanced CRT translocation in mutant CREBBP HNSCC but failed to do so in wild-type CREBBP lines.

Conclusion: HAT/KAT inhibition in CREBBP/EP300 GOF mutant HNSCC leads to increased sensitivity to therapy, possibly via an induction of a BRCA-ness phenotype. Moreover, the combination of HAT/KAT inhibition and DNA damage may be associated with increased immunogenic cell death, with experiments incorporating immune checkpoint blockade currently ongoing.

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Generalized Pairwise Comparisons Method to Assess Total Severe Oral Mucositis Burden and Interventional Benefit in HNC

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Purpose/Objective(s): Severe oral mucositis (SOM, WHO Gr 3-4) is a common and debilitating side effect of intensity-modulated radiation therapy (IMRT) and concurrent cisplatin (CRT) in patients with head and neck cancer (HNC). Patient SOM burden is defined by multiple endpoints (incidence, duration, severity and time to onset) and it is critical to consider all in a "holistic" approach rather than a single endpoint. Generalized pairwise comparisons (GPC) statistical method allows combined assessment, while accounting for testing multiplicity. Two placebo (PBO)-controlled trials (phase 2b and phase 3 ROMAN) showed avasopasem manganese 90mg (AVA) significantly decreased individual endpoints of SOM incidence and duration, with nominal decrease in severity (WHO Gr 4 incidence) and delay in SOM onset. We sought to determine combined Net Treatment Benefit (NTB) of AVA vs. placebo (PBO) for both trials across these 4 key clinically relevant endpoints using GPC.

Materials/Methods: Post-hoc meta-analysis of oral cavity and oropharynx patients in phase 2b (AVA = 76, PBO = 74) and ROMAN (AVA = 241, PBO = 166), stratified by cisplatin schedule (QW vs Q3W) and treatment setting (definitive vs post-op). GPC permitted simultaneous analysis of several prioritized outcomes (endpoints), comparing all possible pairs of 1 active (i.e., AVA) patient and 1 control (i.e., PBO) patient on first outcome, assigning Win, Loss or Tie to AVA per pair. Tied pairings moved on to the next outcome. Outcomes were prioritized as: 1) WHO grade 4 OM incidence (Severity), 2) SOM incidence, 3) days of SOM (Duration), 4) days to SOM onset; with 7 days difference defined as the clinical relevance threshold for (3) and (4). NTB = Wins - Losses on each outcome and combined; 1/NTB = Number Needed to Treat (NNT). Each trial was analyzed separately and integrated in a meta-analysis.

Results: Number of pairs analyzed: phase 2b = 1601, ROMAN = 13969. AVA showed significant NTB on each key outcome and all contributed meaningfully to combined NTB. Phase 2b GPC showed AVA combined NTB of 0.207 (P=0.025) and ROMAN GPC showed AVA combined NTB of 0.189 (P=0.001). Meta-analysis results (Table) show AVA NTB of 0.194 in favor of AVA (P <0.001), resulting in NNT of 1/0.194 = 5.15 patients.

Conclusion: GPC method allows holistic analysis of SOM burden in HNC patients receiving concurrent cisplatin and IMRT. Phase 2b and ROMAN individual GPC analyses and integrated GPC meta-analysis show compelling evidence of AVA clinical benefit as a therapeutic for SOM. Funded by Galera Therapeutics, Inc; ClinicalTrials.gov NCT NCT02508389 & NCT03689712.

Abstract 226 − Table 1: GPC Meta-analysis of Phase 2b and ROMAN Results

	Outcome	Wins	Losses	Ties	Wins-Losses	NTB	P-value
1	Severity	0.256	0.157	0.587	0.100	0.100	0.011
2	SOM Incidence	0.144	0.105	0.337	0.039	0.138	0.003
3	SOM Duration	0.093	0.057	0.187	0.036	0.175	<0.001
4	SOM Onset	0.037	0.017	0.133	0.019	0.194	<0.001
	Total	0.530	0.336	0.133	0.194	0.194	<0.001

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Comprehensive Genomic Characterization of Thyroid Cancers: Real-world Implementation and Impact on Clinical Decisions

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Purpose/Objective(s): With the introduction of targeted therapeutic options for advanced thyroid cancer, molecular characterization has become an important clinical tool for decision making. This is a real-world study to evaluate how next-generation sequencing (NGS) informs treatment decisions and clinical outcomes in advanced thyroid cancer.
Materials/Methods: Patients with advanced or incurable thyroid cancer who were suitable for systemic therapy were offered NGS testing as part of a province-wide multi-centre study since April 2021. Using the AmpliSeq Illumina Focus Panel, 52 key genes were interrogated for SNVs, indels, fusions, and CNVs. Tier-based classification of actionability was based on AMP/ASCP/CAP guidelines. Electronic medical records were reviewed to collect patient demographics, clinicopathologic data, and treatment histories. Descriptive statistics were used. Median overall survival was calculated by the Kaplan Meier method.
Results: Between April 2021 and April 2023, NGS was performed on 118 cases of advanced thyroid cancers. Table 1 summarizes histological distribution, baseline characteristics, genomic alterations, and impact on systemic therapies. For patients with papillary thyroid carcinoma (PTC, n=53) the most common actionable alteration was *BRAF V600E* mutation (47%), followed by 9% *RET* fusions and 4% *NTRK* fusions. In this population, 42% have received standard lenvatinib and 13% have received genotype-matched targeted therapy. Actionable variants were not commonly identified in patients with follicular thyroid carcinomas (FTC, n=27). Among patients with anaplastic thyroid carcinoma (ATC, n=16), 38% had *BRAF V600E* alterations, with a high rate (4/6) of triggering genotype-matched BRAF+MEK inhibitor therapy (25%). Among patients with medullary thyroid carcinoma (MTC, n=16), 81% had *RET* mutations, 4/13 of which received genotype-matched RET inhibitor therapy thus far. There were too few poorly differentiated thyroid cancers (PDTCs) to make generalizations at this time.
Conclusion: In our real-world study, NGS testing revealed high rates of Tier I-II actionable genomic alterations in PTC (77%), MTC (81%), and ATC (31%). NGS-identified *BRAF V600E* mutations in ATC has a high rate of triggering matched targeted therapy. NGS identification of RET-mutated MTC facilitated use of RET inhibitors. Longer follow-up is required to investigate whether NGS-informed treatment strategies translate into population-level overall survival benefits.

Abstract 227 − Table 1

	PTC (53)	FTC (27)	MTC (16)	ATC (16)	PDTC (6)
Median age at diagnosis (y) Sex, M:F	58 43:57	57 22:78	54 81:19	64 44:56	63 67:33
Tier I *BRAF V600E* mutation	64%	0	0	38%	17%
Tier I *RET or NTRK* fusions	13%	0	0	0	0
					(Continued)

(Continued)	PTC (53)	FTC (27)	MTC (16)	ATC (16)	PDTC (6)
Tier I *RET* mutations	0	0	81%	0	0
Non-actionable variants (Tier II-V)	17%	59%	13%	19%	67%
No variants identified	4%	37%	0	38%	17%
Failed sample	2%	4%	6%	6%	0
Median followup (days) Deceased	424 26%	614 11%	544 6%	112 81%	382 17%
Genotype-matched therapy Standard therapy	13% 42%	0 74%	25% 19%	25% 19%	0 50%

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Integrative Single-Cell RNA-Seq, Single Cell ATAC-Seq, and Spatial RNA-Seq Analysis of Heterogeneity in HPV-Related Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): Human papillomavirus (HPV) integration into the human genome is an established driver event in head and neck squamous cell carcinoma (HNSCC). Functionally, HPV oncogenic proteins inhibit tumor suppressor proteins and activate proliferation of infected epithelial cells. Despite seeming homogeneous, individual epithelial cells among a tumor may have significant cellular and molecular heterogeneity which could affect treatment outcomes. This study aimed to better characterize the single cell molecular heterogeneity within HPV-positive HNSCC.
Materials/Methods: Using a well-characterized HPV-positive HNSCC cell line (UM-SCC-47) we performed integrated single cell multiome RNA (scRNA-seq) and ATAC sequencing using 10x and sequencing platforms. Integration site analysis was done using multiple sequence alignment. Multimodal analysis was then performed using the Seurat package. Molecular profiling from sections of four HPV-positive primary tumors was also

performed using the Visium Spatial Platform from 10X Genomics. Cell type identification analysis was performed using SpaceXR. HPV-associated phenotype enrichment was resolved relative to the HPVon signature derived from Puram et al., Nature Genetics, 2023.

Results: Using single cell ATAC-seq data we performed multiple sequence alignment with the transitive consistency score to demonstrate the HPV16 integration at a single cell level. This showed that there are two integration sites for HPV (3:189879025, 3:189895061). Using scRNAseq we also demonstrated that *TP63* expression is positively correlated with *E7* expression (R2 = 0.676). Other HPV-associated genes include KTN1 (R=0.43), ALDH1A3 (0.42), PTMA (0.41), and VMP1 (0.40). Spots containing an enriched HPVon signature also have enrichment of multiple gene sets including, MYC signaling (R=0.77), E2F transcription (R=0.65), and G2-M DNA damage checkpoint (R=0.63). Within the cell type identification analysis, after normalizing by tumor proportion greater than 50%, additional gene set analysis showed enrichment of cytoskeletal regulation and cell adhesion pathways.

Conclusion: Typically, HPV-associated HNSCC has better prognosis than other forms of HNSCC. Recently, there has been a trend towards treatment de-escalation for patients with the goal to maintain excellent prognosis and minimize treatment side-effects. However, our study supports the emerging hypothesis that high levels of intra-tumoral heterogeneity may be a critical feature of HPV-associated HNSCC that will fail therapy. Our multi—omics single cell analyses show there is significant heterogeneity in HPV expression which should be considered in future biomarker studies.

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Tumor Mutational Burden Predicts Survival in Merkel Cell Carcinoma

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Purpose/Objective(s): In Merkel cell carcinoma (MCC), clinical factors, including advanced age and immunosuppression, are variably prognostic and poorly predictive of treatment response. There is a clear need for robust genetic markers of aggressive disease to inform treatment selection and prognostication. In a cohort of 54 MCC patients, we assessed the impact of tumor mutational burden (TMB), single nucleotide (SNV) and copy number variations (CNV), and Merkel Cell Polyomavirus (MCPyV) integration on MCC-specific survival outcomes.

Materials/Methods: Genomic DNA was harvested from paraffin-embedded tissue blocks obtained from patients with biopsy-proven MCC of any anatomic subsite. A total of 54 patients with MCC were included from 2016 — 2019. We performed targeted exome sequencing of a 226-gene panel on a sequencing platform and used our established bioinformatics pipelines for *targeted* TMB, SNV, CNV, and MCPyV integration site calls. We then assessed the prognostic impact of specific genetic alterations on MCC-specific survival using Kaplan-Meier curves and Cox regression.

Results: Demographic and clinical characteristics of our cohort are shown in the **Table**. Median (range) follow-up duration after treatment completion was 43 (1 — 78) months. Five-year MCC-specific survival was 75 % (95 % CI: 56.5 — 85.9%). The median (range) *targeted* TMB was 1 (0 — 69). Frequently altered genes included *LRP1B* (n = 10, 18.5 %), *FAT1* (n = 9, 16.7 %), *KMT2D* (n = 9, 16.7 %), *RB1* (n = 7, 13.0 %), and *ABL1* (n = 6, 11.1 %). In 36 of 44 (81.8 %) MCPyV-positive cases, virus was integrated into the host genome with a median (range) of 2 (1 — 30) distinct integration events. In six tumors, MCPyV integrated into COSMIC Tier 1 or Tier 2 cancer-related host genes, thus possibly altering their native function, including *ABL2, BLM, HIF1A, KMT2A, MYCL,* and *TET2*. A receiver

operating characteristic curve was used to identify a *targeted* TMB = 13 as a cut-point to maximize differences in MCC-specific survival. Using this cut-point, a higher *targeted* TMB strongly predicted MCC-specific survival (*p* = 0.001), even when controlling for clinical nodal status. Tumor MCPyV status, virus state (i.e., integrated vs episomal), and specific SNV/CNVs did not predict MCC-specific survival.

Conclusion: Higher tumor mutational burden portends worse survival in MCC and may be a clinically useful biomarker of treatment response and for prognostication for this challenging disease.

Abstract 229 — Table 1

Characteristic	Cohort (n = 54)
Age, y	73 (38 — 97)
Female Sex	18 (33.3)
Immunosuppression	5 (9.3)
Site of Primary Tumor Head/Neck Other	15 (27.8) 39 (72.2)
Stage at Diagnosis I/II III/IV	20 (37.0) 34 (63.0)
Tumor MCPyV Status Positive Negative	44 (81.5) 10 (18.5)
Recurrence After Treatment Locoregional Distant Locoregional & Distant	12 (24.5) 4 (8.2) 4 (8.2) 4 (8.2)
Vital Status Alive Died of Disease Died of Other/Unknown Cause	38 (70.4) 11 (20.4) 5 (9.2)

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Characterization of Oral Cavity Microbiome in Patients with OCSCC

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Purpose/Objective(s): Known risk factors for head and neck squamous cell carcinoma (HNSCC) include history of tobacco and/or alcohol use, and persistent HPV infection. Some individuals develop HNSCC without any known risk factors, suggestive of another source contributing to these malignancies. One hypothesis involves the microbiome of these patients, which may contribute to the development and progression OCSCC through metabolic, inflammatory, and/or immune-modulating effects. The oral cavity has a unique microbiota made up of approximately 700+ known microbial species. Studies have shown an association between poor oral hygiene and tooth loss with cancer, implicating the oral microbiome in the development of tumors. Our aim is to characterize and investigate the role of the microbiome in oral cavity squamous cell carcinoma (OCSCC). We swabbed different areas of the oral cavity in patients with OCSCC, pre-malignant lesions, and healthy controls.

Materials/Methods: From 2020 to 2023, we swabbed the buccal mucosa, tongue and tumor of patients with OCSCC and controls. Samples were analyzed using 16S ribosomal RNA gene sequencing. Alpha and beta diversity were calculated using Faith's phylogenetic index and compared between cohort using a two-sided t-test.

Results: 91 patients (45 patients with OCSCC, 13 with pre-malignant lesions, 33 controls) were included in our analysis. Patients with OCSCC had significant differences in alpha diversity compared to controls (p=0.018). There was no significant difference in alpha diversity between controls and pre-malignant lesions. Patients with OCSCC had slight differences in beta diversity compared to controls, approaching significance

(p=0.030) and no significant difference compared to pre-malignant lesions (p=0.498). Patients with OCSCC were more likely to harbor Neisseriacea species compared to pre-malignant patients and controls.

Conclusion: This is the first study to date to compare the oral cavity microbiome in patients with OCSCC, pre-malignant lesions, and controls. Here, we show there are significant differences in alpha diversity in patients with OCSCC compared to patients with pre-malignant lesions and controls, meaning patients with OCSCC are more likely to have less diversity of their oral cavity microbiome compared to patients with pre-malignant lesions and controls, implicating microbial dysbiosis as a potential driver of tumor growth/progression.

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Clinical Utility of Pre-Treatment and Surveillance Circulating Tumor Tissue Modified Viral HPV DNA to Detect Recurrence in a Community Based HN Cancer Program

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Purpose/Objective(s): Circulating tumor tissue modified viral (TTMV)-HPV DNA is a tool to aid in the diagnosis and surveillance of patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). Our site was one of the early adopters of the use of TTMV-HPV DNA in a community-based hospital setting, with most of our patients receiving pre- and post-treatment testing.

Materials/Methods: A total of 401 TTMV-HPV DNA assays (liquid biopsies) were prospectively collected on 115 Pts with OPSCC between 2020 and 2023. Initial HPV status was assessed by p16 marker and then by TTMV-HPV DNA assay. Test results were correlated with imaging to assess clinical utility.

Results: The median age of this cohort was 65 years (range: 27-83) with most pts having involved nodes at initial diagnosis (92%). In contrast to other studies, a relatively high proportion of Pts in this cohort were female (21%). All Pts were treated with curative-intent with surgery and risk adaptive adjuvant/neoadjuvant therapies or with definitive chemo-radiation alone. 43% received standard chemo-radiation course, and six patients (5%) received de-escalated dose via the DART regimen. Median follow-up was 14.8 months. The majority of pts had pretreatment testing (87%) with median TTMV of 757 (range: 7 - 407,471). The scores of males and females were not statistically significantly different (t-test of log10-transformed scores, p=0.9). The pretreatment sensitivity of the p16-positive cohort was 88.2% (95% CI: 80.9 - 95.4%). These results correlate well with the combined data of seven other studies published by large academic centers, which showed a sensitivity of 90.4% (95% CI: 87.4 - 93.4%). In pts with a positive pretreatment test, 93% had their score resolved to zero within 3 months after initial treatment and none exhibited clinical evidence of residual disease on imaging. Pts with N2-N3 disease were less likely to achieve test resolution than Pts with N0-N1 disease (Fisher's exact test, p = 0.0294). Surveillance tests were primarily collected every three months after treatment completion for the first two years and every six months thereafter with a median of 3 tests (range: 1-11). Currently, two Pts tested TTMV-HPV DNA positive without clinical detection of recurrence who were treated with the DART regimen. Both Pts are without radiographic recurrence and remain under active surveillance.

Conclusion: As one of the earliest community-based HN-MDC programs to adopt both Pre- and Post treatment TTMV-HPV DNA testing for HPV-

OPSCC, our findings are in line with larger academic centers and support the clinical utility of TTMV-HPV DNA testing in the setting of a community-based practice. The higher percentage of women in our cohort is unusual. Furthermore, although there was no statistical significance comparing pre-treatment test sensitivity in female and male subgroups, there was a trend toward lower sensitivity in females and warrants further investigation in a larger cohort.

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Tumor Genomics and the Association with Survival in Recurrent/metastatic Head and Neck Cancer Patients

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Purpose/Objective(s): Recent research has categorized the genetic make-up of head and neck squamous cell cancers (HNSCC) at initial presentation. However, despite advances in treatment, up to 50% of patients develop a recurrent/metastatic (R/M) disease, with a significant decline in survival at that time. Here, we aim to analyze the genetic composition of patients with R/M HNSCC to establish the most frequent alterations in this population and determine if there are associations with survival.

Materials/Methods: We performed an IRB-approved retrospective analysis of patients with confirmed recurrences of head and neck cancer after treatment for curative intent. We collected clinical data from one institution's electronic health records. Patients were grouped into cancer locations [oropharynx, oral cavity, hypopharynx, larynx, naso-pharynx]. Targeted DNA sequencing of the tumor samples was performed by Tempus. R square analysis was done to compare tumor genetic make-up.

Results: To date, a total of 44 patients with head and neck cancer recurrences were included in the analysis. 43.5% of patients had oral cavity cancer, and 32.6% of patients had oropharynx cancer. Seventeen patients (39%) were p16 positive. The median age at the time of diagnosis was 62.5 years (range 36-82), and the majority of patients were male (n=28, 64%). Twenty-four patients (54%) had a current or former smoking history. The median overall survival time was 721 days from the date of diagnosis. The median disease-free survival was 198 days. Survival rate of the entire cohort was 27.2% at the time of analysis. The most common mutation seen in the cohort was TP53, which was present in 29 patients (65%) and was associated with worse overall and disease-free survival. TERT and CDKN2A mutations were seen in 16 patients (36%), but were not associated with outcomes in this small sample size. Notably, both TERT and CDKN2A mutations are less common for the primary HNSCC diagnosis. Additional alterations were noted in PIK3CA (found in 20% of patients) and LRP1B (found in 9% of patients); while the former is associated with better overall survival, the latter was strongly associated with worse disease-free survival.

Conclusion: In the analysis of the R/M HNSCC cases, we identified genomic alterations similar to those found during primary diagnosis. While HNSCC cancers are genetically heterogeneous, alterations in TP53 remain the most commonly noted. R/M HNSCC populations commonly have CDKN2A and TERT mutations that are rarely found in primary diagnosis. In addition, mutations in LRP1B were associated with worse disease-free survival. Further analysis is ongoing to define the correlation between the mutational landscape of our patients and their response to therapy.

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A Novel Immunocompetent Preclinical Mouse Model to Uncover Oncogenic Initiators of Head and Neck Cancer

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Purpose/Objective(s): Mouse models of HNC have played an essential role in elucidating mechanisms driving tumor development and progression. However, the generation of new mouse models are extremely costly, laborious and time consuming, and are limited to the study of a few, and often "popular," gene targets that do not fully recapitulate the intertumoral heterogeneity of HNCs. Using a novel preclinical model developed in our lab that involves the *in vivo* introduction of human-relevant HNC mutations by CRISPR-mediated gene editing, we aim to functionally interrogate and reveal molecular pathways and mechanisms driving tumor initiation and progression, and to test the highly intriguing, but as yet unproven, hypothesis that HNC initiation is driven by the acquisition and accumulation of mutations in somatic tissue stem cells and their progeny, a process of mutagenesis that may be influenced by sex and accelerated following carcinogen exposure.

Materials/Methods: Our data shows effective AAV transduction and targeted mutagenesis of multiple stem cell lineages (epithelial stem cells, mesenchymal stromal cells, and muscle stem cells) by numerous AAV serotypes after local AAV injection into the tongue, oral epithelium, pharynx/esophagus, and neck. Delivery of a custom AAV-CRISPR-library (10 sgRNAs/gene), targeting the 20 most frequently mutated genes in human HNCs, into male and female mice (n=32) conditionally expressing Cas9 in a lineage-selective manner, produced morphologically and anatomically distinct tumors that recapitulate the genetic heterogeneity and sex-variant emergence of human HNCs.

Results: Individual tumors show distinct combinations of missense (M), nonsense (N) and silent mutations in targeted genes that also are mutated in human HNCs (sample type [tumor vs PAT]: p<0.0001; mutation type [missense vs nonsense vs silent]: p<0.0001; anatomic location: p<0.0001) Molecular sequencing analysis from AAV-CRISPR-HNC tumors (n=29) reveal striking genetic diversity and high mutational burden that is reminiscent of human HNCs. Sequencing analysis from paired adjacent tissue (PAT; n=29) provides evidence of an intermediate precancerous state and field cancerization and points to a subset of the genetic targets in our custom library as particularly consequential for stem cell transformation in this model (gene, p<0.001; mutation type, p<0.001; anatomic location, p<0.001). Frameshift insertions/ deletions accounted for the majority of INDELS observed (>50%; p<0.0001), and further supports the use of our platform to introduce loss of function mutations in HNC tumors.

Conclusion: Taken together, our data suggests for the first time that somatic stem cells can serve as cells-of-origin for multiple, different HNC subtypes, and that HNCs may represent clonal diseases. Future applications of this innovative and translationally-oriented system will help to nominate new therapeutic targets and create a springboard for efforts to prevent and treat HNC.

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Altered Oral Bacteria Abundance Associated with Disease Specific Survival in Oral Squamous Cell Carcinoma

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Purpose/Objective(s): The oral microbiome is altered in the presence of oral squamous cell carcinoma (OSCC). It is unknown if clinical outcomes, such as disease specific survival (DSS), are associated with differences in the abundance of select bacterial genera. The aim of this study is to determine if there are microbiome differences based on DSS in OSCC using The Cancer Microbiome Atlas (TCMA) and an in-tandem analysis of a prospectively collected database.

Materials/Methods: TCMA is a publicly available database containing curated, decontaminated microbial profiles for tumors from 1,772 patients. Data utilized from this database was limited to microbiome profiles and clinicopathologic features for OSCC patients. Separately, our institution collects oral swab samples from OSCC tumors prior to surgical treatment for 16S rRNA sequencing and follows outcomes prospectively. Statistical analysis was performed using R Studio. Predictor variables for DSS were analyzed using logistic regression models reported with hazard ratio (HR) and 95% confidence interval (CI). R Studio was used to plot Beta Diversity and PCoA using Vegan package, and the Wilcoxon signed-rank and Kruskal-Wallis test were performed to evaluate differential abundance between the bacterial genera. Statistical significance was defined as p<0.05.

Results: One hundred five patients with OSCC were included from TCMA with a mean age of 60 (std 13, min 19, max 90), 65% male (N=68) and 92% white (N=95) with diverse oral cavity primary sites with oral tongue most common (N=55, 52%). Twenty-eight (26%) were Stage I-II and 77 (74%) were Stage III-IVA. There were no patients with distant metastases. Rates of lymphovascular invasion (LVI) were 23% (N=18), perineural invasion (PNI) were 56% (N=47) and microscopic or gross extranodal extension (ENE) were 26% (N=20). Negative surgical margins occurred in 83 patients (84%), and the majority had no prior cancer diagnosis (N=100, 95%). Forty-one patients (59%) were disease free with a mean follow up of 35 months (std 31, min 2.2 months, max 173 months). Clinicopathologic features that were predictive of DSS included ENE (HR 2.73, 95% CI 1.18, 6.34, p=0.019) and being a current smoker (HR 3.12, 95% CI 1.08, 9.04, p=0.036). There were 40 bacterial genera identified in TCMA for OSCC tumors. No difference was observed in beta diversity between patients with recurrence versus no recurrence. Examining relative abundance of bacterial genera revealed that *Leptotrichia* (p=0.023) and *Haemophilus* (p=0.045) were differentially enriched based on DSS. Preliminary analysis of a prospectively collected database of OSCC microbiome oral swab samples also showed that changes in the relative abundance of *Leptotrichia* (p=0.00002) and *Haemophilus* (p=0.00023) were associated with recurrence.

Conclusion: Changes in the relative abundance of select oral bacteria genera are associated with recurrent OSCC. Shifts in the microbiome are seen prior to surgical treatment and may be predictive of clinical outcomes.

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Combination of Upfront Systemic Therapy and Radiation in Advanced Non-Melanoma Skin Cancer

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Purpose/Objective(s): Checkpoint inhibitors and hedgehog inhibitors have shown promising results for treatment of locally advanced cutaneous

squamous cell carcinoma (cSCC), Merkel cell carcinoma (MCC), and basal cell carcinoma (BCC) in the neoadjuvant setting. Given high clinical response rates to systemic therapy, we evaluated the role of upfront systemic therapy followed by consolidative radiation as a potential treatment strategy for those anticipated to suffer significant surgically-related morbidity. Herein, we describe our experience using upfront systemic therapy in combination with radiation in advanced non-melanoma skin cancer (NMSC) with 100% complete clinical response.

Materials/Methods: A retrospective cohort study was performed of patients with advanced NMSC treated with systemic therapy with definitive radiation, approved by IRB protocol #806937. Patients had disease that was deemed unresectable, resectable with significant morbidity, or were poor surgical candidates. Patient and disease characteristics, treatment information and response, and outcomes are reported. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to assess radiographic response in those with available post-treatment imaging.

Results: Between 2020 and 2023, 17 patients received treatment with upfront systemic therapy followed by radiation. Of 8 cSCC patients, 7 were treated with cemiplimab and 1 with pembrolizumab. cSCC patients underwent a total of 14.3 ± 8.3 treatment cycles (mean $\pm$ SD) with first documented clinical response at 23 ± 6 days. All 7 BCC patients were treated with sonidegib for a duration of 205 ± 150 days with first documented clinical response at 37 ± 9 days. Two MCC patients were treated with pembrolizumab for 13 and 6 cycles, both with first documented clinical response at 22 days. All 17 patients experienced a complete clinical response on physical exam. On RECIST evaluation of patients with available imaging, 5 had complete and 2 had partial radiographic responses. To date, all patients who have completed treatment remain in remission. One cSCC patient treated with cemiplimab developed hepatitis that resolved with immunosuppression; another treated with pembrolizumab developed dermatitis and colitis not requiring intervention. Sonidegib dosing frequency was reduced from daily to every-other-day due to toxicity in 3 patients.

Conclusion: This ongoing work demonstrates the high efficacy of upfront systemic therapy followed by consolidative radiation for advanced NMSC, with a durable 100% complete clinical response in all patients with available follow-up. In select patients with clear clinical response to systemic therapy, consolidative radiation is a safe and effective strategy for treating advanced NMSC while avoiding surgery. Future studies will evaluate long-term durability of this novel treatment strategy.

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Sinonasal Melanoma Patterns of Care and Outcomes in the Contemporary Therapeutic era: A High-volume Single Institution Experience

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Purpose/Objective(s): Sinonasal melanoma (SNM) is a rare mucosal malignancy with poor outcomes. We sought to assess how clinicopathological features and therapy choices influence outcomes in a cohort of SNM patients (pts) treated at our institution in the immunotherapy era.

Materials/Methods: Using an institutional database we identified 34 SNM pts who were non-metastatic at diagnosis and underwent surgical resection between 2016-2023 with at least one post-treatment follow-up. Outcomes

were calculated using the Kaplan-Meier method with univariate predictors assessed by log-rank test.

Results: Median age was 67 yrs (IQR 58-74) with slight female preponderance (53%, n=18). Tumor locations at diagnosis were nasal only (n=18, 53%), sinonasal excluding base of the skull (BOS) (n=10, 29%), or with BOS involvement (n=6,18%). Two patients had nodal disease (N+) at diagnosis. All but 4 patients (88%) had mutational testing with 33% (n=10) carrying oncogenic NRAS, 7% (n=2) KIT, and 7% (n=2) BRAF. Endoscopic endonasal resection was the most common surgery (n=28, 82%). Twenty pts (59%) underwent upfront surgery with 29 (85%) receiving adjuvant radiation therapy (RT) and 11 (32%) receiving adjuvant systemic therapy. Fourteen pts (41%) received 1-4 cycles neoadjuvant Ipilimumab and Nivolumab (Ipi/Nivo). In the setting of progression on neoadjuvant Ipi/Nivo, one patient proceeded to RT followed by 6 cycles of Carboplatin/Paclitaxel. Including this patient who received pre-operative RT and chemotherapy, 4 pts (29%) had pathologic evidence of response to neoadjuvant therapy. With a median follow-up of 28 months from treatment start (IQR 10-57). 2-yr event rates were: 66% local control (LC), 68% nodal control, and 38% progression-free survival (PFS). RT was associated with better LC (2-yr LC 72% vs. 25%, p=0.05). Neoadjuvant Ipi/Nivo was not associated with better PFS (2-yr PFS 29% vs. 43%, p=0.16) but this was in the setting of likely biased selection. However, in the cohort receiving neoadjuvant Ipi/Nivo, pathologic response was associated with better PFS (2-yr PFS 75% vs. 10%, p=0.01). Having greater than 12 mitoses/mm2 was also associated with worse PFS (2-yr PFS 20% vs. 63%, p=0.003).

Conclusion: Despite the use of contemporary systemic therapy in this modern cohort of SNM pts, disease outcomes continue to be poor with high recurrence rates. However, pts who responded to upfront Ipi/Nivo had significantly better outcomes. Further studies are needed to improve response rates to neoadjuvant therapy and improve overall outcomes.

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Efficacy and Safety of Surufatinib for Recurrent or Metastatic Malignant Salivary Gland Tumors: An Open-Label, Single-Arm, Phase II Study

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Purpose/Objective(s): Recurrent or metastatic malignant salivary gland tumors (R/M MSGTs) of the head and neck portend a poor prognosis, and therapeutic options are currently limited. Surufatinib is a potent, small-molecule tyrosine kinase inhibitor (TKI) that selectively targets VEGF receptors (VEGFR) 1, 2, and 3, FGFR 1, and CSF-1R. Recent studies have demonstrated encouraging efficacy of small molecule antiangiogenic inhibitors in head and neck cancer. This study was therefore conducted to investigate the antitumor activity and safety of surufatinib in R/M MSGT patients.

Materials/Methods: Patients aged 18-75 years with incurable and progressive R/M MSGTs received surufatinib at a dose of 300 mg once daily until intolerance or disease progression occurred. Based on a Simon's two-stage minimax design, 13 patients would be enrolled in stage 1; if 1 or more responses were observed, the trial would proceed to stage 2 in which an additional 14 patients would be enrolled, for a total sample size of 32 patients. The primary endpoint was objective response rate (ORR) as assessed by RECIST 1.1 criteria, and secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. This study was prospectively registered with ClinicalTrials.gov (NCT04910854).

Results: From May 2019 to March 2023, 12 patients were enrolled and received at least one dose of treatment. The median age was 45.5 years (range 27-60), 83.3% were female, and 41.7% had an ECOG performance status of 2. The most common histological tumor types were adenoid cystic carcinoma (ACC, 41.7%) and mucoepidermoid carcinoma (MEC, 41.7%). The most frequent metastatic sites were the lungs (83.3%). 5 patients (41.7%) had previous chemotherapy, and 4 (33.3%) had previous antiangiogenic therapy. 6 patients (50.0%) had two or more prior lines of treatment before enrollment. As of the September 2023 data cutoff, 2 patients achieved a partial response (PR), 9 had stable disease (SD), yielding a confirmed objective response rate (ORR) of 16.7% (95% confidence interval [CI]: 2.1-48.4%), and a disease control rate (DCR) of 91.7% (95% CI: 61.5-99.8%). The median progression-free survival (PFS) was 8.57 months (95% CI 4.76-11.33), with 3-month and 6-month PFS rates of 83.3% (95% CI: 51.6-97.9%) and 41.7% (95% CI 15.2-72.3%), respectively. Median overall survival (OS) was immature. Most treatment-related adverse events (TRAEs) were grade 1-2, including hyperuricemia (58.3%), hypertension (41.7%). The most common grade ≥ 3 AEs were hypertension (25.0%), proteinuria (25.0%), and nephrotic syndrome (8.3%). There were no treatment-related deaths.

Conclusion: This trial demonstrated that surufatinib showed promising antitumor activity in patients with R/M MSGTs. The safety profile observed in this study aligned with prior clinical studies, requiring continued monitoring and management.

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The Microbiome is Associated with Responses to Neoadjuvant Therapy in Primary Nasopharyngeal Carcinoma

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Purpose/Objective(s): The microbiome has been noted to be altered in a variety of malignancies including nasopharyngeal carcinoma (NPC). Microbiome dysbiosis is postulated to affect the tumor immune microenvironment and potentially responses to radiotherapy, chemotherapy and immunotherapy. Here we sought to elucidate the role of the microbiome in predicting responses to neoadjuvant therapy.

Materials/Methods: Profiling of the human microbial communities in patients with primary nasopharyngeal carcinoma in stool, oral rinse and nasopharyngeal swab samples were collected simultaneously. Age and gender matched healthy control samples were also collected. Amplicon sequencing of the bacterial microbiome with 16S rRNA V3-V4 hypervariable region was done. A two-sided p value of <0.05 was considered statistically significant. A false discovery rate (FDR)-adjusted p value (q value) of <0.05 was used as the threshold for significance.

Results: We profiled the human microbial communities in patients with primary nasopharyngeal carcinoma (N=17), including 6 and 11 patients with complete or non-responder to neoadjuvant therapy respectively. Compared with their age- and gender-matched healthy controls (N=18), decreased alpha-diversity of oral rinse, stool and nasopharyngeal swab microbiota, as measured with Shannon index, Simpson index, evenness and richness, were observed in nasopharyngeal carcinoma patients (Figure 1A). We also observed distinct microbiota between communities from different anatomic sites, and also the shift between NPC patients and healthy controls (Figure 1B). At the genus level, interestingly, a significant increase in the relative abundance of *Flavonifractor, Bilophila* and *Parabacteriodes* in stools, and *Halomonas* in nasopharyngeal swabs was associated with non-responder to neoadjuvant therapy in NPC (p < 0.05) (Figure 1C). In addition, greater species level of *Flavonifractor.plautii* and *Bilophila.wadsworthia* in stool samples were found to be potentially associated with poor response to neoadjuvant therapy.

Conclusion: Overall, our data supports the association of dysbiosis of the human microbiota with primary nasopharyngeal carcinoma, and the change in the relative abundance of bacterial genus may play a role to the response to neoadjuvant therapy in NPC. Further studies are needed to evaluate the potential role of the microbiome in neoadjuvant therapy in NPC as a biomarker and treatment.

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Scalp Irradiation with 3D-Milled Bolus: Dosimetric, Toxicity, and Oncologic Outcomes

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Purpose/Objective(s): Bolus is required when treating scalp lesions with photon radiation therapy. Traditional bolus materials face several issues, including air gaps and setup difficulty due to irregular, convex scalp geometry. 3D-milled bolus is custom formed to match individual patient anatomy, allowing improved dose coverage and homogeneity. Here, we report outcomes for patients with scalp malignancies treated with Volumetric Modulated Arc Therapy (VMAT) utilizing 3D-milled bolus.

Materials/Methods: All patients treated from 2016-2022 using 3D-milled bolus and VMAT were included.

Results: Twenty-two patients were included. Histologies included squamous cell carcinoma (n=14, 64%) and angiosarcoma (n=8, 36%). 7 (32%) patients were treated in the intact and 15 (68%) in the postoperative setting. Median prescription dose was 66.0 Gy (range:60.0-69.96). The target included the entire scalp for 8 (36%) patients; in the remaining 14 (64%), the median ratio of PTV to scalp volume was 35% (range:25-90%). Median dose homogeneity index was 1.07 (range:1.03-1.15). 6 (27%) patients experienced acute grade 3 dermatitis and 1 (5%) patient experienced late grade 3 skin ulceration. With a median follow-up of 21.4 months (range:4.0-75.4), the 18-month rates of LRC and OS were 75% and 79%, respectively.

Conclusion: To our knowledge, this is the first study to report clinical outcomes for patients with scalp malignancies treated with the combination of VMAT and 3D-milled bolus. This technique resulted in favorable clinical outcomes and an acceptable toxicity profile in comparison with historic controls and warrants further investigation in a larger prospective study.

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Observational Cohort Study of Immune Checkpoint Inhibitor Therapy for Anaplastic and Poorly Differentiated Thyroid Carcinoma

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Purpose/Objective(s): Anaplastic thyroid carcinoma (ATC) and poorly differentiated thyroid carcinoma (PDTC) are aggressive malignancies with dismal prognoses. Studies such as the Phase II ATLEP trial have suggested favorable efficacy and safety of immune checkpoint inhibition (ICI) with pembrolizumab in ATC and PDTC, but real world data on ICI therapy in ATC/PDTC is limited. This study aims to evaluate the efficacy and tolerability of ICIs for the treatment of ATC and PDTC in a real-world cohort which may not have met the inclusion criteria of previous trials.
Materials/Methods: We conducted a single-institution study of patients diagnosed with ATC or PDTC from 1/1/2010 to 1/1/2022 who received ICI treatment. Baseline patient and disease characteristics, treatments, and clinical outcomes were collected by chart review. Progression-free and overall survival was estimated using Kaplan Meier methodology. Chi-square analyses were used for univariate comparisons.
Results: We identified 10 patients, 4 (40%) with ATC and 6 (60%) with PDTC, who received ICI. Median age was 61 years (range, 54-88); 50% (5/10) were male; and 80% (8/10) were White. All patients had an ECOG of 0 or 1; 7/10 (70%) had IVC disease. NGS was performed on all patients; 3/10 (30%) had a TP53 mutation, and no patients had BRAF, NTRK, or RET alterations. In patients with PD-L1 testing, 57% (4/7) had PD-L1 >50% and 28.6% (2/7) had PD-L1 1-49%. Prior to systemic therapy, 8/10 patients (80%) had surgical resection and 10/10 (100%) had radiation . ICI-containing treatment included pembrolizumab with lenvatinib (n=6), pembrolizumab (n=2), and nivolumab (n=2); 7/10 patients received ICI as first systemic therapy, whereas 3/10 patients received ICI after prior carboplatin/paclitaxel. One patient had a complete response (10% CR), 4 had partial response (40% PR), 1 had stable disease (10% SD), and 4 had progressive disease (40% PD). Of the 5 patients who had response, 3 had PD-L1>50%; 1 had PD-L1 1-49%; and one did not have PD-L1 checked. Median DoR was 6 months (mo), and the 1 patient with CR remained progression-free for 20 mo. Median PFS was 6.3 months (range 0.5-20.4), and median OS was 7.0 mo (range 1.0-23.0). Median ICI treatment duration was 3.2 mo (range, 0.5-19.3); one patient had Gr2 dermatitis, and no hemorrhage or fistula was seen. Factors associated with numerically worse overall survival included ATC vs PDTC (4.4 vs 10.9mo; p=0.1366), TP53 mutation (2.9 vs 10.8 mo, p=0.0683), and treatment with ICI alone vs. ICI with lenvatinib (4.7 vs 10.9 mo, p =0.1366).
Conclusion: In a single-institution cohort of patients treated with ICI for ATC/PDTC, treatment was well tolerated, objective responses were seen in half of patients (5/10), and durable (>6 month) responses were seen.

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Expression of Circulating Prostate-specific Membrane Antigen Extracellular Vesicles in Blood of Patients with Recurrent and Metastatic Salivary Gland Cancer

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Purpose/Objective(s): Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein known to be overexpressed in prostate cancer and certain types of salivary gland cancer (SGC). Extracellular vesicles (EVs) are membrane-bound vesicles released from cells that are emerging as a promising blood biomarker for disease monitoring. The purpose of this exploratory analysis is to determine if circulating PSMA EVs can be detected in patients with recurrent or metastatic (R/M) SGC and to explore whether the direction of PSMA EV change correlates with tumor volume change.
Materials/Methods: Research blood samples were collected prospectively from patients with R/M SGC being treated on a clinical trial. Blood samples and controls were incubated with fluorescent antibody-matched isotypes or antibodies against PSMA and analyzed by nanoscale flow cytometry. Positive counts in the controls were subtracted from the counts observed in corresponding samples to correct for the level of non-specific binding. Total tumor volume was approximated using two-dimensional measurements on cross-sectional imaging and converted to volume using a validated formula.
Results: 19 individual patients had 27 blood samples available for analysis (57.9% male, median age 60 years, range 43-79) with the following histologies: 6 adenoid cystic, 5 acinic cell, 4 salivary duct, 1 high grade mucoepidermoid (MEC), 2 adenocarcinoma, 1 poorly differentiated carcinoma NOS. Number of prior lines of cancer therapy (1 missing value): 1 line in 12 patients (66.7%), 2 lines in 5 patients (27.8%), and 3+ lines in 1 patient (5.6%). 8 patients had paired samples at baseline (BL) and 3-month post-treatment. All patients had detectable circulating PSMA EVs across all histologies. The median concentration of PSMA EVs for all 27 samples was 1.73E+06 (historical comparison 1.64E+06 for oligometastatic hormone sensitive prostate cancer). Baseline PSMA EVs/mL, total EV particles/mL, and relative fluorescence intensity of PSMA by histology are listed in Table 1. In patients with paired samples, the direction of the change was concordant between volume change and EV change in 6 out of 8 patients (75%).
Conclusion: Circulating PSMA EVs appear to represent a possible novel biomarker of disease across salivary cancer histologies. Further prospective data collection is warranted.

Abstract 241 − Table 1: Baseline PSMA-EV measurements by SGC histology

	PSMA-EVs	Total particles per mL	Fluorescence intensity
Adenoid cystic carcinoma	1.87E+06 1.47E+06 1.48E+07 2.53E+06 9.07E+06	1.95E+10 2.43E+09 3.38E+10 1.22E+10 1.15E+10	5292.00 4864.00 4989.00 4483.00 5226.00
Salivary duct	2.27E+06 9.33E+05 2.00E+06	5.13E+09 1.56E+09 1.03E+09	4864.00 7291.00 6571.00
Acinic cell	2.53E+06 1.20E+06 1.20E+06	1.50E+09 1.83E+10 4.29E+09	6212.00 4396.00 4509.00
			Adenocarcinoma
1.20E+06 1.47E+06	6.70E+09 3.43E+09		7169.00 5102.00
High grade MEC	3.33E+06	1.54E+09	4677.00
Poorly	differentiated carcinoma, NOS	4.53E+06	3.71E+09
			7669.00

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Survival Outcomes following Pulmonary Metastasis-Directed Local Therapy (PM-LT) Relative to No Metastasis-Directed Intervention in Adenoid Cystic Carcinoma (ACC)

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Purpose/Objective(s): ACC has a high rate of recurrence and distant metastasis (DM), despite aggressive curative-intent primary therapy. The lung is the most common site of DM, most often with indolent disease growth. Given the lack of FDA-approved systemic therapy for metastatic ACC, PM-LT is frequently used. The survival impact of PM-LT is not known and there is no consensus on whether routine PM-LT is appropriate. The purpose of this study was to assess the survival outcomes of ACC patients (pts) who underwent PM-LT and compare to those who did not.

Materials/Methods: Retrospective study of ACC pts with at least one pulmonary metastasis ≥5 mm. Pts were divided into two cohorts: pts who underwent PM-LT and pts who did not. PM-LT included surgical metastasectomy and radiotherapy-based PM-LT. Clinicopathologic characteristics of both groups were compared by chi-square test, Fisher's exact test and/or Wilcoxon rank-sum test. Primary endpoint was overall survival (OS) from pulmonary metastasis diagnosis. For analysis of OS due to PM-LT, landmark analysis for OS from metastasis was performed using six months, one year, two years, and three years as time-points. Log-rank test evaluated difference in OS between cohorts. Subgroup analysis by ACC histology (solid vs. non-solid) was performed. Cox proportional hazard models were used for multivariable analyses.

Results: Of 658 ACC pts in our database, 219 met inclusion criteria; of these, 119 (54%) did not receive PM-LT, while 100 (46%) pts did. Pts who underwent PM-LT were more likely to have indolent ACC, with significantly more non-solid histology (p=0.0008), oligometastatic disease (p<0.0001), exclusively pulmonary metastases (p=0.02), and longer median disease-free interval (57 vs. 27 mos [p<0.0001]). On univariate analysis, PM-LT significantly increased OS when done at six months, one year, and two years from lung metastasis diagnosis, but not at three years. On multivariate analysis, PM-LT did not significantly increase OS when done at six months (p=0.12), one year (p=0.08) or three years (p=0.08) but did have a borderline significant increase in OS at two years (p=0.045). At all time-points, ACC histology was the most significant covariate (p<0.0001). When considering only the 104 pts with non-solid ACC histology, 50 had PM-LT and 54 did not. On univariate analysis for non-solid pts, PM-LT was not associated with significantly increased OS at any time-point, a negative result confirmed on multivariate analysis.

Conclusion: This is the largest study of survival outcomes of PM-LT in metastatic ACC. Our results suggest that PM-LT does not increase OS in ACC patients. The negative results from the non-solid subgroup are especially important for ACC clinical management, as these are often the patients directed towards PM-LT due to their indolent nature and its association with pulmonary metastasis.

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Efficacy and Tolerability of Vascular Endothelial Growth Factor Receptor Inhibitors (VEGFRi) for Recurrent/Metastatic Adenoid Cystic Carcinoma (R/M ACC): a Systematic Review and Meta-Analysis

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Purpose/Objective(s): ACC has a high rate of recurrence and distant metastasis. There is no FDA-approved systemic therapy for R/M ACC. Given high VEGFA expression in ACC and association with poorer prognosis, various clinical trials have assessed VEGFRi in R/M ACC but are mostly single-arm studies with small sample sizes. The relatively low level of evidence has led to debate over the adoption of VEGFRi in ACC management. Given remaining uncertainty, we performed a systematic review and meta-analysis evaluating efficacy, safety, and tolerability of VEGFRi in R/M ACC.

Materials/Methods: Electronic databases PubMed, Embase, and Cochrane Library were systematically searched until August 31st, 2023 for prospective clinical trials of R/M ACC treated with VEGFRi. Data was extracted according to PRISMA guidelines and pooled using a random-effects generalized linear mixed model with 95% confidence interval (CI). Efficacy outcomes were best overall response (BOR) to VEGFRi, including objective response rate (ORR), stable disease (SD) and progressive disease (PD) rate; 6-month disease control rate (DCR); and 6 and 12-month progression-free survival (PFS) rate. Safety outcomes were rate of patients off trial due to PD or drug-related toxicity; dose reduction rate (DRR); and rate of grade 3 or higher adverse events (≥G3AEs). Heterogeneity was assessed with I^2 test (I^2>40% significant) and explored through influence analysis. Subgroup meta-analysis by VEGFRi was done for each outcome, pooling results for each VEGFRi with two or more studies.

Results: Seventeen studies with a total 560 ACC patients treated prospectively with VEGFRi were included. Despite known prognostic value in ACC, only one study reported histological subtype. SD was the most frequent BOR (82%; 95%CI 74-87%; I^2=67%), with 6% ORR (95%CI 3-12%; I^2=71%). DCR was 54% (95%CI 45-62%; I^2=52%), with 6 and 12-month PFS of 70% (95%CI 59-79%; I^2=79%) and 33% (95%CI 20-49%; I^2=82%), respectively. VEGFRi were moderately tolerated, with 57% (95%CI 43-70%; I^2=83%) of patients on therapy until PD and 21% (95%CI 15-28%; I^2=62%) suspending treatment for toxicity. The pooled rate of patients with ≥G3AEs was 53% (95%CI 42-64%; I^2=81%), with a DRR of 59% (95%CI 40-76%; I^2=90%). In the subgroup analysis by VEGFRi, lenvatinib had 14% ORR, 76% SD, and 61% of patients on treatment until PD, but with 78% DRR; axitinib had 8% ORR, 85% SD, and 73% of patients on treatment until PD, with 22% DRR; and rivoceranib had the highest ORR (24%), however with high heterogeneity between studies (I^2=95%), and lowest rate of patients on therapy until PD (35%).

Conclusion: VEGFRi induces high disease stabilization rates in R/M ACC. Of 10 included VEGFRi, lenvatinib and axitinib offer best-combined efficacy and safety profiles, with rivoceranib a potentially effective drug warranting further research.

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Prognostic Value of Time To Progression vs. Tumor Volume Doubling Time in Patients with Adenoid Cystic Carcinoma Metastatic To The Lung

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Purpose/Objective(s): Adenoid cystic carcinoma (ACC) tends to recur despite aggressive local therapy, with the lung being the most common site of distant metastasis. The optimal timing for initiating systemic therapy in patients with metastatic ACC remains a matter of debate. The objective of this study was to retrospectively assess the natural history of ACC lung metastasis and evaluate tumor dynamics using RECIST criteria and tumor volume doubling time (TVDT).

Materials/Methods: Patients with histologically proven metastatic ACC with at least one pulmonary metastasis ≥5 mm and ≥ two chest CT scans were eligible for this study. Radiology assessment was performed with commercially available software (v6.9.8) from the first scan where the metastasis was detected until the initiation of any intervention or death. Time to progression (TTP) was assessed per RECIST 1.1. To assess whether the tumor growth rate (TGR) was constant, we calculated the correlation coefficient (R) and the coefficient of determination (R^2) for all measured lung nodules. TVDT was calculated using the Schwartz formula.

Results: Out of 581 ACC patients in our database, 75 met eligible criteria. Most had non-solid histology (63%) and had lung as the sole site of metastases upon initial CT scan (89%). TGR was predominantly constant (median R^2=0.974). The median TTP was 11.2 months (mos), and the median TVDT was 7.5 mos. Poor survival outcomes were associated with solid histology (2.2 vs. 8.5 years; p=0.002), presence of synchronous extrapulmonary metastases (7.9 vs. 2.7 years; p=0.009), and development of metastasis within the first year after diagnosis for M0 (5.6 vs. 11.4 years; p<0.0001). Given the common eligibility criterion of disease progression within 6 mos for ACC patient enrollment in clinical trials, we established TTP and TVDT cutoffs for assessing both variables as prognostic factors. A shorter TVDT (<6 mos) was significantly linked to poorer OS (HR=0.48; p=0.037), while there was no statistically significant correlation between TTP and OS (HR=1.02; p=0.96). A Cox-regression analysis indicated that TVDT, but not TTP, significantly correlated with OS, suggesting TVDT superior prognostic value in this population. Considering tumor segmentation is not feasible in the clinical practice, we explored whether estimating tumor volume using only one measurement in up to two lung lesions would suffice for calculating TVDT. We found that TVDT calculated using estimated tumor volume significantly correlated with TVDT based on tumor segmentation (p<0.0001). In a multivariate analysis that included this new variable, estimated TVDT emerged as a predictor of survival in lung metastatic ACC (p=0.048).

Conclusion: Most ACC lung metastases exhibit a constant growth rate. TVDT may serve as a more robust prognostic indicator than TTP per RECIST for lung metastatic ACC. TVDT can be estimated through a single longitudinal measurement in clinical practice.

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The KEYNOTE-630 Trial: A Phase 3 Study of Adjuvant Pembrolizumab in High-Risk Locally Advanced (LA) Cutaneous Squamous Cell Carcinoma (cSCC)

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Purpose/Objective(s): In high-risk LA cSCC, approximately 20% of patients (pts) experience local disease recurrence within 5 years after surgical resection and adjuvant radiotherapy (RT). Therefore, improved treatment options are needed. The PD-1 inhibitors pembrolizumab (pembro) and cemiplimab have demonstrated durable antitumor activity in advanced metastatic cSCC. The randomized, double-blind, placebo-controlled, phase 3 KEYNOTE-630 (NCT03833167) trial will evaluate adjuvant pembro in pts with resectable, high-risk, LA cSCC.

Materials/Methods: Eligible pts have histologically confirmed LA cSCC as the primary site of malignancy and have undergone complete macroscopic resection of all disease with ≥1 high-risk feature: histologically involved nodal disease with extracapsular extension, with ≥1 lymph node >2 cm in diameter or ≥2 lymph nodes involved; any gross cortical bone, skull base, and/or skull base foramen invasion; any index tumor with ≥2 of the following: tumor ≥4 cm with >6-mm depth or invasion beyond subcutaneous fat, multifocal perineural invasion for nerves <0.1 mm in diameter (≥3 foci) or any involved nerve ≥0.1 mm in diameter, poor differentiation and/or sarcomatoid and/or spindle cell histology, recurrent disease (recurrence within 3 years in the previously treated area), or satellite lesions and/or in-transit metastases, lymphatic or vascular involvement. Pts must have received adequate postoperative dose of hypofractionated or conventional RT, including a BED EQD2 >48 Gy, have ECOG PS of 0 or 1, and completed adjuvant RT ≥4 and ≤16 weeks from randomization. Pts are required to provide tumor tissue for PD-L1 testing. Eligible pts will be randomly assigned 1:1 to receive pembro 400 mg IV Q6W or placebo for approximately 1 year (≤9 cycles) and will be followed up for as long as 5 years. Stratification factors are extracapsular extension, cortical bone invasion, and prior systemic therapy (all, yes vs no). Placebo pts may switch to pembro treatment (≤18 cycles) if they have a recurrence within 5 years. In the pembo arm, pts may also receive up to 18 cycles of pembro retreatment. Primary end point is RFS per investigator assessment with biopsy confirmation and secondary end points include OS, HRQoL, and safety. Computed tomography/magnetic resonance imaging will be performed at screening and every 12 weeks until end of year 2, then every 6 months until end of 5 years. Adverse events will be monitored throughout the study and for 30 days after treatment end and graded per NCI CTCAE v4.0.

Results: Approximately 570 pts will be enrolled at sites in Asia, Australia, Europe, and North and South America.

Conclusion: Results of KEYNOTE-630 will elucidate the role of adjuvant pembro among pts with high-risk, LA cSCC.

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Mucoepidermoid Carcinoma in the Oropharynx: A Review of the Literature

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Purpose/Objective(s): There is a lack of evidence-based recommendations for patient work up, counseling, and management of mucoepidermoid carcinoma of the oropharynx (OPMEC). We aim to perform a systematic review and summarize the demographics, clinical presentation, histology, treatment, and oncologic outcomes of OPMEC.

Materials/Methods: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid Ebase, Ovid Cochrane Central Register of Controlled Trials, and Scopus were searched for articles published through July 7, 2023. The search strategy was designed and conducted by a medical librarian following PRISMA guidelines. Review articles, national database studies, abstracts, and studies that did not report any of the outcomes of interest were excluded. The review was conducted by two independent reviewers (GAC and AEB) and conflicts were resolved by the senior author (KVA).

Results: A total of 23 publications were included with 76 patients. When reported, sex was predominantly female (27/51, 52%) with a mean age of 48 years (19 − 76). OPMEC was most common in the base of tongue (40/51, 78%) and most patients had an oropharynx mass on exam at presentation. Tumor stage was poorly documented but was frequently T1/2 when reported (25/37, 69%). Histological grade was most often reported as intermediate grade (31/70, 44%). There was a total of 32 patients with nodal involvement. One publication (n= 25) reported 68% (17/25) of patients who underwent neck dissection had pathologic lymph nodes. When pathologic lymph nodes were reported, the majority of tumors were intermediate grade (10/19, 52%). For only 26 patients, treatment was described. Among these, the primary treatment modality was surgery only (14/26, 53%) or surgery with adjuvant radiotherapy (9/26, 34%). Three additional patients were reported to receive chemotherapy during their treatment, but it is unclear if this was for primary treatment or recurrence. 55% (11/20) of final margins reported were positive. Follow-up length varied significantly (mean 35 months, range 0-146) and the overall survival was found to be 88% (range 0-100) at the time of publication, with two deaths not attributed to OPMEC and one likely attributed to OPMEC. Only one publication (n=26) included specific findings on survival outcomes, with 75% 5-year and 65% 10-year overall survival and 86% 5-year and 86% 10-year distant recurrence-free-survival.

Conclusion: The heterogeneity of studies highlights the lack of evidence supporting the understanding and management of OPMEC. OPMEC most often presents in middle aged females as a base of tongue mass and has a high potential for nodal metastasis, especially when the primary tumor is intermediate grade or higher. Oncologic outcomes appear to be fair following surgery with or without adjuvant therapy. However, further research is needed to develop an evidence-based treatment strategy for patients with OPMEC.

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Prognostic Performance of Sentinel Lymph Node Biopsy for the Clinically Negative Neck in High-Risk Cutaneous Squamous Cell Carcinoma

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Purpose/Objective(s): Even though cutaneous squamous cell carcinoma (cSCC) is one of the most commonly diagnosed malignancies in the United States, there is a lack of prospective data that can inform risk stratification for regional metastasis in the clinically node-negative neck. Regional nodal disease is considered the strongest predictor for recurrence and survival, yet available literature on the rate of occult regional metastases is largely limited to retrospective reviews. Sentinel lymph node biopsy (SLNB) is standard of care and established as a major prognostic marker for melanoma, yet its role in the management of high risk cSCC has not yet been studied in a prospective fashion.

Materials/Methods: We designed a prospective, single-arm study (NCT05108090) for patients to undergo tumor resection via Moh's or wide local excision with concurrent SLNB. Inclusion criteria included adult patients with resectable cT2-4 N0 M0 cSCC (AJCC8). Exclusion criteria include evidence of satellite or in-transit lesions; synchronous primary cSCC of the head and neck; pregnant patients; and patients unable to tolerate contrasted imaging, 99-technetium sulfur colloid, or general anesthesia. The primary objective is to identify rates of occult metastasis in clinically and radiographically node-negative cSCC. Secondary aims are to identify clinical and tumor characteristics associated with occult, regional metastatic disease. As an exploratory aim, we will evaluate associations of clinicopathologic characteristics with common oncogenic mutations through a validated 40-gene expression profile. Patients will be followed for a minimum of one year.

Results: The study began in October 2021, with an anticipated accrual of 94 subjects. Preliminary data analysis is planned for 2025.

Conclusion: High level evidence for appropriate risk prediction of occult regional nodal disease in cSCC is lacking. This prospective study of SLNB in high-risk cSCC is designed to quantify the risk of and clinicopathologic predictors of occult regional metastasis.

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Local Therapy in the Management of Mucosal Melanoma: An NCDB Analysis

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Purpose/Objective(s): Mucosal melanoma of the head and neck is a rare and deadly disease. The optimal treatment for mucosal melanoma remains uncertain, and there is no consensus on the most effective treatment approach, including the extent of surgical resection, the use of adjuvant therapy, and the role of immunotherapy. Current controversies and unknowns about disease treatment and outcomes stem from the rarity of mucosal melanoma, the lack of large-scale clinical trials, and the heterogeneity of the disease. This study aims to determine the survival benefit of immunotherapy, surgery and radiation in setting of mucosal melanoma.

Materials/Methods: We extracted data from NCDB database with histology codes (ICD-O 2 melanoma codes M872−M879) for patients with mucosal melanoma diagnosed from year 2000-2020 with a total sample size 3937. The patients' characteristics were summarized by median and interquartile range (IQR) for a continuous variable and by frequency and percentage for a categorical variable. We considered the different

combinations of treatments in terms of surgery, chemotherapy, radiation therapy, and immunotherapy. The outcome variables are (1) time to death since diagnosis, and (2) death. Kaplan-Meier survival estimates were used. The log-rank test was employed to compare the survival distributions of the different treatment groups. Cox Proportional Hazard Regression model was performed to evaluate the association between the treatment combinations and survival outcome, adjusting the clinical and demographic variables (e.g., sex, age, stage of cancer). Hazard ratio (HR) and 95% confidence interval (CI) were reported. Mortality rate for each treatment combination was also reported, and the multiple logistic regression model was used to examine the effect of different treatment on mortality.

Results: The median overall survival (OS) time for all patients diagnosed with mucosal melanoma was 25.7 months. Among them, 50.1% were males, 9.4% younger than 50 years old and 50.6% older than 70, 88.7% white, and 57.6% with Medicare. Cox proportional hazard model showed that the survival time is significantly associated with the following factors: age group 60-70 (HR 1.25, 95%CI [1.06, 1.48]) and >70 (HR 1.83, 95%CI [1.56, 2.13]) comparing with age group <50. Male sex increased the risk of death (HR 1.13, 95%CI[1.04, 1.22]). Surgery decreased the risk of death (HR 0.49, 95%CI [0.44, 0.55]). The use of radiation and immunotherapy had no association with survival. Chemotherapy increased the risk of death (HR 1.33, 95%CI [1.18,1.51]), and was associated with more advanced age and high tumor stage. The multiple logistic regression model showed similar impact of these factors on mortality.

Conclusion: Treatment paradigms for mucosal melanoma vary widely. Local therapy remains important for improved survival. Further analyses should be done to explore the benefits of multi-modality treatment.

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Phase II trial of Abemaciclib in Unresectable or Metastatic Anaplastic Thyroid Cancer

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Purpose/Objective(s): Anaplastic thyroid cancer (ATC) is an aggressive malignancy with poor survival and limited treated options. Preclinical data suggest a possible therapeutic role for CDK4/6 inhibition. We report our clinical trial with abemaciclib, an oral CDK4/6 inhibitor, in patients with incurable ATC after FDA-approved treatment options.

Materials/Methods: This phase 2 study evaluated the efficacy of oral abemaciclib, 200 mg twice daily. The primary endpoint was overall response rate (ORR) by RECIST v1.1 within 8 weeks of treatment initiation by RECIST v1.1. Secondary endpoints included safety, PFS, and OS. A Simon two-stage design was used with a target ORR of 30%, null hypothesis ORR of 5%, and a 5% type 1 error rate. One response within 8 weeks (n=9 pts) was required to proceed to stage 2 (n=17 pts total). Whole exome sequencing was performed to determine correlations between response and genomic findings.

Results: Nine patients received abemaciclib. Baseline demographics: median age of 73, 66% female gender. Median treatment duration on abemaciclib was 8 weeks (range 1-117 weeks). Eight pts were disease evaluable; 4 had stable disease on their 8 week scans while 4 pts experienced no clinical benefit. This resulted in a disease control rate (DCR) of 45%. Adverse events (AE) by grade: 1 G5 (lung infection) and 1 G4 (hallucination); unrelated to abemaciclib. G3 (n = 9) and G2 (n = 4) AEs were similar to

previous abemaciclib studies. Three pts had *CDKN2A/B* loss on baseline WES: 1 had stable disease for 8 months prior to being lost to follow-up. The other reported clinical benefit but stopped therapy due to an external drug reaction. Two patients were BRAF V600E-altered; 1 achieved an ongoing partial response >8 weeks from abemaciclib initiation and remains on study for 27 months. This patient also had a CDKN2A loss and had rapidly progressed on dabrafenib+trametinib, pembrolizumab then neck radiation. No response correlations were seen with *KRAS* mutation, *RB1* loss, and *ATM* alteration. No patients on study had high tumor mutation burden or *RET/NTRK* abnormalities.

Conclusion: In 9 pts with advanced ATC, abemaciclib had acceptable tolerability. The study was terminated as it did not meet the prespecified 8 week ORR goal, though there was a dramatic, ongoing partial response after rapid progression on standard therapies. Patients with CDKN2A abnormalities appear had better outcomes. BRAF mutant/wildtype status was not an impediment to benefit. Future directions include CDK 4/6i combination trials, or selecting patients for abemaciclib monotherapy based on genomic characteristics.

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Reflectance Confocal Microscopy Mapping of Non-melanoma Skin Cancers to Guide Definitive Radiation Therapy

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Purpose/Objective(s): Basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) are the most prevalent non-melanoma skin cancer types (NMSCs). For patients with lesions in cosmetically challenging areas or for patients with significant comorbidities, non-surgical management with radiation therapy can be an excellent alternative to surgery. As a surrogate for pathological margin assessment of surgical techniques, non-invasive tools to define the at-risk area can be extremely helpful when employing radiation, to preserve normal tissue from radiation side effects and minimizing the risk of local recurrence concurrently. Reflectance Confocal Microscopy (RCM) allows for real-time, non-invasive "virtual-histologic" assessment on cutaneous neoplasms. Because of its success in pre-surgical mapping, our center uses RCM for lesion's margin mapping in patients receiving definitive radiation for BCC and SCC. Herein we present our 4 year experience with this pre-treatment assessment for margins delimitation.

Materials/Methods: All patients underwent for dermatologic evaluation and RCM mapping with the the Vivascope 3000 (hand-held probe) of the area to be treated immediately prior to radiation simulation. For the 16 patient cohort, clinical characteristics such as histology, radiation type, dose fractionation, and field size were recorded. Acute treatment toxicities and treatment outcomes were subsequently evaluated.

Results: The patient cohort included 12 BCC and 4 SCC patients; 13 received electron therapy and 3 received superficial x-rays. Median dose fractionation was 40 Gy in 8 fractions treated twice per week, and median field size was 39cm^2. Acute grade 2+ and 3 radiation dermatitis occurred in 47% and 18% of patients, respectively. At median 6 month follow up (maximum 42 months), no local or locoregional recurrences were seen.

Conclusion: The report demonstrates the benefit of utilizing RCM (Vivascope 3000) to delimit treatment margins in patients receiving definitive radiation for NMSCs. With limited short follow-up, patients tolerated radiation well without local recurrence up to 4 years after the radiation. Because current radiation techniques add substantial margin (1-2cm) around lesions to account for presence of subclinical disease, RCM may enable

reduction of radiation field margins to reduce treatment toxicity while preserving local control.

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Hypofractionated Radiotherapy for Merkel Cell Carcinoma

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Purpose/Objective(s): Merkel cell carcinoma (MCC) is a radiosensitive skin cancer. Historically, radiation treatment for MCC has involved standard 1.8-2 Gy fractions treated daily over 4-6 weeks. For other cutaneous malignancies, radiation treatment with daily doses >2 Gy has increased in prevalence in order to reduce treatment time and increase patient convenience. The equivalence of such hypofractionated treatment regimens to standard fractionation regimens for tumor control and skin toxicity has been shown for common cutaneous malignancies such as basal cell and squamous cell carcinomas. Recent publications have shown efficacy of hypofractionated radiotherapy for MCCs when treating with palliative and definitive intent. Herein we report the outcomes of hypofractionated versus standard fractionation radiotherapy for MCC at our institution.

Materials/Methods: The study involved a retrospective review of 29 cases of patients with localized MCC. Treatment characteristics and patient outcomes were analyzed. Pertinent patient characteristics such as age, gender, performance status, prior surgical and systemic therapy history, and tumor-related characteristics, including histology, location, stage, and nodal status, were recorded. Treatment parameters such as target field size and radiation modality were obtained. Subsequent patient outcomes, including acute toxicities, as well as recurrence and survival results, were collected. The cumulative incidence of local and distant failures was estimated, with death as a competing risk.

Results: A total of 29 patients were included, of which 13 received standard fractionation (2 Gy/day x 25-30 fractions) with curative intent, 10 received hypofractionated radiotherapy (4 Gy/day x 10 fractions) with curative intent, and 6 received single fraction (8 Gy) palliative radiation. Half the patients were treated to a head/neck site. A subset of patients treated adjuvantly with curative intent included 8 standard fractionation and 8 hypofractionated radiotherapy patients. Median treatment time was 39 days versus 25 days for standard fractionation versus hypofractionated radiotherapy patients, respectively. At median 10 month follow up, no local failures occurred in the standard fractionation group, and 1 local failure occurred in an untreated nodal basin in the hypofractionated radiotherapy group. No statistically significant differences in local and/or distant failure or overall survival was observed between the patient groups.

Conclusion: Hypofractionated radiotherapy for MCC was associated with similar treatment outcomes relative to standard fractionation. In our limited patient sample, hypofractionated radiation treatment achieved similar results with similar toxicity and fewer treatments. Further analysis of a larger patient population with longer follow up is needed to confirm treatment tolerability and efficacy.

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First-line ADP-A2M4CD8 T-cell Receptor T-cell Therapy plus Pembrolizumab in Head and Neck Cancers: An Additional Cohort of the Phase 1 SURPASS Trial

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Purpose/Objective(s): ADP-A2M4CD8 is an autologous CD4+ and CD8+ T-cell therapy under investigation for treatment of advanced cancers in human leukocyte antigen (HLA)-A*02−eligible participants. It expresses a genetically modified T-cell receptor (TCR) targeting melanoma-associated antigen A4 (MAGE-A4) and an additional CD8α co-receptor to increase functionality of CD4+ T cells. ADP-A2M4CD8 monotherapy has demonstrated an acceptable benefit-risk profile in the ongoing Phase 1 SURPASS trial (NCT04044859), with clinical responses in multiple tumor types in the late-line setting. As of November 23, 2022, in four SURPASS patients with head and neck (H&N) squamous cell carcinoma, best overall responses were three partial responses and one stable disease (median [range] duration of response, 8.7 [7.4−20.1] weeks) (Hong DS, et al. Presentation S152, AHNS 2023, Montreal, Canada). These results, along with data that suggest inhibition of immunosuppressive pathways may enhance ADP-A2M4CD8 anti-tumor activity (Kim PS, Ahmed R. *Curr Opin Immunol.* 2010;22:223; Gray KG, et al. *Clin Cancer Res.* 2020;26:6003), provided rationale for opening a new SURPASS cohort investigating safety and efficacy of first-line ADP-A2M4CD8 TCR T-cell therapy combined with pembrolizumab in patients with H&N cancers.

Materials/Methods: The dedicated H&N cohort will comprise ≤15 participants with newly metastatic or unresectable locally advanced H&N tumors with combined PD-L1 positive score ≥1 who are receiving pembrolizumab with or without chemotherapy as first-line standard-of-care therapy, with no evidence of disease progression before lymphodepletion. Key eligibility criteria include ≥30% of tumor cells expressing MAGE-A4 (≥2+ by immunohistochemistry); positivity for HLA-A*02:01, 02:02, 02:03, or 02:06 alleles; measurable disease per RECIST v1.1 before lymphodepletion; and ECOG performance status of 0 or 1. Participants will undergo leukapheresis, and collected T cells will be transduced with a lentiviral vector expressing the MAGE-A4-specific TCR and CD8α co-receptor and expanded ex vivo. Lymphodepletion chemotherapy consisting of cyclophosphamide 600 mg/m^2/day for 3 days and fludarabine 30 mg/m^2/day for 4 days is administered, followed by ADP-A2M4CD8 infusion ($1-10 \times 10^9$ transduced T cells). Participants will then continue to receive pembrolizumab 400 mg every 6 weeks for ≤2 years, or unacceptable toxicity or disease progression. Primary and secondary objectives are to evaluate safety and anti-tumor activity, respectively.

Results: TBD

Conclusion: In a dedicated H&N cohort, participants will receive ADP-A2M4CD8 in combination with pembrolizumab in the first-line setting to evaluate the efficacy and safety of the combination. Study sponsor: Adaptimmune; writing/editing: Excel Scientific Solutions, funded by Adaptimmune.

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Neoadjuvant Immunotherapy for Regional Metastatic Melanoma: A Systemic Review and Meta-analysis

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Purpose/Objective(s): Neoadjuvant immunotherapy has emerged as a potential solution to improve outcomes for patients with advanced resectable melanoma, particularly in the head and neck region, where the disease is prevalent. Despite advances in adjuvant immunotherapy, locally advanced melanoma continues to pose significant morbidity and mortality challenges. This review aims to evaluate the effectiveness of neoadjuvant immunotherapy for stage III locally metastatic melanoma, considering its impact on pathological response and adverse events.

Materials/Methods: Following PRISMA guidelines, a comprehensive search was conducted across PubMed, Embase, and Web of Science, yielding 1,257 results, with 88 studies selected for full-text review. Inclusion criteria encompassed English language studies of patients aged over 18 with stage III melanoma treated with neoadjuvant immunotherapies. Various study designs, including randomized controlled trials, prospective cohorts, case-control, and case series, were considered. Quality assessment was performed using relevant checklists.

Results: 6 studies were included in the final analysis, each with different treatment regimens. Notably, neoadjuvant immunotherapy demonstrated the potential to induce a major pathological response (MPR), associated with improved survival. Radiological response consistently underestimated pathological response. Immune-related adverse events (irAEs) were common, with grade 3+ toxicity varying between 10% and 90%. A meta-analysis revealed improved 3-year relapse-free survival (RFS) with neoadjuvant immunotherapy compared to adjuvant, albeit not statistically significant. IrAE rates were similar between the two approaches.

Conclusion: Neoadjuvant immunotherapy demonstrates potential in enhancing survival and reducing tumor burden in stage III melanoma patients, with a particular focus on head and neck cases. Pathological response surfaces as a predictor of outcomes and may influence surgical decisions. While meta-analysis results hint at improved survival with neoadjuvant therapy, larger studies are required for definitive conclusions. Addressing irAEs and optimizing treatment regimens remain crucial for future research in this field.

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Anti-CD47 and Anti-PDL1 Immunotherapy Synergize for Antitumor Activity in Preclinical Models of Head and Neck Cancer

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Purpose/Objective(s): Recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) has a poor prognosis, with only ~20% of patients responding to anti-PD-1 checkpoint immunotherapy. CD47 is another targetable immune checkpoint. By interacting with SIRPα, CD47 triggers a "don't eat me" signal to inhibit macrophage phagocytosis which is upregulated in the HNSCC tumor microenvironment. The aim of our study was to examine the effect of anti-CD47 as monotherapy and in combination with anti-PD-L1/PD-1 checkpoint blockade, on tumor growth response and survival in syngeneic orthotopic models of HNSCC.

Materials/Methods: Syngeneic murine HNSCC cell lines were injected orthotopically (tongue) into C57/B6 mice: MOC1, ROC1, and ROC3 (n=5-10 per group). The MOC1 mice were then subjected to immunotherapy intraperitoneally with either control (IgG), anti-CD47, anti-PD-L1 or the combination. ROC1 and ROC3 mice were injected intratumorally with anti-CD-47 and anti-PD-1 was administered intraperitoneally to ROC3 mice in combination with anti-PD-1. Tumor rechallenge (via inoculation of cancer cells was performed in mice exhibiting complete responses to therapy). Tumor volumes were recorded, and survival curves were generated. RNA was isolated from treated tumors and mRNA expression data was collected. Statistical analysis was performed.

Results: In MOC1 implanted mice, anti-CD47 monotherapy resulted in no significant difference in tumor volume or survival compared to control (IgG). However, when used in combination with anti-PD-L1, anti-CD47 treatment resulted in a statistically significant decrease in tumor volume and significantly increased overall survival (p<0.05). There were 6/10 complete responders in the combination group (and no mice grew tumors after re-challenge at 100 days). ROC3 implanted mice treated with anti-CD47 treatment showed a significant decrease in tumor volume with monotherapy, compared to control, and maintained complete responses after tumor cell re-challenge (p<0.05). Conversely, the more aggressive ROC1 mouse model showed no significant difference in treatment arms which included anti-CD47, anti-PD-1 and the combination. RNA expression analysis of MOC1 tumors treated with anti-PD-L1 demonstrated significantly increased CD47 expression.

Conclusion: We have demonstrated that anti-CD47 and anti-PD-L1 have a synergistic effect in MOC1 tumor models while monotherapy with anti-CD47 works effectively in the ROC3 model. Combination therapy showed no response in the ROC1 model. PD-L1 treatment of MOC1 tumors caused increased expression of CD47 in tumors, indicating that increased CD47 may be an immunosuppressive mechanism that may contribute to PD-L1 immune checkpoint inhibitor resistance. Combining anti-CD47 with anti-PD-L1 immunotherapy may be effective in HNSCC patients with higher baseline immune cell infiltration.

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Safety and Tolerability of Magrolimab Combination Therapy in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (RM-HNSCC)

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Purpose/Objective(s): Novel combination therapies are needed to improve outcomes in RM-HNSCC. Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal overexpressed on cancer cells. Magrolimab induces macrophage-mediated phagocytosis of tumor cells and may synergize with chemotherapy agents through enhancement of phagocytic signals. The phase 2 ELEVATE HNSCC multicenter, open-label study (NCT04854499) is evaluating magrolimab-containing regimens in patients (pts) with RM-HNSCC. Here, we report data from 2 safety run-ins

(SRI1 and SRI2) designed to assess safety/tolerability and recommended phase 2 dose (RP2D) of magrolimab in combination with standard of care.

Materials/Methods: Pts in SRI1 with previously untreated RM-HNSCC received magrolimab+pembrolizumab+platinum+5-fluorouracil; pts in SRI2 with locally advanced or RM-HNSCC (1-2 lines of prior systemic therapy) received magrolimab+docetaxel. Magrolimab was first administered as a 1 mg/kg priming dose, followed by weekly 30 mg/kg doses for two 21-day cycles and then a maintenance dose of 60 mg/kg Q3W. Pembrolizumab and chemotherapy were given per standard of care. Primary endpoints of the SRI were incidence of adverse events (AEs) and dose-limiting toxicities (DLTs). Safety was assessed in pts who received ≥1 dose of study drug. The incidence of DLTs was assessed using pts who experienced a DLT during the DLT evaluation period or who completed ≥2 magrolimab and ≥1 combination agent doses. To select an RP2D, ≤2 of 6 DLT-evaluable pts could experience a DLT, or the magrolimab dose would be de-escalated and a new cohort would be assessed.

Results: At least 6 pts from each SRI were DLT-evaluable. The safety analysis population was 6 pts in SRI1 and 7 pts in SRI2. No DLTs were reported. Treatment-emergent AEs (TEAEs) occurred in 6/6 (SRI1) and 7/7 (SRI2) pts. In SRI1, the most common (≥4 pts) TEAEs were fatigue (5/6), diarrhea, nausea, decreased platelet count, stomatitis, and decreased white blood cell count (4/6 each). In SRI2, the most common (≥4 pts) TEAEs were anemia (5/7) and fatigue (4/7). TEAEs leading to magrolimab discontinuation occurred in 1/6 pts in SRI1 (fatigue) and 1/7 pts in SRI2 (oral cavity fistula unrelated to study drug). In SRI1, no deaths were reported; in SRI2, 3 deaths were reported as unrelated to study treatment and occurred after the DLT evaluation period: oral cavity fistula, pneumonia, and disease progression (during long-term follow-up).

Conclusion: The observed safety profile was as expected based on the known toxicity profiles of the individual agents. Magrolimab appears tolerable in these combinations. No DLTs or treatment-related deaths occurred. Magrolimab RP2D was declared at the initial dose level tested in both SRIs.

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A Randomized, Double-Blind, Phase 2 Study of Perioperative MK-4280A (Coformulation of Favezelimab and Pembrolizumab) vs Pembrolizumab in Patients with Resectable Cutaneous Squamous Cell Carcinoma (cSCC)

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Purpose/Objective(s): The immune checkpoint receptor lymphocyte-activation gene 3 (LAG3) is upregulated in many tumor types including melanoma and cSCC and is frequently coexpressed with PD-L1. In the phase 3 RELATIVITY-047 study, 1L relatlimab (anti−LAG3 antibody) + nivolumab (nivo; anti−PD-1 antibody) prolonged PFS vs nivo in patients (pts) with unresectable advanced melanoma; and a phase 2 study showed high pathologic complete response (pCR) rate in resectable disease. Early phase studies have also shown promising antitumor activity and manageable safety with favezelimab (anti−LAG3 antibody) + pembrolizumab (pembro; anti−PD-1 antibody). MK-4280A-010 is an ongoing basket study (NCT06036836) evaluating MK-4280A (coformulation of a fixed-dose combination of favezelimab + pembro) in selected solid tumors. We describe cohort A of this study, which evaluates MK-4280A vs pembro in pts with resectable cSCC.

Materials/Methods: Cohort A of this randomized, double-blind, phase 2 study will enroll pts aged ≥18 yrs with histologically confirmed stage II−IV cSCC as the primary site of malignancy (without M1; staging per AJCC 8th ed. for head/neck tumors or UICC 8th ed. for other tumor sites). Pts must have had no prior systemic therapy or radiotherapy (RT) to the index lesion and must have cSCC amenable to curative intent surgery, ECOG PS 0/1, and a tumor sample for biomarker analysis. Approximately 80 pts (40 per arm) will be randomized 1:1 (stratified by non-nodal vs nodal disease and head/neck vs other tumor site) to MK-4280A (favezelimab 800 mg + pembro 200 mg) or pembro 200 mg IV Q3W for ≤3 cycles in the neoadjuvant period, followed by surgical resection; and then MK-4280A or pembro, as allocated, Q3W for ≤14 cycles in the adjuvant period (with adjuvant RT per investigator discretion before the start of adjuvant treatment if no pCR by local assessment). Treatment duration (neoadjuvant + adjuvant) will be ∼ ≤1 yr or until PD/recurrence or intolerable AEs. Imaging occurs after the last neoadjuvant cycle before surgery, then Q12W starting day 1 of the adjuvant period through ≤1 yr. AEs are assessed throughout the study and graded per NCI CTCAE v5.0. Primary endpoint is pCR (no viable tumor in resected sample) by blinded central pathology review (BCPR). Secondary endpoints are pCR or clinical CR (no residual tumor per clinical exam/imaging) with negative biopsy, event-free survival and ORR (before surgery) per RECIST v1.1 by investigator review, major pathological response (≤10% viable tumor in resected sample) by BCPR, OS, and safety. pCR will be compared between treatment groups using the stratified Miettinen and Nurminen method. Enrollment began in Sep 2023 and is ongoing.

Results: TBD

Conclusion: TBD

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A Phase 1 Dose-escalation and Expansion Study of CUE-101, Given As Monotherapy in 3rd Line and in Combination with Pembrolizumab in 1st Line Recurrent/Metastatic (R/M) HPV16+ Head and Neck Cancer Patients

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Purpose/Objective(s): Immuno-STATs are T cell engagers which activate tumor-antigen specific CD8+ T cells via targeted delivery of cytokines. CUE-101 is a human leukocyte antigen (HLA) complex, HLA-A*0201, plus an HPV16 E7 peptide, and 4 molecules of attenuated IL-2 designed activate HPV16-specific CD8+ T cells.

Materials/Methods: CUE-101-01 is an ongoing first-in-human study in HLA-A*0201 patients with HPV16+ R/M HNSCC. Escalating doses of CUE-101 were evaluated in platinum or ICB refractory R/M HNSCC, or with pembrolizumab in 1st line R/M HNSCC, followed by expanded enrollment at the RP2D. Safety, PK/PD, and antitumor activity were assessed.

Results: As of Oct 1, 2023, 76 patients have been enrolled. Following monotherapy and combination therapy dose escalation, 4 mg/kg of CUE-101 was chosen as the RP2D for both cohorts. Enrollment in both monotherapy and combination cohorts is now complete. Grade 3 treatment-related AEs reported include infusion-related reaction (4.2%), fatigue, maculopapular rash, stomatitis and diarrhea (all 2.7%). Among 19 evaluable monotherapy RP2D patients, 1 PR and 6 durable SD (SD ≥ 12 weeks) were observed, with mOS of 20.8 months. Among 17 evaluable RP2D combination patients, 1 CR, 7 PRs, and 3 durable SDs were observed. Complete Response and 5 out of 7 PRs occurred in tumors with CPS of 20 or less. Of the 8 patients with objective responses, 5 achieved >99% reduction in HPV16 cfDNA, 4 by week 6, with 3 patients pending analysis at time of data cut-off.

Conclusion: CUE-101 demonstrates safety, tolerability and meaningful anti-cancer activity. Patients treated with CUE-101 monotherapy in 3L showed a long OS. CUE-101 and pembrolizumab combination resulted in an ORR of 47% and decrease in HPV16 cfDNA in the 1L treatment of patients with HPV16+ R/M HNSCC.

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Neutrophil-to-Lymphocyte Ratio Kinetics and Survival with Neoadjuvant Immuno-chemotherapy and Response-Stratified Chemoradiation in Locoregionally Advanced Head and Neck Cancer

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Purpose/Objective(s): Efficacy of immune checkpoint inhibitors (ICI) in curative head and neck squamous cell carcinoma (HNSCC) may be hampered by therapeutic ablation of tumor-draining lymphatics with standard chemoradiation (CRT). Recent emergence of neoadjuvant immunotherapy in HNSCC highlights the need for biomarkers to optimize anti-tumor immunity while eliminating locoregional microscopic disease. An elevated neutrophil-to-lymphocyte ratio (NLR) may reflect an unfavorable balance between pro-tumor inflammation and anti-tumor immunity and is associated with poor immunotherapy outcomes, yet its role as a biomarker of neoadjuvant HNSCC immunotherapy is unknown. We studied the association between NLR dynamics and prognosis in HNSCC patients treated with neoadjuvant immuno-chemotherapy followed by dose and volume response-stratified CRT.

Materials/Methods: 106 (71 HPV positive and 35 HPV negative) locoregionally advanced HNSCC patients prospectively enrolled in two clinical trials (NCT03107182; NCT039449150) were treated with neoadjuvant nivolumab and chemotherapy followed by dose and volume response-stratified treatment with reduced or standard CRT (including elimination of

elective nodal radiation). NLRs for each patient were calculated at baseline, after neoadjuvant therapy, and 1, 3, 6, 9, and 12 months after treatment completion. NLRs at baseline and after neoadjuvant therapy were divided into quartiles, with high NLRs being the highest quartile (>3.66 and >5.63, respectively). NLR differences between reduced and standard CRT groups were analyzed by Wilcoxon ranked sum test. Overall survival (OS) and progression free survival (PFS) were analyzed by Kaplan-Meier and Cox regression methods.

Results: Among HPV positive patients, 37% were Stage II/III; among HPV negative patients, 97% were Stage IV (AJCC 8th ed.). 77% of all patients received reduced CRT. Median follow-up was 26.7 months. High NLRs after neoadjuvant nivolumab/chemotherapy were associated with worse OS and PFS (*p*=0.006 and *p*=0.03, respectively), while baseline high NLRs demonstrated a non-significant trend toward worse OS and PFS (*p*=0.16 and *p*=0.10, respectively). In multivariate analysis controlling for tobacco use, ECOG, stage/HPV status, treatment stratification, and PD-L1 CPS, high NLRs after neoadjuvant nivolumab/chemotherapy remained independently associated with worse OS (HR: 5.58, 95% CI: 1.51-20.56, p=0.01) and PFS (HR: 3.09, 95% CI: 1.10-8.67, *p*=0.03). During follow-up, NLRs were significantly lower in patients receiving reduced CRT compared to those receiving standard CRT at all time points after treatment (p<0.05).

Conclusion: High NLRs after neoadjuvant immuno-chemotherapy associated with worse survival in locoregionally advanced HNSCC patients. Reduced CRT led to more favorable NLRs which may enhance anti-tumor immunity after neoadjuvant immunotherapy. Further work characterizing dynamic changes in immune phenotype with neoadjuvant HNSCC immunotherapy is warranted.

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Updated Dose Expansion Results of a Phase 1/1b Study of the Bifunctional EGFR/TGFβ Inhibitor BCA101 with Pembrolizumab in Patients with Recurrent, Metastatic Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): BCA101 is a first-in-class bifunctional EGFR/TGFβ inhibitor with a manageable safety profile and preliminary efficacy in advanced solid tumors (ESMO 2022 731MO). Pembrolizumab is approved for recurrent, metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) in the CPS≥1 population. Here we report updated results from the fully enrolled expansion cohort combining BCA101 + pembrolizumab as first line therapy in R/M HNSCC.

Materials/Methods: This ongoing single-arm, multicenter dose expansion cohort enrolled patients (pts) with R/M HNSCC as part of a phase 1/1b trial. Pts with tumor PD-L1 CPS≥1 with no prior systemic therapy for R/M disease, ECOG 0-1, and measurable disease (RECIST v1.1) were eligible. Pts received BCA101 (1500 mg IV on days 1, 8, 15) with pembrolizumab (200 mg IV on day 1) every 21-days. Primary endpoint: safety; secondary endpoints: overall response rate (ORR), duration of response, progression-

free survival (PFS), overall survival. Exploratory: molecular and immunologic predictors of response.

Results: Forty-two pts received at least one dose of study drug and 39 pts were evaluable for efficacy. Pts were more often men (30, 71%); median age: 63 (range: 31-84). Twenty pts (48%) had baseline PD-L1 CPS scores of 1-19 and 22 (52%) were ≥20. Oropharynx (20, 48%) [12/20 (60%) HPV/p16-positive] and oral cavity (13, 31%) were the most common subsites. Thirty-three pts (79%) had distant metastases. The ORR was 46% (5 CR, 13 PRs) with 57% (16/28) of HPV/p16-negative pts achieving response. Similar response rates were observed for HPV-negative pts with CPS scores 1-19 (54%, 7/13) and CPS≥20 (60%, 9/15), as well as in pts with distant metastasis (55%, 12/22) and locoregional disease (67%, 4/6). Median PFS (mPFS) continues to mature and currently has not been reached among HPV-negative pts with 13/28 responses ongoing (>30% for more than 6 months), with updates expected to be available at the time of the meeting. Grade 3+ treatment-related adverse events (TRAEs) were observed in 17/42 pts (40%). There were no treatment-related deaths. Acneiform rash was the most common TRAE of any grade (31/42, 74%). Permanent discontinuation of study treatment due to TRAEs was required in 6/42 pts (14%).

Conclusion: BCA101 + pembrolizumab exhibits encouraging safety and anti-tumor activity in first line R/M HNSCC, particularly among HPV-negative pts in both CPS 1-19 and ≥20. Further investigation in HPV-negative pts is planned in a larger randomized study. Study funded by Bicara Therapeutics Inc. and conducted in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (NCT04429542).

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Toripalimab: A Next Generation Designed Anti-PD-1 Antibody for Treatment of Nasopharyngeal Carcinoma

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Purpose/Objective(s): Toripalimab is a PD-1 targeting humanized IgG4 monoclonal antibody (mAb) that is currently under review by US Food and Drug Administration (FDA) for first-line treatment of nasopharyngeal carcinoma (NPC) in combination with chemotherapy. Currently approved PD-1 monoclonal antibodies (mAbs) have demonstrated significant clinical benefit particularly in patients with PD-L1 expressing tumors. However, in three multicenter on-going phase 3 trials (including NPC, Jupiter-02),

toripalimab in combination with chemotherapy has demonstrated good clinical efficacy irrespective of the PD-L-1 status. Here, we are investigating the molecular and functional characteristics of toripalimab that differentiates it from pembrolizumab, an anti-PD-1 antibody currently used in several indications.

Materials/Methods: NPC patients were treated with toripalimab plus chemotherapy or placebo plus chemotherapy (JUPITER-02 clinical trial), and post-hoc analysis was performed using tumor proportion score (TPS) as PD-L1 scoring. Binding affinity and kinetics for PD-1 mAbs toripalimab and pembrolizumab were determined by performing surface plasmon resonance (SPR) experiments. HDX-MS was employed to discern the PD-1 epitope dynamic binding in solution for PD-1 mAbs. The ability of the PD-1 mAbs to activate T cells was characterized using T-cell based assays: 1) staphylococcal enterotoxin B (SEB) stimulated human peripheral blood mononuclear cells (PBMCs) and 2) anti-CD3 and anti-CD28 activated human CD8+ T cells. Efficacy was further tested in an ex-vivo system using dissociated tumor cells from treatment naïve non-small cell lung cancer (NSCLC) patients in the presence of anti-CD3/CD28 antibodies. Activation of PD-1 receptor by the PD-1 mAbs was determined using a Jurkat cell based SHP1 /SHP2 recruitment assay.

Results: Toripalimab plus chemotherapy improved overall survival (OS) irrespective of PD-L1 status in JUPITER-02 trial. Toripalimab exhibited 12-fold higher binding affinity for PD-1 and mainly binds to the PD-1 FG loop when compared to pembrolizumab. Functional assays showed that in comparison to pembrolizumab, toripalimab significantly enhanced T cell activation in-vitro and upregulated IFN-g gene signature in the ex-vivo system with NSCLC tumors. Additionally, toripalimab also demonstrated lower agonistic potential than pembrolizumab upon binding to PD-1, by recruiting lower levels of SHP-1 and SHP-2 in Jurkat-PD-1 cells.

Conclusion: Our study demonstrates that toripalimab is differentiated from pembrolizumab with stronger PD-1 binding and uniquely at the FG loop of PD-1, more potent in-vitro T cell activation and lower agonistic potential. These characteristics of toripalimab present it as a next generation PD-1 checkpoint inhibitor with potential for favorable clinical outcomes in treating cancer patients in combination with chemotherapy irrespective of their PD-L1 status.

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CHS-114: A Cytolytic Anti-CCR8 Antibody that Depletes Tumor-infiltrating Regulatory T Cells as a Treatment for Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): Depletion of intratumoral regulatory T cells (itTregs) represents an attractive therapeutic strategy to enhance antitumor responses. Chemokine receptor CCR8 is preferentially expressed on itTregs compared to peripheral Tregs and other immune cell types. In this study, we evaluate the frequency, localization, and phenotype, of CCR8+ Tregs within resected tumor samples from head and neck squamous cell carcinoma (HNSCC) patients. We demonstrate the effect of CHS-114 (formerly SRF114), an afucosylated anti-CCR8 antibody (Ab), on itTreg depletion and further show that treatment of a mouse tumor model with antiCCR8 Abs depletes itTregs, reduces tumor growth, and enhances anti-PD-1 anti-tumor activity in PD-1 resistant tumors.

Materials/Methods: CCR8+ itTregs were characterized by flow cytometry in HNSCC dissociated tumor cells (DTCs), and by immunofluorescence on FFPE tumor samples (BioIVT). HNSCC DTCs were cultured with CHS-114 to examine immune cell activation and itTreg depletion. Specific depletion of CCR8+ Tregs by CHS-114 was tested in humanized mice generated by reconstituting NSG mice with human PBMC. The activity of anti-CCR8 Ab treatment in combination with anti-PD-1 Ab was assessed in the B16F10 tumor model. Statistical tests were performed using a scientific 2-D graphing and statistics software and P values p<0.05 considered significant.

Results: CCR8 expression in the tumor microenvironment (TME) is highly restricted to itTregs. Across several solid tumor types, >50% of itTregs are CCR8+ cells. Immunofluorescence on FFPE samples shows that CCR8+ itTregs predominantly localize in the stroma but can also be found within tumor nests and tertiary lymphoid structures (TLS), potentially involved in constraining TLS-mediated anti-tumor immune responses. HNSCC tumors had a high abundance and frequency of CCR8+ itTregs (>70%) that exhibited a highly activated phenotype indicated by increased expression of FOXP3, HLA-DR, and Ki-67 compared to CCR8− Tregs. CHS-114 treatment of HNSCC DTC samples resulted in selective depletion of Tregs, NK cell activation, and IFNg production. In NSG mice reconstituted with human PBMCs, CHS-114 treatment, resulted in a dose dependent decrease in frequency of peripheral CCR8+ Tregs that led to a significant increase in ratio of CD8+ Teff to Tregs. Mice implanted with subcutaneous B16F10 tumors survived longer with a combination of anti-murine CCR8 Ab and anti-murine PD-1 Ab treatment.

Conclusion: Together data from this study provides strong evidence that specific depletion of CCR8+ itTregs could be used as an attractive treatment approach as monotherapy and with current immunotherapies for HNSCC. CHS-114 depletes CCR8+ itTreg cells and activates a proinflammatory immune response in the HNSCC TME and in mouse tumor models, supporting its clinical development for cancer treatment. CHS-114 is currently being evaluated in a Phase 1 clinical trial (NCT05635643).

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Phase II Trial Assessing Safety, Efficacy and Immune Correlates of Heterologous Prime-Boost with pBI-11 (IM) and TA-HPV (IM) Plus Pembrolizumab for Advanced, PD-L1 CPS≥1, hrHPV+ Oropharyngeal Cancer

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Purpose/Objective(s): HPV-related OPSCC occurs in younger patients, has a significantly better prognosis, and is most often caused by HPV subtype 16. There is a 90% overall survival for HPV+/p16+ OPSCC (40% for HPV-/p16- OPSCC), which can be cured with multimodality care. For patients with R/M disease, treatment with pembrolizumab (P) +/- chemotherapy is palliative, with a median OS of approximately 12 months for patients with PD-L1 combined positive score (cps) >1 treated with pembrolizumab (P) alone. Heterologous prime boost with DNA priming followed by vaccinia-based boosting against HPV16 viral antigens will be studied using the priming of pBI-11 DNA [pNGVL4a DNA construct encoding HPV16 E7(detox)/ HPV18 E7(detox)/HPV16 E6(detox)/HPV18 E6(detox) fusion protein linked to *mycobacteria tuberculosis* heat shock protein 70] followed by boosting of TA-HPV (recombinant vaccinia-human papillomavirus (denoted TA-HPV) derived from the Wyeth strain of vaccinia which carries modified E6 and E7 genes from HPV types 16 and 18). This study is approved by the Vanderbilt University IRB and is

open (NCT NCT05799144). Additional sites will include the University of Michigan, Mayo Clinic Scottsdale and Mount Sinai Medical Center Miami Beach

Materials/Methods: Patients with R/M, HPV positive OPSCC without prior therapy for R/M disease, without contraindications to immunotherapy and with a PD-L1 cps > 1 will be screened. There is a 6 patient safety run-in. Treatment with pBI-11 vaccine (2 IM injections on weeks 1 and 4) plus one IM administration of TA-HPV on week 7 will be given in combination with P IV on weeks 1, 4, and 7. Following restaging, all patients will continue (including those with PD) with 3 more cycles of P followed by restaging. The primary clinical outcome is RR to addition of vaccine in the 50% of predicted P non-responders (NR) who proceed to Part II (ie conversion to responders). All responders will continue to receive P until progression. Approximately 54 patients with be enrolled. Two research tumor biopsies and blood draws will be obtained pre- and on treatment (week7-9). Tumor tissue cores will be utilized for immunohistochemical and molecular tests (e.g., expression of immune cell and viral markers, TCR sequencing and total transcripts). Blood with be tested for HPV16/18 E6, E7 antibodies and vaccinia virus neutralizing antibodies; proliferative responses of peripheral blood lymphocytes to stimulation by HPV16/18 E6 and E7; HPV16/18 E6- and E7-Specific T cells; and HPV DNA in plasma.

Results: 2 patients enrolled.

Conclusion: Accrual ongoing.

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Pre- and Post-treatment Serum Cytokine Expression Signatures and Survival Outcomes in Patients with Head and Neck Squamous Cell Cancer on Anti-PD-1 Therapy

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Purpose/Objective(s): Clinically relevant biomarkers for anti-programmed death (PD)-1 therapy in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) are limited to PD ligand-1 combined proportion score (PD-L1 CPS) on tumor biopsies. Cytokines are soluble proteins that act as a bridge between innate immunity, inflammation, and cancer. Given the interest in circulating biomarkers, this study sought to evaluate pre- and post-treatment serum cytokine expression signatures in R/M HNSCC treated with anti-PD-1 therapy.

Materials/Methods: In this ongoing, prospective multi-center study, 33 paired pre- and post-treatment (cycle 2 day 1) blood samples were analyzed for 92 cytokine biomarkers (Olink Target 96 Immuno-Oncology) in patients with R/M HNSCC on anti-PD-1-based therapy. Associations between pre-treatment, post-treatment, and change of pre- to post-treatment cytokine levels, overall survival (OS), and progression-free survival (PFS) were assessed using Kaplan-Meier curves, multivariable Cox proportional hazards (adjusted for age, sex, smoking, PD-L1 CPS, ECOG performance status, and platelet count), and unsupervised clustering analyses.

Results: There was a statistically significant association between pre-treatment cytokine expression signature, and both immune composition (e.g., relative fractions of circulating immune cell subtypes) and platelet count. Comparing pre- and post-treatment samples, expression levels of most cytokines exhibited a statistically significant increase (p <0.05). In pre-treatment samples, several cytokines exhibited nominally statistically significant associations (p < 0.05) with both OS and PFS in multivariable model. Similar results were seen in analyses of serum cytokines with PFS in post-treatment samples. Machine learning analysis using Elastic Net models identified a panel of cytokines (CD40.L, EGF, ANGPT1, MCP.4, CXCL1, IL10) that predicted survival with high prognostic performance (Cross Validated C-index of 0.75) in pre-treatment samples. Notably, a different panel of cytokines (ANGPT1, IL10, FGF2, TNFSF14, Gal.1, HGF, PTN, VEGFA, CCL20) predicted survival with even higher prognostic performance (Cross Validated C-index of 0.90) in post-treatment samples. Unsupervised clustering analysis based on the change in pre- versus post-treatment cytokine expression identified two subgroups which differed in their survival trajectories (log-rank p =0.09 and 0.01 for OS and PFS, respectively), where the subgroup with smaller changes in serum cytokine levels was associated with higher survival.

Conclusion: Our results highlight the potential prognostic and predictive value of serum cytokine expression signatures in R/M HNSCC treated with anti-PD-1 therapy and underscore the importance of longitudinal on-treatment assessments in peripheral blood.

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2024 Multidisciplinary Head and Neck Cancers Symposium Late-Breaking Abstracts

LBA 01

Early Disease Recurrence Following Post-operative HPV ctDNA Directed Active Surveillance in Oropharyngeal Carcinoma — Outcomes of a Prospective Pilot Study

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Purpose/Objective(s): Human papilloma virus cell-free tumor DNA (HPV ctDNA) may be able to detect minimal residual disease prior to clinically apparent recurrence. We hypothesized that undetectable post-operative HPV ctDNA can be used to select patients for active surveillance and conducted a pilot study (NCT05307939) omitting or delaying adjuvant radiation until patients develop detectable HPV ctDNA (cohort A).

Materials/Methods: HPV ctDNA was assessed using a liquid biopsy assay which quantifies circulating tumor tissue modified viral (TTMV)-HPV DNA. Eligible subjects had a preoperative TTMV-HPV DNA Score of ≥50 fragments/mL, underwent surgical resection of all gross disease confirmed by post-operative MRI, had a minimum of one pathologic risk factor for adjuvant therapy, and negative post-operative HPV ctDNA at two draws 2-6 weeks after surgery. During active surveillance, patients were monitored with TTMV-HPV DNA testing, imaging, and exam every 3 months (mo). Patients were only treated with delayed adjuvant radiation on study if they develop detectable TTMV-HPV DNA without evidence of gross disease. Our primary endpoint declares this approach worthy of further study if ≥ 85% of evaluable patients (n=15 in each cohort) are gross disease progression-free at one year.

Results: From 3/23/22-8/25/23, 53 patients were screened and 12 patients enrolled on Cohort A before early enrollment closure. Patients were excluded due to TTMV-HPV DNA Score <50 frag/mL (n=21) and positive margin or extracapsular extension (n=11) inclusive of n=2 patients with a positive post-operative TTMV-HPV DNA score. Among patients enrolled in Cohort A, the median pre-treatment TTMV-HPV DNA Score was 448 (Range: 59-2135 frag/mL). Median follow-up was 12.5 mo (Range: 3.7-21 mo). TTMV-HPV DNA was detected during surveillance in 1 of 12 initially enrolled patients 6 mo after surgery without evidence of gross disease, and the patient was treated with 60 Gy of adjuvant radiotherapy on study. 3 additional patients developed radiographic detected disease progression at the 6-mo surveillance time point, and recurrence occurred either synchronously (n=2) with or before TTMV-HPV DNA was detected (n=1). As 3 of 12 patients developed gross recurrent disease, Cohort A closed due to failure to meet our primary endpoint. Cohort B (de-escalated post-operative therapy) remains open and will be reported separately.

Conclusion: Our pilot study approach of using HPV ctDNA based selection of patients for post-operative active surveillance resulted in a high rate of gross disease recurrence and failed to meet our primary endpoint. Radiographic recurrence was not preceded by detectable TTMV-HPV DNA during 3 mo interval surveillance, and additional clinical factors are needed to select patients for active surveillance and initiation of delayed adjuvant therapy prior to recurrence.

LBA 02

Efficacy of a Navigation-Based Intervention vs Usual Care for Decreasing Delays in Starting Guideline-Adherent Adjuvant Therapy for Patients with Head and Neck Cancer

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Purpose/Objective(s): Delays in initiating guideline-adherent postoperative radiation therapy (PORT) affect 50% of patients with head and neck squamous cell carcinoma (HNSCC), disproportionately burden racial minorities, are associated with worse survival, and contribute to racial disparities in mortality. This study tests the hypothesis that NDURE (Navigation for Disparities and Untimely Radiation thErapy), a patient navigation-based intervention, will decrease delays in starting guideline-adherent PORT relative to Usual Care (UC).

Materials/Methods: This randomized clinical trial (RCT) included adults with locally-advanced HNSCC (i.e., oral cavity, oropharynx, hypopharynx, larynx or paranasal sinuses) planning to undergo curative-intent surgery and PORT. Preoperatively, patients were randomized to NDURE, a navigation-based intervention that addresses barriers to timely PORT at the patient-, healthcare team-, and organizational-levels, or UC. The primary endpoint was delay in initiating guideline-adherent PORT, defined as starting PORT > 6 weeks after surgery. The secondary endpoint was time-to-PORT (TTP). The difference in PORT delay between arms was evaluated using a binary regression generalized linear model with randomization stratification factors (race, expected PORT facility) as covariates. The difference in TTP between arms was evaluated by estimating hazard ratios (HRs)

from Cox proportional hazards models, adjusting for stratification factors. Interactions between race and treatment arm were subsequently added to the binary regression and Cox models to compare racial disparities between arms. To detect a 20% reduction in the primary endpoint of PORT delay (45% vs 25%) assuming a two-sided $\alpha = 0.1$ and power of 83%, we planned to accrue n=75 patients/arm evaluable for the primary endpoint, up to a total of n=180.

Results: Among 177 eligible patients randomized to NDURE (n=88) or UC (n=89), 146 patients underwent surgery and had a pathologic indication for PORT. NDURE decreased delays in initiating guideline-adherent PORT relative to UC (model-based PORT delay, 26% vs 61%; risk difference = -35%; 90% CI -48% to -23%; p < 0.001). Median TTP was 39 and 47 days in NDURE and UC, respectively. NDURE improved TTP relative to UC (HR = 1.92; 90% CI 1.43 to 2.58; p < 0.001). The difference in delays in initiating guideline-adherent PORT between Black and White patients was 12% in NDURE vs 24% in UC (p = 0.51). The difference in median TTP between Black and White patients was 1 day in NDURE vs 10 days in UC (NDURE Black/White HR = 0.89; 90% CI 0.48 - 1.53; UC Black/White HR = 0.65; 90% CI = 0.41 - 1.02; p = 0.53).

Conclusion: In this RCT of patients with HNSCC undergoing surgery and PORT, NDURE decreased delays in starting guideline-adherent PORT and improved TTP. These data support conducting a large efficacy trial to evaluate patient navigation-based approaches to improving the timeliness and equity of PORT for patients with HNSCC and their effect on oncologic outcomes.

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