SMOKING DURING THERAPY NEGATES SIGNIFICANT SURVIVAL BENEFIT ASSOCIATED WITH HUMAN PAPILLOMA VIRUS (HPV) POSITIVE SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

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**Purpose:** To evaluate the interaction of smoking status (current compared to former/never smokers) and human papilloma virus (HPV) status on survival in patients with oropharyngeal squamous cell carcinoma (OPSCC).

**Methods:** This retrospective study included patients with OPSCC who were diagnosed and/or treated at Roswell Park Cancer Institute between 2007 and 2013. All patients were evaluated for high risk HPV types 16 or 18 using in-situ hybridization technique. Demographic, clinical history, staging, therapy, and outcomes data were collected. Multivariate Cox-regression analysis and log-rank test were used to compare survival difference between smoking groups. Results were presented as multivariate Hazard Ratio (HR) and 95% confidence intervals (CI). A p-value of 0.05 or lesser was considered statistically significant.

**Results:** A total of 172 patients diagnosed with OPSCC underwent tumoral testing for HPV. Of these, 28 OPSCC tumors (16%) overlapped with other sub-sites within the head and neck. HPV positivity rate was 70% for the tumors confined to the oropharynx and 43% for the overlapping tumors (p-value: 0.005). More than 88% of patients had stage III or IV disease. Concurrent chemo-radiation was used as the sole therapy in 62.8% of patients. Current and former/never smokers were 30% and 71% of the cohort, respectively. Median follow-up for those alive at last visit was 22 months (range: 1 to 66 months). The median overall survival for HPV positive current smokers was 34 months, versus >60 months for former/never smokers (p value: 0.001). The median overall survival for HPV negative current smokers was 25 months versus >60 months for former/never smokers (p value: 0.70). In the never/former smoker group, the HPV positive patients had a significantly better overall survival (HR: 0.29, 95% CI: 0.08 - 1.00, p-value: 0.05) and disease specific survival (HR: 0.13, 95% CI: 0.02 - 0.67, p-value: 0.02), compared to HPV negative patients. In the current smokers, there was no significant difference in overall survival (HR: 1.47, 95% CI: 0.35 - 6.14, p-value: 0.60) or disease specific survival (HR: 0.89, 95% CI: 0.19 - 4.18, p-value: 0.88) in HPV positive, when compared to HPV negative patients.
Conclusions: Smoking during cancer therapy is a poor prognostic factor, independent of HPV status, in patients with OPSCC. Every effort should be made to get current smokers with OPSCC to stop smoking.
SURVIVAL ANALYSIS OF 323 PATIENTS WITH ADVANCED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA STRATIFIED BY SMOKING STATUS, P16 POSITIVITY AND TREATMENT MODALITY

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Background:

The treatment options for oropharyngeal squamous cell carcinoma (OPSCC) have expanded with the advent of the new transoral approaches and techniques. Current treatment pathways are evolving to include surgery in selected patients with tailored approaches that incorporate p16 and smoking status with the traditional anatomic and pathologic variables. Tobacco smoking and p16 status are significant prognostic variables in OPSCC but there is a paucity of studies comparing survival of patients with different treatment modalities that include surgery and incorporates these two factors.

Objective:

This population based study determined the five year survival outcomes in patients with stage 3 and 4 OPSCC when stratified by smoking status, p16 and treatment modality.

Materials/Methods:

Demographic, pathologic and survival data was obtained from all patients diagnosed with stage 3 or 4 OPSCC from 1998-2009 in northern Alberta. Tissue microarrays (TMAs) were constructed to include all patients treated within this time frame with sufficient pathologic specimen available (n=323). TMAs were and stained by immunohistochemistry for p16 and scored for positivity using standardized, automated digital threshold values. Treatment groups were stratified as follows:

1) Primary surgery + chemoradiation (S+CRT), n = 84
2) Primary surgery + post-operative radiation (S+RT), n = 86
3) Primary chemoradiation +/- salvage surgery (CRT), n = 60
4) Radiation only, n = 33
5) Surgery only, n = 33
6) Palliative treatment, n = 27

Kaplan-Meir analysis was used to perform pairwise univariate comparisons (Log-rank) of overall and disease specific survival (DSS) between strata. The Cox proportional hazards model was used to perform multivariate analyses of survival.

Results:
The prevalence of smoking in our population was 74.9% and 46.6% of the patients were P16 positive. Five year DSS according to p16 status was as follows.

1) S+CRT: p16-, 63.3 %; p16+, 87.9 %.
2) S+RT: p16-, 52 %; p16+, 73.2 %
3) CRT: p16-, 37.4 %; p16+, 63.7 %.

Five year DSS according to smoking status was as follows.

1) S+CRT: smoker-, 82.4 %; smoker +, 77.6 %.
2) S+RT: smoker -, 91.7 %; smoker+, 55.9%.
3) CRT: smoker-, 80.2 %; smoker+, 39.4%.

Combining smoking and p16 positivity, significantly poorer survival outcomes were seen across treatment groups for p16 -, smoker+ patients. Multivariate analysis identified significant hazard ratios (HR) associated higher ECOG (HR=1.56, 95% CI 1.2-2.06), Non-smoking status (HR=0.34, 95% CI 0.17-0.92), p16 positivity (HR=0.54, 95% CI 0.34-0.86). In reference to S+CRT (HR=1), significantly poorer prognosis was associated with CRT (HR=3.23, 95 % CI 1.61-6.47). Age, gender, Charlson Comorbidity Index and increasing tobacco smoking from 10-50+ pack years had no significant impact on survival differences between groups.

Conclusions:

This represents the largest population cohort of OPSCC survival comparing surgical and non-surgical treatment modalities, stratified by smoking and p16 status. S+CRT and S+RT treatment modalities offer the most significant survival advantage over CRT in patients with a positive smoking history, regardless of p16 positivity, and in P16 negative patients regardless of smoking status. All three treatment modalities offer equivalent survival outcome for patients that are non smokers and p16 positive.
Background

A close/positive margin following surgery for head and neck cancer is widely accepted as an absolute indication for postopCTRT following randomized clinical trials reported by Bernier J (NEJM, 2003) and Cooper et al (NEJM, 2003). However, this recommendation was made without any knowledge of HPV status in these trials. Since Human papilloma virus is now responsible for 75% of oropharyngeal cancers, it is important to determine if margin status predicts outcome in HPV positive patients compared to HPV negative patients. The objective of our study was therefore to analyze a cohort of patients treated primarily with surgery and postoperative RT (ie chemotherapy naive) to determine the impact of margin status on outcome stratified by HPV status.

Methods

After IRB approval, 300 patients with oropharynx cancer treated with open surgical resection +/-PORT at Memorial Sloan Kettering Cancer Center between 1985 and 2005 were identified. Tissue was available for p16 analysis in 201 patients. There were 66 (33%) tonsil, 46 (23%) soft palate and 89 (44%) base of tongue cancer patients. Patients were stratified into HPV positive and negative groups using p16 immunohistochemistry as a surrogate marker. Margin status was categorized into close (<5mm)/positive versus negative (>5mm). Impact of margin status on disease specific survival (DSS) was calculated by the Kaplan Meier method in all patients and in patient groups stratified by p16 status and tumor subsite.

Results: The median age was 58 years (range 27-84). The median follow up was 65 months (range 1-277). 30% of patients had T3T4 disease and 79% had a pathologically positive neck. 66% of patients required either a mandibulotomy or mandibulectomy for resection and 69% had PORT. 53% were p16 positive. 47% had close/positive margins. When stratified by p16 status, close/positive margins was predictive for poor outcome in p16 negative patients (DSS 50% versus 79%, p=0.009) but not in p16 positive patients (DSS 82% versus 84%, p=0.592). When stratified by tumor subsite close/positive margins were not significant for poor outcome in p16 positive tonsil cancer patients (DSS 89% vs 87%, p=0.83) and also p16 positive base of tongue cancer patients (DSS 80.4% vs 86.2%, p=0.331).

Conclusion:

This data provides preliminary evidence that in patients with HPV positive oropharyngeal cancer treated with surgery, close/positive margins do not predict an adverse prognosis.
Primary Surgery as Compared to Primary Chemoradiation Significantly Improves Disease-Free Survival Independent of Human Papillomavirus Status in Oropharyngeal and Oral Tongue Squamous Cell Carcinoma

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Objective: Recent studies have shown that up to 80% of oropharyngeal cancer in the U.S. is attributable to infection with the human papillomavirus (HPV). Although numerous studies have consistently shown that HPV-related oropharyngeal cancer has excellent survival outcomes following primary chemoradiation, the prognostic value of HPV positivity is less clear among patients treated with primary surgery. The aim of our study was to evaluate the impact of primary surgery in treating HPV-related head and neck squamous cell carcinoma (HNSCC) as compared to primary chemoradiation.

Methods: This retrospective cohort study was conducted at the University of Pennsylvania Health System. We identified in the Penn Tumor Registry 389 adult oropharyngeal and oral tongue SCC patients who had their initial definitive treatment between 1/1/2010 to 12/31/2011 using the Penn Tumor Registry, out of which we further identified 267 patients with known p16 status as a surrogate for HPV positivity. Patients who received palliative, unknown, or no treatment were excluded. Patient demographics, cancer stage, and treatment types were collected at baseline, with follow-up through 9/30/2013. The primary outcome was 2-year disease-free survival (DFS). Cox regression model was performed, and hazard ratios (HRs) were calculated.

Results: Our analysis included 196 patients who had primary surgery and 54 patients who had primary chemoradiation. The mean follow-up time was 18 ± 8 months. Of the 250 patients, 80% had oropharyngeal cancer (OPC) (n=199) and 20% had other tongue squamous cancer (n=51). 74% of patients were positive for p16 (n=185). The p16 positive rate increased to 87% (n=173) in OPC and decreased to 24% (n=12) in oral tongue cancer, and this difference was significant (p<0.001). Compared to HPV-negative patients, HPV-positive patients were significantly more likely to be male (86% vs. 57%, p<0.001); and be AJCC TNM stage 4 (77% vs. 40%, p<0.001); HPV-positive patients were also more likely to have received radiation (78% vs. 38%, p<0.001) and chemotherapy (58% vs. 26%, p<0.001), but were significantly less likely to have received surgery (75% vs. 88%, p=0.034). After adjusting for HPV status, treatment and other factors, there was no significant difference in DFS between OPC and oral tongue SCC (HR=0.49, p=0.106), so we combined them and adjusted for the effect of cancer site in the analysis. Of the 250 patients included, the overall 2-year DFS rate was 70% (n=174): 75% (n=138) in HPV-positive patients and 55% (n=36) in HPV-negative patients. After adjusting for all potential confounders in the multiple Cox regression model, primary surgery with or without adjuvant therapy significantly improved 2-year DFS in both HPV positive and negative patients as compared to primary chemoradiation (77% vs. 43%, adjusted-HR=0.24, 95%CI 0.13-0.41, p<0.001). In our sub-analysis of HPV-positive patients, similar improvement in DFS was found comparing primary surgery to primary chemoradiation (83% vs. 48%, adjusted-HR=0.22, 95%CI 0.11-0.44, p<0.001). In our sub-analyses of all-cause mortality, none of the results were significant.

Conclusion: Primary surgery significantly improved 2-year DFS in oropharyngeal and oral tongue SCC as compared to primary chemoradiation. This effect was independent of HPV status, cancer site and AJCC TNM stage.
Aim: Chemoradiation is the treatment of choice for tumors of the oropharynx. In most cases the main indication to use the surgery is the treatment of recurrent of primary tumor or regional metastases. The development of optimal algorithm of treatment within recurrent cancer of the oropharynx after chemoradiation therapy for establishing criteria of resectability, the volume of surgical treatment, methods of surgical access and plastic replacement of the defect to improve the results of treatment of recurrence in oropharyngeal region.

Material and methods: The surgical treatment for recurrent oropharyngeal cancer have been performed in 53 patients (pt.) (47 - mail, 9 - female) after ineffective chemoradiotherapy from 1995 till 2013. The distribution of the localization was as follows: lateral wall - 31 pts, base of the tongue - 14 pts., soft palate - 8 pts. 16 pts. were operated on because of persistent disease 3 months after chemoradiation and 37 pts. - because of recurrence more than 6 months after chemoradiation. CT and MRI are very important to estimate the spread of the tumor. Pterygoid muscle and mandible involvement determines the type of operation. The median mandibulotomy have been made in 38 pts., segmental mandibulectomy - in 15 pts. In 21 cases the operations were limited by the resection of the same anatomic region and plastic replacement of the defect was performed with local tissues. Otherwise 32 pts. hold a combined resection with the use of the pectoralis major muscle flap (26 pts.) and temporal fascial-aponeurotic flap (6 patients).

Results: Functional and aesthetic rehabilitation were achieved in 51 pts. (96.2%). Progression of the disease was diagnosed in 24 pts (45.3%) as local recurrence - 15 pts. (28.3%), regional metastasis - 6 pts. (11.3%) and distant metastasis 3 pts. (5.7%). Soft palate is the worst localization of the tumor because of 75% progression disease (6 cases in 8 pts.). We obtain better results in persistent tumor group - 4 cases of progression (25%) in contrast to the recurrence tumor group - 20 cases of progression (54.1%, p<0.05).

Conclusions: Surgery treatment of recurrent tumors of the oropharynx requires the rigorous selection of patients according to inspection and examination. Mandibulotomy is an appropriate surgical approach for tumors of the oropharynx in cases of uninvolved mandible. Multidisciplinary team and careful observation after chemoradiation are necessary to achieve the better results. Persistent tumor of the oropharynx (in comparison with the recurrence group) is the group of patients with favourable prognosis - 75% progression free 3-years survival.
Objectives: To analyze local failure following lateral pharyngotomy for selected untreated invasive squamous cell carcinoma (SCC) of the lateral oropharynx.

Study Design: Retrospective review from a university teaching hospital.

Methods: Inception cohort of 91 patients who underwent lateral pharyngotomy for an isolated and previously untreated selected invasive carcinoma of the lateral oropharynx classified as T1 (26), T2 (47), T3 (11) and T4 (7). Induction chemotherapy, neck dissection and post-operative radiation therapy were used in 91.2%, 94.5% and 53.5% of patients.

Results: The 5-year Kaplan-Meier estimate of local failure was 16.6% for T1, 19% for T2, 38.6% for T3 and 16.7% for T4 lesions (p = .46). In a logistic regression model, only positive margins of resection statistically increased (p = .01) the risk for local failure. In patients with safe margins of resection, the 5-year Kaplan-Meier estimate of local failure was 5.6% for T1, 10.7% for T2, 23.8% for T3 and 20% for T4 lesions (p = .4). Local failure had a significant impact on increased nodal failure (p= .001) and on reduced survival (p < .0001).

Conclusion: The lateral pharyngotomy approach should be viewed as a valuable oncologic alternative to mandibulotomy approaches and chemoradiation protocols in patients with selected SCC of the lateral oropharynx.
SURVIVAL FOLLOWING SALVAGE SURGERY FOR HPV-ASSOCIATED HEAD AND NECK CANCER
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Background: Definitive chemoradiation therapy is playing an increasing role in the primary treatment of oropharyngeal squamous cell carcinoma, while surgical resection is frequently being used to "salvage" cases that show persistence or recurrence. The outcomes of salvage surgery in the setting of HPV-associated oropharyngeal cancer have not been well described.

Materials & Methods: Patients who presented to the Johns Hopkins Hospital between 2008-2012 with Head and Neck Squamous Cell Carcinoma (HNSCC) were identified. Patients who underwent salvage surgery for persistence or recurrence of HPV-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC), and who had adequate tissue as well as clinicopathologic parameters for analysis, were included. Patients who underwent salvage surgery for glottic or supraglottic HNSCC were included for comparison.

Results: A total of 48 patients were included in this study. Eighteen patients with HPV-OPSCC and 30 patients with glottic/supraglottic HNSCC were included. Following salvage surgery, the 2-year overall survival was 73% (95% confidence interval [CI]: 42%-89%) in HPV-OPSCC, vs. 52% (95% CI: 32%-69%) for laryngeal SCC. This difference was not statistically significant after adjustment for confounders (p=0.84). The 2-year disease-free survival was also similar between oropharyngeal (47%; 95% CI: 21%-69%) and laryngeal (51%; 95% CI: 0.28-0.70) cancer following salvage (p=0.81). Age, race, gender, smoking status, tumor-stage, lymph node-stage, and HPV-status were not found to be predictive of disease-free or overall survival.

Conclusion: The ability to salvage patients with persistent or recurrent oropharyngeal squamous cell carcinoma is acceptable with overall 2-year survival of 73%. However, the 2-year disease free survival of 47% suggests that it is challenging to achieve durable cures with salvage surgery. Long term predictors of outcome and survival following salvage surgery for HPV-HNSCC remain to be identified. Furthermore, prospective randomized studies comparing primary chemoradiation to primary surgery are necessary to determine the optimal treatment paradigm for patients with HPV-HNSCC.
Background: Trans-oral robotic surgery (TORS) is becoming a favored primary treatment for early staged tonsil cancers. Tumor ablation requires a radical tonsillectomy (RT) and provides access to the contralateral tonsil. Thus, begging the question: should the contralateral tonsil be removed as well? The advantage of contralateral tonsillectomy (CT) is extirpating potential occult disease in a cancerized field. Opponents may counter by citing unnecessary surgery with potential increased morbidity.

Objective: To determine the risks and benefits of CT with RT for early staged tonsil cancers treated with primary TORS.

Design: Retrospective review.


Methods: Patients with tonsil cancer who underwent RT +/- CT via TORS were included. Primary outcome was the rate of detecting occult cancers in the contralateral tonsil. Secondary outcome was comparison of clinical outcomes between RT and RT+CT including: blood loss (EBL), complications, length of hospital stay (LOS), oropharyngeal strictures, and GTube rates.

Results: 79 patients underwent TORS for tonsil cancer. 49 patients had unilateral RT. 30 patients had RT+CT. 3 (10%) patients were found to have occult synchronous contralateral tonsil cancers. All were excised with negative margins. EBL was 13.5cc for RT and 25cc for RT+CT (p=0.0001). 6% of patients with RT had a complication and 10% of patients with RT+CT had a complication (p=0.53). The GTube rate for RT and RT+CT at 3 months post-surgery was 21% and 23%, respectively (p=0.59). Median LOS for each group was 4.0 days (p=0.12). There were no instances of circumferential scarring with BT.

Conclusion: RT+CT via TORS for tonsil cancer is recommended to detect occult cancer in 10% of patients. Complication rates are similar to RT alone.