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Smoking cessation associated with improved survival in oropharynx cancer treated by chemoradiation

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Abstract

Objectives—The effect of smoking and human papilloma virus (HPV) on overall survival (OS) of oropharyngeal squamous cell carcinoma (OPSCC) patients undergoing concurrent chemoradiation (CCRT) remains unclear.

Study Design—Retrospective Review

Methods—Clinical characteristics of OPSCC patients treated between 2008–2015 with CCRT were abstracted from medical records. OS curves and multivariate cox proportional hazard ratios (HR) were examined.

Results—Out of 120 evaluable patients, 71% had HPV+ tumors. Median follow-up duration for the entire cohort was 41.5 months (6–88 months). HPV+ current smokers experienced significantly worse 5 year OS (73% alive vs. 36% alive, $p=0.01$) with a similar trend in HPV–current smokers (66% alive vs. 31% alive, $p=0.28$) compared to former/never smokers undergoing CCRT. In a multivariate cox proportional hazard model adjusted for age, gender, and overall tumor

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stage, HPV+ current smokers experienced nearly a four-fold increase in overall mortality in comparison to HPV+ never/former smokers (HR= 3.68, 95% CI=1.35–10.0). Similarly, current smokers with HPV– tumors (HR= 6.8, 95% CI=1.11–41.67) had increased mortality compared to never/former smokers.

Conclusions—Current smoking is associated with poor prognosis, independent of HPV status, in OPSCC CCRT treated patients. Current smoking produced an approximately 4 to 7 fold increase in risk of mortality for HPV+ and HPV– patients respectively. Regardless of pack-years, efforts should be made to achieve smoking cessation before CCRT regardless of HPV status.

Keywords

Tobacco; Nicotine; HPV; SCCHN; base of tongue

Introduction

Squamous cell cancer of the head and neck (SCCHN) occurs annually in over 550,000 people worldwide ¹. In the US in 2015 59,340 incident SCCHN cases are expected and 12,290 people are expected to die of SCCHN ². Tobacco use has been the major risk factor for developing SCC of the head and neck ³. In recent decades, a higher rate of human papilloma virus (HPV) associated SCCHN has been reported, especially in tumors arising in the oropharynx ⁴⁵.

The 2014 Surgeon General's Report (SGR) concludes that smoking by cancer patients and survivors causes adverse outcomes in cancer patients, including increases in overall and cancer specific mortality (In: The Health Consequences of Smoking 2014) ⁶. Several large studies report current smoking increases overall mortality in head and neck cancer patients ⁷⁸⁹¹⁰¹¹¹² and mortality is further linked to pack years ¹¹¹³. Importantly, current smoking by SCCHN patients is associated with increased overall and cancer specific mortality as compared with patients who quit smoking within the past year ¹⁴. However, there are limited data on the relationship between smoking, cessation, HPV, and mortality.

In 2010, Roswell Park Cancer Institute initiated an automated tobacco assessment and referral program where all patients were screened for tobacco use and automatically referred to a dedicated phone based cessation program ¹⁵. We have previously shown that lung cancer patients who quit smoking after diagnosis using this program had significant improvements in overall survival as compared with patients who continued to smoke ¹⁶. The purpose of this study is to evaluate the relationship between smoking, smoking cessation, HPV status, and survival in a cohort of OPSCC patients treated with definitive concurrent chemoradiotherapy (CCRT).

Materials and Methods

The Roswell Park Cancer Institute (RPCI) Institutional Review Board approved this retrospective study of OPSCC patients diagnosed and treated with CCRT between 2008 and 2015. To be included in this study the primary tumor had to be: (1) an invasive squamous cell carcinoma limited to the oropharynx or an oropharyngeal primary overlapping other

adjacent anatomical sites (ICD-O-3: C09-C10), (2) evaluated for high risk HPV types 16 or 18 using in-situ hybridization (ISH) technique, (3) treated with curative CCRT and (4) have no prior history of SCCHN. No patients with metastatic disease were included. Overall, 198 consecutive OPSCC patients were diagnosed or treated at RPCI between 2008 and 2015. Of these, 120 (61%) patients qualified based on the above selection criteria. All of these 120 patients had HPV testing conducted on clinical request by in situ hybridization (HPV 16/18 biotinylated DNA probe -Y1412- Dako, Carpinteria, CA). In the first few years of this study period HPV testing was not routinely done and was performed only if specifically ordered. In the later years of the study, HPV testing was routine and omitted only if there was insufficient tumor sample due to diagnosis by fine needle aspiration. P16 staining as a surrogate marker for HPV positive has been routinely done for many years but was not available for the early patients in this cohort and was therefore not analyzed.

Demographic and clinical characteristics of study subjects, including age, gender, social habits and previous cancer history, were collected by a detailed medical chart review. Clinical information regarding the current cancer such as stage, grade, anatomical sub-site, treatment modality, cancer recurrence, survival status, survival duration, and cause of death were also collected. The follow-up patient schedule as well as the cisplatin based chemotherapy (weekly or every three weeks) and intensity modulated radiation therapy regimens (70 Gray to the primary tumor and 56 Gray to the elective lymph nodes in 35 fractions) applied in this cohort have been previously described in detail ^{17,18}.

Patients were categorized as current, former or never smokers based on the history noted on their clinical record at diagnosis. Patients identified as currently smoking at consult visits were referred to an automated smoking cessation service ¹⁵. Prior to 2010, the single treating radiation oncologist (AS) for this cohort provided formal smoking cessation support to all current smokers. Patients who reported having used tobacco within the 30 days prior to treatment were considered current smokers. Pack-years of smoking was calculated by multiplying packs of cigarettes smoked per day by the number of years smoked. All patients, if committed to smoking cessation, were given 30 days to try to quit smoking prior to the start of radiation therapy. If successful, these patients were categorized as former smokers.

Descriptive statistics of the overall cohort were summarized and clinical characteristics were compared between HPV+ and HPV- patients using Pearson Chi Square test for categorical variables and Wilcox Rank Sum test for continuous variables.

The effect of HPV status and the effect of smoking status on overall survival (OS) and disease-specific survival (DSS) were examined using multivariate cox proportional hazard regression models. Models were adjusted for age, gender, and overall tumor stage. Survival trends were estimated using Kaplan-Meier (K-M) survival curves. A p-value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS software (SPSS for Windows, Version 16.0. Chicago, SPSS Inc.).

Results

Table 1 contains descriptive characteristics for the entire OPSCC cohort. The median age of this predominantly male cohort was 58.5 years old (36–85 years old). Among the 120 OPSCC patients included, 81% had an overall tumor stage of 4 and 75% had a nodal stage of N2 or N3. Current smoking was noted in 23% of patients (n=28) and 22% of patients (n=26) reported never smoking. Median follow-up duration for the entire cohort was 41.5 months (6–88 months).

Seventy-two percent of the patients were HPV+ and 28% were HPV– (Table 2). There was no statistically significant difference in age, gender, tumor stage, or nodal stage between HPV+ and HPV– patients. HPV– patients trended toward higher median pack years than HPV+ patients (30 vs. 18, $p=0.075$). HPV+ patients had a greater proportion of poorly differentiated tumors compared to HPV– patients ($p<0.01$).

The Kaplan Meier curve for OS favored patients with HPV+ tumors vs. those with HPV– tumors ($p=0.08$) (Figure 1). When HPV status was stratified by smoking status, the Kaplan Meier curves for OS favored never/former smokers vs. current smokers but the difference only reached statistical significance for patients with HPV+ tumors ($p=0.01$) though there was a similar trend in HPV– patients (Figure 2). The cumulative survival rates at the end of 5 years for each group are as follows: HPV+ never/former smokers=73%, HPV+ current smokers, 36%, HPV– never/former smokers=66% and HPV– current smokers=31%.

Results from the univariate and multivariate analysis for the effect of smoking status on overall survival stratified by HPV status are shown in Table 3. In a multivariate cox proportional hazard model adjusted for age, gender, and overall tumor stage, HPV+ current smokers experienced nearly a four-fold increase in overall mortality in comparison to HPV+ never/former smokers (HR= 3.68, 95% CI=1.35–10.0). Similarly, current smokers with HPV– tumors (HR= 6.8, 95% CI=1.11–41.67) had increased mortality compared to never/former smokers.

As shown in Table 2, the cohort ultimately included 26, 66, and 28 never, former, and current smokers respectively. Starting in 2010, automated referrals to a smoking cessation program were completed for 32 patients identified prior to treatment. Of these 32 patients, 22 patients participated in at least one call and 14 participated in follow-up calls and support through the program. Eleven (78.6%) of the 14 patients that participated were alive at their last follow up. Of the 10 patients who quit smoking 30 days prior to CCRT, 9 (90%) were alive at last follow up. Of the 4 patients who reported continued smoking, 2 (50%) were alive at last follow-up.

Discussion

This study has several important findings. First, HPV+ and HPV– OPSCC patients treated with CCRT and who were current smokers have a 4 and 7-fold increased risk of mortality respectively. HPV+ current smokers experienced significantly worse 5 year OS (73% alive vs. 36% alive, $p=0.01$) with a similar trend in HPV– current smokers (66% alive vs. 31% alive, $p=0.28$) compared to former/never smokers undergoing CCRT. Though preliminary

and too few for definitive statistical comparisons, among the 14 smoking cessation program participants there was a greater proportion of deaths in the patients that did not quit smoking compared to the patients that did quit smoking (50% vs 10%). All deaths were due to progression of disease. These relative proportions suggest that quitting smoking 30 days prior to CCRT has a significant impact on mortality risk.

That current smoking portends a significantly poorer prognosis in head and neck cancer is consistent with the extensive literature summarized in the SGR⁶. It has been argued that smoking status should be an important part of staging and treatment for head/neck cancer patients¹⁹. Previous studies have demonstrated that survival is improved in HPV+ OPSCC patients when compared to HPV- OPSCC^{13,20-25}. In addition to HPV, Ang et al¹³ showed that survival could be further stratified with a +/- 10 pack year variable. Such an analysis of this cohort (data not shown) produced similar curves to Ang et al. However, our data further highlights the need to consider current smoking as a prognostic factor independent of HPV. Indeed, current smoking was associated with worse survival as compared with former and never smokers in both HPV+ and HPV- groups (Fig 2) suggesting that pack-year status may be a less robust prognostic factor than current smoking in OPSCC patients undergoing CCRT. Moreover, previous pack-years smoked is immutable, whereas current smokers can choose to become former smokers thus opening an avenue for intervention to possibly improve outcome.

Smoking and constituents of tobacco increases tumor aggressiveness in cancer cells by stimulating proliferation, angiogenesis, migration, invasion, and decreased response to cytotoxic cancer agents such as chemotherapy and radiotherapy^{26,27}. The fact that smoking causes adverse survival and therapeutic outcomes in virtually all cancer disease sites and for all cancer treatments, as suggested by the 2014 SGR⁶, suggests that many of the biologic effects of cigarette smoke may extend across a spectrum of histologic and genetic variants. The time and dose dependent biologic effects of cigarette smoking and/or smoking cessation and the interaction with HPV remain unknown.

Overall, this is consistent with data showing that 2 to 4 weeks of smoking cessation may be necessary to improve outcomes in cancer patients treated by surgery^{28,29,30,31}. Data from our study suggest that cessation for 4 weeks prior to start of therapy is associated with improved survival in the HPV+ group, and though there was a similar trend, too few patients were available to more definitively confirm this association in the HPV- group.

The exact mechanism by which smoking cessation improves outcome in patients treated with chemoradiation is unknown. In a study of 393 laryngeal cancer patients treated with radiation therapy (RT), those who quit smoking after diagnosis had reduced toxicity³². Notably, in a cohort of head and neck cancer patients treated with radiation, 43% of smokers treated in the morning experienced Grade 3+ mucositis compared with 72% of smokers treated in the afternoon (p=0.04), suggesting that some effects of smoking on toxicity may be reduced within hours³³.

Based on such data, some may postulate that a benefit of smoking cessation may be related to the additive toxicity of smoking and CRT which may lead to reduced compliance with

therapy or follow-up. We could not draw any conclusions, however, about toxicity as all but one patient in this series completed CCRT in 47 days or less¹⁷³⁴. Additionally, there was excellent compliance with follow-up in this cohort regardless of smoking status.

This study is limited by several factors. First, although the median follow-up was 41.5 months, the minimum follow-up was 6 months. Second, though structured tobacco assessments were used to evaluate tobacco use, there were no biochemical confirmation assessments. We and others have shown that approximately 30% of current smokers may misrepresent tobacco use³⁵³⁶³⁷. As a result, some proportion of self-reported former smokers may actually be current smokers. Moreover, even those patients who successfully quit during therapy may start smoking again following therapy. Though smoking status following completion of therapy was not captured in our database, the estimate of the single treating radiation oncologist (AS) who continues to follow this cohort is that approximately half of all patients who quit during therapy will return to smoking following therapy. Common re-inciting factors include: anxiety, death in the family, or job loss. Nonetheless, our data suggest that smoking cessation 4 weeks prior to initiation of CCRT in OPSCC patients may improve survival, which is analogous to our prior results showing improved survival with cessation in lung cancer patients¹⁶.

Future Directions

This data extends prior findings from the SGR, and other studies, that current smoking by SCCHN patients decreases survival in both HPV+ and HPV- patients. Smoking cessation as a standard part of cancer care is now advocated by the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO)³⁸³⁹. Recent guidelines from NCCN now support smoking cessation as a standard part of cancer care for all patients who report using tobacco within the past 30 days and support for patients who have quit smoking to prevent relapse⁴⁰. However, smoking cessation is still not widely incorporated into clinical practice with most oncologists asking about tobacco use but few assisting patients with quitting tobacco use⁴¹⁴². Though smoking affects overall survival, cancer specific survival, and cancer treatment toxicity, many active cooperative group clinical trials do not assess tobacco use⁴³. Much work is needed to implement structured smoking assessments and cessation support into cancer care⁴⁰. Unfortunately, even in our center where an automated smoking cessation program exists, more than half of all patients referred did not stop smoking. This suggests that further work is still needed to optimize smoking cessation programs.

Conclusions

Current smoking during CCRT in OPSCC patients in this cohort was strongly associated with a 4 to 7 fold increase in risk of mortality for HPV+ and HPV- patients respectively. Given this finding, and the number of acute and often reversible changes that occur with current smoking, regardless of pack-years already smoked, every effort should be made to motivate current smokers with OPSCC to stop smoking.

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Figure 1.
Kaplan-Meier overall survival curve for HPV+ (Green line) and HPV- (Blue line) $p=0.08$

Figure 2. Kaplan-Meier curves of overall survival for HPV+ (A) ($p=0.01$) and HPV- (B) ($p=0.28$) patients: never/former smokers (Blue line) vs current smokers (Green line)

Table 1

Characteristics of the Overall Cohort (n=120)

Characteristic	Value
	Median (range)
Median age at diagnosis	58.5 (36-85)
Median follow up time (months)	41.5 (6-88)
Characteristic	Value
	Frequency(%)
Gender	
Male	96 (80.0)
Female	24 (20.0)
Tobacco Status	
Never	26 (21.7)
Former	66 (55.0)
Current	28 (23.3)
Anatomical Subsite	
Base of the Tongue	42 (35.0)
Tonsil	49 (40.8)
Soft Palate	2 (1.7)
Overlapping Subsites	26 (21.7)
Oropharyngeal Wall	1 (0.8)
Overall Tumor Stage	
Stage II	6 (5.0)
Stage III	17 (14.2)
Stage IV	97 (80.8)
T-Stage	
T1	20 (16.8)
T2	49 (40.8)
T3	37 (30.8)
T4	6 (5.0)
T4a	7 (5.8)
T4b	1 (0.8)
N-Stage	
N0	12 (10.0)
N1	18 (15.0)
N2	5 (4.2)
N2a	13 (10.8)
N2b	38 (31.7)

Characteristic	Value
	Median (range)
N2c	26 (21.7)
N3	8 (6.7)
Grade (n=114)	
Well Differentiated	2 (1.8)
Moderately Differentiated	51 (44.7)
Poorly Differentiated	61 (53.5)

Table 2

Cohort characteristics by HPV status (n=120)

	HPV- (n=34)	HPV + (n=86)	
Characteristic	Median (range)	Median (range)	^a p-value
Age at Diagnosis in years	58.5 (36-85)	58.5 (37-82)	0.775
Median Follow Up Time (months)	45 (10-82)	39 (6-88)	0.309
Tobacco pack-years (range)	30 (0-68)	18 (0-160)	0.075
Characteristic	Frequency (%)	Frequency (%)	^a p-value
Gender			
Male	25 (73.5)	71 (82.6)	
Female	9 (26.5)	15 (17.4)	0.265
Tobacco Status			
Never	4 (11.8)	22 (25.6)	
Former	22 (64.7)	44 (51.2)	
Current	8 (23.5)	20 (23.3)	0.228
Overall tumor stage			
Stage II	2 (5.9)	4 (4.7)	
Stage III	6 (17.6)	11 (12.8)	
Stage IV	26 (76.5)	71 (82.6)	0.744
T-Stage			
T1/T2	17 (50.0)	50 (58.1)	
T3/T4	17 (50.0)	36 (41.9)	0.418
N-Stage			
N0/N1	11 (32.4)	19 (22.1)	
N2/N3	23 (67.6)	57 (77.9)	0.242
Grade (n=114)	n=33	n=81	
Well/Moderately differentiated	23 (69.7)	30 (37.0)	
Poorly differentiated	10 (30.3)	51 (63.0)	0.002

HN head and neck, *T* clinical tumor stage, *N* clinical nodal stage

^a Wilcoxon Rank Sum test (or Kruskal-Wallis test) was used to examine differences for age and tobacco pack-years and Pearson Chi-square test was used to examine differences for categorical variables

Cox Proportional Hazards Regression Modeling- Overall survival by HPV status and tobacco use

Table 3

Variable	n	Univariate		Multivariate	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
HPV Status					
HPV+	86	1.00		1.00	
HPV −	34	1.71 (0.84, 3.50)	0.142	1.61 (0.77, 3.37)	0.209
HPV+					
Never/former smokers (ref)	66	1.00		1.00	
Current smokers	20	2.80 (1.16, 6.80)	0.022	3.68 (1.35, 10.0)	0.011
HPV−					
Never/former smokers (ref)	26	1.00		1.00	
Current Smokers	8	2.46 (0.78, 7.75)	0.125	6.8 (1.11, 41.67)	0.038

The multivariate model is controlled for age, sex, HNC history, and overall stage.

The referent groups are never/former smokers.

Table 4

Summary statistic for smoking cessation patient referrals

Status	Patients Referred to Smoking Cessation Program			Former/Never Smokers n (%)
	Not Successfully Contacted n (%)	Non-Participant n (%)	Participant n (%)	
Alive	6 (33.3)	4 (50.0)	11 (78.6)	77 (81.9)
Dead	12 (66.7)	4 (50.0)	3 (21.4)	17 (18.1)
Program Participants (n=14)				
Survival	Quit Smoking n (%)			Did Not Quit Smoking n (%)
Alive	9 (90.0)			2 (50.0)
Dead	1 (10.0)			2 (50.0)