Refining UICC TNM Stage and Prognostic Groups for HPV-Related Oropharyngeal Carcinomas


Purpose/Objective(s): The current TNM staging for oropharyngeal cancer (OPC) was designed empirically for HPV-unrelated [HPV(-)] disease. Emerging evidence suggests it is unsuited for HPV-related [HPV(+)] OPC. This study refines stage grouping for HPV(+) OPC patients and proposes additional prognostic risk groups within the guidelines of the UICC/AJCC TNM framework.

Materials/Methods: We retrospectively analyzed a prospectively assembled OPC cohort treated with primary radiotherapy with or without chemotherapy from 2000-2010. Overall survival (OS) was compared among the current TNM stages (I-IV) for HPV(+) and HPV(-) patients separately. Recursive partitioning analysis (RPA) with ordinal T and N elements derived new RPA-stages objectively. Cox regression calculated relative mortality risk (RMR) to derive additional RMR-stages. The performance of RPA- and RMR-stages was assessed against current UICC stages in predicting OS based on 4 widely accepted criteria: hazard consistency within each stage level; hazard discrimination between stage levels; outcome prediction, and sample size balance. Prognostic risk groups were further derived by RPA combining T-, N-classification, age, and smoking pack-years (PY).

Results: A total of 810 HPV ascertained (by p16 staining) non-metastatic OPCs were identified, including 573 HPV(+) (UICC stage I: 8; II: 25; III: 79; IV: 461) and 237 HPV(-) (I: 8; II: 31; III: 38; IV: 160) OPC. Median follow up was 5.1 years. Reduced 3-year OS with higher UICC TNM stage was evident for HPV(-) (88, 67, 62, and 39% respectively, p=0.003). However, OS was similar within HPV(+) (88, 87, 81, and 80% respectively, p=0.712). RPA and RMR methods were applied to the HPV(+) cohort to refine current UICC stage groupings. RPA divided non-metastatic HPV(+) into RPA-I (T1-3N0-2b), RPA-II (T1-3N2c), and RPA-III (T4 or N3) with corresponding 3-year OS of 88, 81, and 63%, respectively (p<0.001). M1 disease (20% OS at 3-years) was classified as RPA-stage IV. RMR also provided a valid stage grouping scheme (not shown) but was more cumbersome compared to RPA-stage. RPA-stage and RMR-stage were the two best stage groupings while UICC stages performed least well. Prognostic risk groups by RPA sub-divided all HPV(+) cohort to refine current UICC stage groupings. RPA divided non-metastatic HPV(+) into RPA-I (T1-3N0-2b), RPA-II (T1-3N2c), and RPA-III (T4 or N3) with corresponding 3-year OS of 88, 81, and 63%, respectively (p<0.001). M1 disease (20% OS at 3-years) was classified as RPA-stage IV. RMR also provided a valid stage grouping scheme (not shown) but was more cumbersome compared to RPA-stage. RPA-stage and RMR-stage were the two best stage groupings while UICC stages performed least well. Prognostic risk groups by RPA sub-divided all HPV(+) into: group I (T1-3N0-N2c _<20 PY), group II (T1-3N0-N2c_<=20 PY), group IIA (T1-3N0-N2c_>20 PY), group IIIB (T4 or N3, age <=70), group III (T4 or N3, age >70), and group IV (M1 disease), with corresponding 3-year OS of 93, 74, 67, 44, and 20% respectively.

Conclusions: This large cohort study confirms that current UICC TNM stage is unsuited for HPV(+) OPC although acceptable for HPV(-). A refined RPA-based TNM stage grouping significantly improved survival prediction performance for HPV(+) OPC. Prognostic risk groupings are further enhanced by incorporating non-anatomical factors. The result should be validated in an independent dataset.

expression in patient saliva during curative RT at our institution.

**Materials/Methods:** Between July 2012 and November 2013, 12 patients were enrolled on a prospective trial. We collected their saliva before, during, and after curative-intent RT for previously untreated HPV-positive SCC of the oropharynx. Saliva samples were collected and stabilized using a commercial microbial buffer kit (OMNigene DISCOVER OM-505) before the first fraction of RT, once before each of the first 5 RT fractions, once weekly for the remaining duration of RT, and then at the first follow up visit after RT. High-risk HPV viral L1 DNA and E6/7 mRNA were then quantitatively measured using real-time PCR and branched-chain amplification probe (DiaCarta QUANTIVIRUS RNA 3.0), respectively. Viral L1 DNA and E6/7 mRNA levels were normalized in each sample to GAPDH expression and the relative change in saliva expression levels were plotted during the course of therapy.

**Results:** Ten patients completed the planned therapy and full saliva collection as intended. HPV high-risk L1 DNA and E6/7 mRNA were detectable in the saliva of all tested patients before RT was delivered. The relative amounts of viral L1 DNA and E6/7 mRNA increased during the course of radiation therapy with a maximum increase of 138 and 72.3 ratio, respectively (ranges, 0.13 to 34.76, and 0.02 to 31.42). All patients had a peak spike in the quantity of DNA and mRNA early in their radiation treatment with a mean peak recording at 720 cGy and 3240 cGy, respectively. Viral DNA and mRNA were undetectable at the completion of therapy in all but 1 patient and was not detected in any patient at their first follow up visit.

**Conclusions:** High-risk HPV DNA and mRNA are detectable in the saliva of patients with P16-positive oropharynx cancer. Radiation therapy increases the amounts of L1 DNA and E6/7 mRNA detectable in saliva and peaks early in the course of curative treatment. The relative increase in DNA compared to mRNA suggests that RT induces viral activation and may explain the improved outcome seen in HPV-associated oropharynx cancer compared to uninfected patients. Furthermore, at the completion of RT HPV DNA and mRNA are undetectable in the saliva of most patients and 4 to 6 weeks later.

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**Presentation Number: 218**

**Long-Term Quality of Life (QOL) After Chemo-IMRT for Locally Advanced Oropharyngeal Cancer (OPC): A Prospective Longitudinal Study**

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**Purpose/Objective(s):** While organ-sparing IMRT has improved the toxicity profile of chemoradiotherapy (CRT) for head and neck cancer (HNC), prospective long-term patient-reported QOL (PRQOL) outcomes remain scarcely reported. Amidst concerns of delayed-onset dysphagia and other toxicities, we evaluated long-term PRQOL in two prospective studies of chemo-IMRT for OPC.

**Materials/Methods:** 69 of 91 patients enrolled on two consecutive prospective single-institution studies of organ-sparing IMRT with concurrent carboplatin and paclitaxel for stage III/IV OPC between 2003 and 2011, who remained alive and HNC-free > 3 years after CRT, were eligible. All patients received protocol IMRT intended to minimize dose to the swallowing and salivary structures. QOL was collected for all patients pre-treatment and throughout the initial 2 year study period using three validated instruments (HNQOL questionnaire, University of Washington [UW] QOL questionnaire, and xerostomia questionnaire [XQ]). Eligible patients were mailed the three QOL instruments and a qualitative follow-up questionnaire. Long-term PRQOL was compared with prior patient responses during the initial 2-year study period using paired samples t-tests.

**Results:** 40 patients (58%) responded to the mailed questionnaires. Median follow-up was 6.5 years with follow-up of > 5 years for 30 patients (75%) and > 7 years for 16 patients (40%). Primary tumors were HPV+ in all respondents. PRQOL at 2 years did not differ between respondents and non-respondents (p = 0.51). Compared to 2 years post-CRT, no significant change in any PRQOL measure was detected with long-term follow-up, including all HNQOL domains (eating [p = 0.33], communication [p = 0.51], pain [p =
0.085], emotion [p = 0.49], overall bother [p = 0.13]), swallowing (UWQOL swallowing question: p = 0.48), and xerostomia (XQ summary score: p = 0.65). Late dysphagia and HN-related complications > 2 years post-CRT were uncommon. No patient reported late PEG tube placement; four patients (10%) reported new onset dysphagia of whom two required stricture dilation (all > 5 years post-CRT). Compared to pre-treatment, long-term PRQOL mean summary scores for eating, swallowing, and pain increased by <10 points (out of 100), indicating minimal clinical change, while long-term emotional and overall bother domains decreased by >10 points, indicating clinically meaningful improvements from pre-treatment.

**Conclusions:** At long-term follow-up of two prospective studies of chemo-IMRT for OPC, PRQOL remained excellent and unchanged compared to earlier 2-year follow-up, with rare self-reported de novo late toxicity. To our knowledge, these are the longest prospective PRQOL outcomes with comparisons to pre-treatment baseline after chemo-IMRT in HNC.


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**Presentation Number:** 268

**Functional Outcomes with Surgical and Non-surgical Management of Locally Advanced Oropharyngeal Cancer**

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**Purpose/Objective(s):** Transoral robotic surgery (TORS) is increasingly utilized in the management of oropharyngeal cancers. However, patients with high risk features such as positive or close margin and/or extracapsular extension require adjuvant chemoradiation/bioradiation (CRT/BRT) following primary resection (trimodality therapy). We hypothesize a poorer functional outcome with trimodality therapy compared to definitive CRT/BRT.

**Materials/Methods:** An IRB approved retrospective review was performed evaluating all consecutive patients treated in our department for primary oropharyngeal cancers from January 2010 through December 2013. Patients treated by definitive CRT/BRT received IMRT to 70 Gy at 2 Gy/fraction. CRT patients were treated with q3 weekly cisplatinum and BRT patients were treated with q weekly cetuximab. Adjuvant therapy consisted of IMRT 54-66 Gy and in high risk cases q3 weekly concurrent cisplatinum at 100 mg/m². Functional outcomes were analyzed for patients with ≥ 12 month follow-up by comparison of patients receiving TORS trimodality versus definitive CRT/BRT with Fisher’s exact test.

**Results:** 103 patients were identified among whom 40 underwent primary resection (33/40 TORS). Distribution of patients is listed in Table 1. Majority of patients were stage IVA (86%). The 4 year actuarial OS for the TORS group was 79% vs 74% (NS) and 4 year actuarial local control was 94% in TORS vs 86% (NS). 14 patients with TORS trimodality and 52 with definitive CRT/BRT had follow-up ≥ 12 months. TORS trimodality patients had higher rates chronic aspirations (5/14 vs 6/52, p=0.046), velo-pharyngeal dysfunction (4/14 versus 3/52, p=0.032) and fistula formation (1/14 vs 0/52). PEG dependency at 12 months with TORS trimodality therapy was 5/14 versus 8/52 for definitive CRT/BRT (p=0.13). 11 patients were treated with both TORS and adjuvant radiation alone with ≥ 12 month follow-up. TORS and adjuvant radiation alone had low rates of chronic aspirations (1/11), velo-pharyngeal dysfunction (1/11) and fistula formation (0/11).

**Conclusions:** Data suggests that patients requiring trimodality therapy have worse functional outcomes at ≥ 12 months versus those receiving definitive CRT/BRT. TORS is best reserved for select patients with lower stage primary and nodal volume disease to reduce risk of post-operative high risk features and thus limit toxicity from trimodality therapy.
### Patient Treatment Demographics

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<th>TORS (33)</th>
<th>Non-TORS Resection (7)</th>
<th>Non-Surgical (63)</th>
<th>Total (103)</th>
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<tr>
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<td>16 (48%)</td>
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<td>17 (52%)</td>
<td>6 (86%)</td>
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<tr>
<td><strong>Definitive CRT/BRT</strong></td>
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<td>-</td>
<td>63 (100%)</td>
<td>63</td>
</tr>
<tr>
<td><strong>T1/T2</strong></td>
<td>30 (91%)</td>
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<td>19 (30%)</td>
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</tr>
<tr>
<td><strong>T3/T4</strong></td>
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<tr>
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<td>3 (5%)</td>
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<tr>
<td><strong>N1/N2a</strong></td>
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<td>2 (29%)</td>
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**Author Disclosure:**
- C.E. Wooten: None.
- W.A. Wilson: None.
- S.M. Arnold: None.
- T. Gal: None.
- R. Aouad: None.
- J. Valentino: None.
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### Presentation Number: 267

**Risk Factors for Locoregional Recurrence after Transoral Robotic Surgery for HPV+ Oropharyngeal Squamous Cell Carcinoma**

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**Purpose/Objective(s):** Traditional risk factors predicting locoregional recurrence (LRR) following surgery for head and neck squamous cell carcinomas were identified in the pre-HPV era. Patients with HPV positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) present at younger age and have an approximately 50% reduction in death when compared to their HPV- counterparts. Furthermore, transoral robotic surgery (TORS) allows for more detailed intraoperative assessment of microscopic margins. It is unknown if traditional risk factors fully apply to the HPV+ population who undergo TORS. We examined whether traditional indications for adjuvant radiation therapy (RT) (perineural invasion (PNI), angiolymphatic invasion (ALI), T3-4, or N2a-b) or adjuvant chemoradiation therapy (CRT) (extracapsular extension (ECE), or positive margins) also predict for LRR in patients with HPV+ OPSCC.

**Materials/Methods:** After IRB approval, the medical record of 296 consecutive patients treated with TORS for OPSCC were reviewed to identify patients with HPV+ tumors who had indications for adjuvant therapy but did not receive adjuvant therapy.

**Results:** Twenty-one patients with HPV+ base of tongue (n=7) or tonsil (n=14) OPSCC with a median age of 61 years (range 39-81) who did not receive adjuvant therapy despite the presence of intermediate or high risk features were identified. All patients were p16+, 16 were HPV+ by DNA *in situ* hybridization. Indications for adjuvant therapy were ALI (n=1), PNI (n=3), T3 (n=5), T4a (n=1), N2a (n=8), N2b (n=5), or ECE (n=7). All patients had close margins due to the nature of TORS. Eight patients had multiple indications for adjuvant therapy. No positive margins were noted on final path. Median followup after surgery was 22.4 months (range 7.5-58.7). Four of 21 (19%) patients developed LRR at 3.2, 3.4, 4.8, and 5.7 months, respectively. One of 14 (7%) patients with intermediate risk factors only had a LRR, while 43% (3/7) of patients with ECE had a LRR (p=0.049). LRR occurred locally (n=2, base of tongue), in ipsilateral regional lymph nodes (n=1), or in contralateral regional lymph nodes (n=1). These patients had 0, 5, 0 and >10 pack-years smoking history, respectively. Two patients were treated with reexcision and adjuvant RT or CRT respectively and are without evidence of disease 19 months later. The third patient received definitive CRT at an outside institution and was lost to followup. The final patient refused further definitive CRT after 5200 cGy of a planned 7000 cGy). Further follow-up is pending.
Conclusions: In the HPV+ population, ECE remains a risk factor for LRR without adjuvant therapy. However, the role of intermediate risk factors after TORS requires further evaluation with a larger number of patients.


Presentation Number: 266

Dose-Escalated Stereotactic Radiosurgery (SRS) Boost for Unfavorable Locally Advanced Oropharyngeal Cancer, Phase I/II Trial

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Purpose/Objective(s): Management of unfavorable locally advanced oropharyngeal cancer is a common therapeutic dilemma. Large prospective trials have reported poor outcomes after RT or CT-RT, even after an intensive therapeutic approach. We report results of an IRB-approved prospective trial for dose escalation in intermediate and high-risk oropharyngeal cancer.

Materials/Methods: Patients with stage III and IV HPV unassociated oropharyngeal cancer or smokers with high nodal stage (i.e., N2b to N3) and unfavorable biomarkers were enrolled in the study. RT dose to gross tumor volumes were escalated using stereotactic radiosurgery (SRS) boost 1 week after CT-RT consisting of concurrent 80 mg/m2 Cisplatin / 3 weeks and 60 Gy of IMRT at 2Gy/fraction with a strategy of protecting swallowing organs at risk (SWOAR-IMRT). Acute radiation toxicities (= 90 days from start of RT) were scored using (CTCAE) Version 4.0 guidelines and late complications by RTOG/EORTC Scheme. Swallowing functional outcomes were monitored using the Performance Status Scale for H&N Cancer Patients (PSS-HN). Overall feeding tube dependence was calculated from the end of RT. Local-regional control and disease free survival was recorded.

Results: Eleven patients completed (SRS) boost initial dose level 8 Gy in 1 fraction with median follow-up of 26 months (range 8-30 months). 16 patients received their (SRS) boost with dose escalation to 10 Gy fraction and median follow up of 12 months (range, 6 -22 months). Acute G 3 pharyngitis was observed in 53% within the last 2 weeks of CT-RT and no G 4 toxicities were reported. 45% of patients who completed treatment without a feeding tube had rapid recovery to baseline functional outcomes in PSS-HN. Patients who required a feeding tube during treatment experienced a delayed and incomplete recovery of their baseline swallowing function. The 6-month and 1-year rates of feeding tube dependence were 24% and 15%, respectively. Local-regional control and disease free survival were 81%, 100% and 81%, 93%, respectively, for both cohorts. Late G3 dysphagia secondary to extensive tumor necrosis was observed in 4 patients and resulted in pharyngeal hemorrhage in two. All four required surgical intervention.

Conclusions: Radiation dose escalation with radiosurgery boost offers a viable treatment option for unfavorable oropharyngeal cancer patients who are deemed to be unlikely to be cured with conventional irradiation strategies. This offers patients a therapeutic option with moderate toxicities and functional preservation.

Survival Outcomes of Patients With T4a Larynx Cancer Following Initial Management With Surgery Vs. Larynx Preservation Therapy

S. Grover, S. Swisher-McClure, A. Lin, University of Pennsylvania, Philadelphia, PA

Purpose/Objective(s): Consensus practice guidelines recommend total laryngectomy (TL) as initial management for medically operable patients with T4a larynx cancer. In addition, patients with T4a larynx cancer are frequently excluded from clinical trials of larynx preservation (LP) because of anticipated poor larynx preservation rates and concerns for inferior survival outcomes. Using a large national cancer registry, we examined recent practice patterns among patients with T4a larynx cancer, and compared survival outcomes between patients receiving TL vs. LP.

Materials/Methods: Our study included 1,307 patients diagnosed with non-metastatic invasive T4a squamous cell carcinoma of the larynx from 2003-2006 in the National Cancer Database. Treatment groups were defined as initial surgery (TL + adjuvant therapy) vs. LP with chemoradiation (CRT). Patients receiving surgery only, radiation alone, or those not receiving any treatment within 100 days of diagnosis were excluded. Univariate and multivariate (MVA) logistic regression models were used to assess predictors (year of diagnosis, age, gender, race, insurance status, type of treatment facility, distance from center, center case volume, N stage and comorbidity index) of receiving surgical treatment. Survival outcomes were compared using Kaplan-Meier and Cox proportional hazards regression methods.

Results: Overall, 65% (n=856) of patients received LP and 35% (n=451) underwent TL + adjuvant RT or CRT. On MVA, patients with advanced nodal disease were less likely to receive TL compared to patients with N0 disease (N2 vs. N0, 25.4% vs. 41.2%, OR 0.46, 95% CI 0.15-0.82; N3 vs. N0, 22.2% vs. 41.2%, OR 0.34, 95% CI 0.15-0.82). Patients treated in facilities with high case-volume were more likely to receive TL compared to those treated at low case-volume facilities (47.1% vs. 28.6%, OR 2.03, 95% 1.51-2.73). Patients diagnosed in 2006 were less likely to receive TL compared to patients diagnosed in 2003 (28.1% vs. 40%, OR 0.60, 95% 0.43-0.86). Median survival among patients receiving TL vs. LP was 60 vs. 31 months (p<0.001). After controlling for potential confounders, patients receiving LP had inferior overall survival compared to those receiving TL (HR 1.51 95% CI 1.28-1.75).

Conclusions: Approximately two out of three patients with T4a larynx cancer receive LP rather than TL, despite practice guidelines suggesting TL as the preferred initial approach. Use of TL appears to be declining over time. Patients treated in high case-volume centers are more likely to receive primary surgical management. Further research should investigate treatment decision counseling by physicians to their patients, patient decision making, and potential strategies to reduce observed differences in patient survival outcomes.

Author Disclosure: S. Grover: None. S. Swisher-McClure: None. A. Lin: None.

Potential Cure in HPV-related Oropharyngeal Cancer with Oligometastases


Purpose/Objective(s): To identify survival predictors for HPV-related [HPV(+)] and unrelated [HPV(-)] oropharyngeal cancer (OPC) patients with distant metastasis (DM) following primary radiotherapy +/- chemotherapy (RT/CRT).

Materials/Methods: All HPV status confirmed (by p16 staining) OPC cases managed with RT/CRT between 2000-2011 were included. DMs were detected based on radiologic and/or histologic confirmation. DM characteristics and survival after DM were compared between HPV(+) and HPV(-) cohorts. Cox regression models identified survival predictors.
**Results:** HPV status was ascertained in 934/1238 (75%) consecutive OPC cases. DMs were detected in 138/934 (15%) including 87 HPV(+) and 51 HPV(-) cases at a median 1.42 vs. 0.69 years following RT (p<0.001). Lung was the most common DM site [HPV(+) 68 (78%) vs HPV(-) 46 (90%)]. Multi-organ (>=2) DMs occurred in 46 (53%) HPV(+) vs 10 (20%) HPV(-) cases (p<0.001). HPV(+) single-organ DM were more likely to be oligometastases (defined as 1-5 lesions confined to one organ) (25/41, 61%) vs HPV(-) (11/41, 27%) (p=0.002). Concurrent LRF was documented in 21 (24%) HPV(+) vs 19 (29%) HPV(-) cases. More HPV(+) than HPV(-) patients received treatment for DM (60% vs 31%, p<0.001). Median FU after DM for surviving patients was 1.86 years. HPV(+) DM patient had longer OS vs HPV(-): 26% vs 16% and 17% vs 0% at 2- and 3-years respectively (p=0.01). Potential cure (no evidence of disease at last follow up, 1.9-7.7 years post-DM) was seen in 9/25 (36%) HPV(+) (7 surgery, 1 RT, 1 chemo) and 1/11 (10%) HPV(-) (surgery) case, all with oligometastases in lung. Multivariate analysis identified untreated DM (HR 4.8, p<0.001), presence of concurrent locoregional failure (LRF) (HR 1.61, p=0.03), multi-organ DM (HR 1.91, p=0.01), and smoking pack-years (every 10 pack-year increment) (HR 1.09, p=0.03) as adverse predictors for survival. HPV status (p=0.37), age at DM (p=0.32), and interval to DM (p=0.80) did not predict survival.

**Conclusions:** This study confirms that HPV(+) vs HPV(-) patients have different DM characteristics. The majority of HPV(+) DM involved more than 2 organs. Multi-organ DM and presence of LRF reduces survival. Patients who received treatment for DM have prolonged survival, although decision-to-treatment may be multi-factorial. Potential ‘cure’ is possible in a subset (9/25, 36%) of HPV(+) patients with single-organ oligometastases. Active treatment should be considered for DM patient with acceptable performance status, especially for those with oligometastases.