Received: 12 September 2019 | Revised: 25 October 2019 | Accepted: 10 December 2019

DOI: 10.1002/lio2.342

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Childhood tonsillectomy alters the primary distribution of HPV-related oropharyngeal squamous cell carcinoma

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Abstract

Objectives: We investigated how tonsillectomy during childhood may influence the distribution of human papillomavirus (HPV) positive cancer of the tonsils in adult life using p16 as a surrogate marker for HPV infection.

Study Design: Retrospective observational study.

Methods: A total of 280 patients diagnosed with oropharyngeal squamous cell carcinoma (OPSCC) and known p16 status were eligible for this study. Each participant was called to obtain the childhood tonsillectomy history. Respondents were subgrouped by p16 status and the primary tumor location. Patient demographic and clinical information was analyzed for association with Fisher's exact and Wilcoxon rank sum tests. Location of tumor was modeled using univariate (UVA) and multivariate (MVA) logistic regression with associated odds ratios (OR) and 95% confidence intervals.

Results: Of the 280 patients, 115 (41%) were respondents: 104 (90.4%) were p16 positive and 11 (9.6%) were p16 negative. For p16 positive patients, we observed a majority (93%) of intact tonsils in those with tonsil cancer, compared to 45% of intact tonsils in patients with p16 positive cancer elsewhere in the oropharynx ($P < .001$). MVA logistic regression showed that female gender (OR = 4.16, $P = .0675$), prior smoking history (OR = 2.6, $P = .0367$), and intact tonsils (OR = 15.2, $P < .0001$) were associated with tonsillar OPSCC.

Conclusion: We found that patients with p16 positive OPSCC at a non-tonsil site were much more likely to have had prior tonsillectomy vs those with p16 positive OPSCC arising within the tonsil. Nevertheless, we do not advocate tonsillectomies as a public health policy to reduce HPV-related OPSCC.

Level of Evidence: 6

KEYWORDS

human papillomavirus (HPV), p16, tonsil cancer, tonsillectomy

Brannon Altenhofen and Todd A. DeWees contributed equally to this study.

1 | INTRODUCTION

Head and neck carcinomas account for 3.5% of all malignancies in western society, approximately 400 000 cases per year, and 90% of those are head and neck squamous cell carcinoma (HNSCC).[1] The etiology of HNSCC has been shown to correlate with long-term exposure to carcinogens, especially tobacco and alcohol abuse.[2,3] Although the overall incidence of HNSCC had declined over past decades with the decrease in tobacco smokers, the incidence of a subset of HNSCCs (those neoplasms associated with transcriptionally active human papillomavirus [HPV]) has actually increased,[4] leading to a significantly increased incidence of oropharyngeal squamous cell carcinoma (OPSCC) worldwide.[5]

The increasing incidences of these HNSCCs have been linked to oral HPV infection. In what has been termed a cancer "epidemic,"[6,7] these HPV positive cancers now account for 40% to 90% of HNSCCs arising from the oropharynx, mainly in individuals aged 40 to 55.[1,2] These neoplasms characteristically have a non-keratinizing histology, but also can be keratinizing, basaloid, lymphoepithelial, or papillary and occur predominantly in the palatine tonsils or base of tongue.[8] Patients with HPV positive HNSCCs have a distinct risk factor profile that differs from those with HPV negative HNSCCs: the former associated with increased number of oral sexual partners and marijuana use, and the latter associated with measures of tobacco smoking, alcohol use, and poor oral hygiene.[9]

The high-risk viral subtype HPV16 accounts for 90% of all HPV positive OPSCC. High-risk HPV has been linked to HNSCC tumorigenesis by a mechanism involving viral oncogenes E6 and E7, responsible for the overexpression of heparanase and p16, respectively.[10] The extremely high correlation rates, as much as 90%—between p16 immunohistochemistry and more specific tests (such as the gold standard presence of HPV 16 E6/E7 mRNA), has allowed p16 immunohistochemistry to emerge as a robust and practical surrogate marker for the transcriptionally active virus[11] A series of 1093 HNSCC cases demonstrated that the presence of HPV16 E6/E7 antibodies was significantly correlated with improved survival of HNSCC and OPSCC.[12,13] The recently published MARCH meta-analysis also supported these results.[13] Moreover, according to a retrospective evaluation of the IMCL-9815 study, p16 positive patients with OPSCC had improved overall survival (OS), locoregional control, and progression-free survival than the p16 negative patients.[14] Ang et al demonstrated in a recursive-partitioning analysis of RTOG 0129 that the HPV status of the tumor was the major determinant of OS, followed by the number of pack-years of tobacco smoking (≤10 vs >10) and then nodal stage (N0 to N2a vs N2b to N3), for HPV-positive tumors.[15] For this reason, HPV status is one of the strongest prognostic indicators for OPSCC.

It is interesting to speculate whether or not surgical removal of the palatine tonsils, a fairly routine procedure when performed in childhood, reduces the likelihood of developing HPV-related tonsil cancer later in life. A multiple-registry study of 3 859 967 Danish residents born between 1920 and 1972, of whom 90 755 had tonsillectomies, demonstrated a significant reduction in the incidence of tonsil cancer after tonsillectomy,[16] although the exact magnitude of this reduction is still unknown. In this study, we investigated how previous tonsillectomy, often occurring in childhood, impacts the distribution of HPV/p16 positive OPSCC in adults.

2 | MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Washington University in Saint Louis.

2.1 | Eligibility and patient selection

Medical records of patients with OPSCC were retroactively accessed for patients diagnosed from 1996 to 2013. From a prospectively assembled database of 309 patients who received radiotherapy at Washington University in St. Louis, 280 candidates were identified based on having OPSCC and positive HPV status, using p16 positivity as a surrogate marker for HPV. Each patient's name and phone number were retrieved from the medical records for purposes of the interview. These candidates were subsequently contacted by telephone.

Of the candidates, we were successfully able to interview 115 respondents (nonresponse was due to outdated contact information or failure to respond after multiple attempts) who, upon giving consent to participate, were asked the following two questions:

1. Did you have your tonsils removed at least 5 years before you were diagnosed with head and neck cancer?
2. What year or how old were you when you had your tonsils removed, whichever you remember best?

Patients who had a tonsillectomy along with the age at the time of surgery are presented in Figure 1. In four cases, the patients were

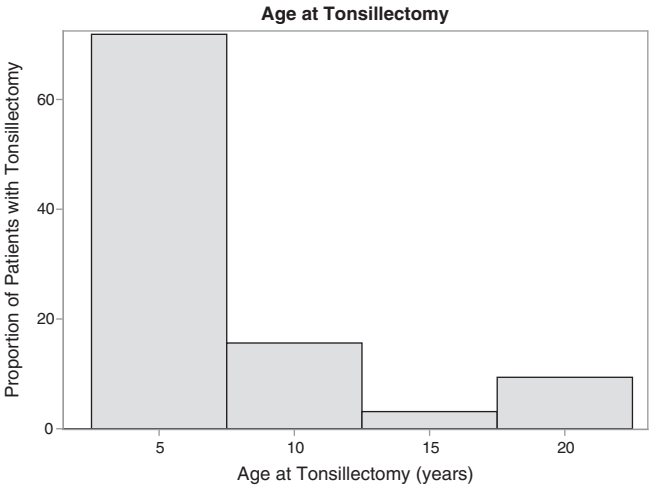

FIGURE 1 Histogram for the range of ages at tonsillectomy for the 32 patients with prior tonsillectomy

deceased, so the questions were posed to the answering member of the household (spouse, partner, or sibling.)

2.2 | p16 immunohistochemistry

Immunohistochemistry was performed on 4 μm sections from formalin-fixed, paraffin-embedded tissue blocks using an antibody to p16 (MTM Laboratories; monoclonal; 1:1 dilution) on a Ventana Benchmark LT automated immunostainer (Ventana Medical Systems, Inc., Tucson, Arizona) according to standard protocols. Antigen retrieval, standard on the machine, utilized the Ventana CC1, EDTA-Tris, pH 8.0 solution. A known p16 expressing OPSCC or ovarian papillary serous carcinoma case was used as a positive control with each run.

Cases were reviewed independently by the study pathologist (J.S. L.) without knowledge of the other features of the cases and strong P16 immunopositivity in over 75% of tumor tissue was considered positive.

2.3 | Study design and statistics

The primary endpoint of this retrospective cohort study was to assess for a potential association between OPSCC distribution, p16 status, location of malignancy, and history of prior tonsillectomy. Patients were grouped according to tumor location (tonsil vs non-tonsil cancer) and p16 status. Association with prior tonsillectomy and all patient demographic and clinical variables, including tumor location and p16 status, was assessed via Fisher's exact test or Wilcoxon rank sum test where appropriate. Univariate logistic regression (UVA) was implemented to model tumor location by patient age at diagnosis, sex, race, history of smoking, and TNM prognostic stage. Statistical significance was assessed via Wald's Chi-Square test statistic with

TABLE 1 Patient demographics

Patient characteristic	All patients	Tonsil tumors	Non-tonsil tumors	*P* value
N	**115**	**62**	**53**	
Location of tumor, N (%)				
Tonsil	62 (53.9%)	62 (100%)		
Base of tongue	47 (40.9%)		47 (88.7%)	
Other	6 (5.2%)		6 (11.3%)	
Sex, N (%)				.0834[a]
Male	101 (87.8%)	51 (82.3%)	50 (94.3%)	
Female	14 (12.2%)	11 (17.7%)	3 (5.7%)	
Race, N (%)				.5094[a]
Black	10 (8.7%)	4 (6.5%)	6 (11.3%)	
White	105 (91.3%)	58 (93.5%)	47 (88.7%)	
Smoking status, N (%)				.0249[a]
Prior or current smoker	57 (49.6%)	37 (59.7%)	20 (37.7%)	
Nonsmoker	58 (50.4%)	25 (40.3%)	33 (62.3%)	
P16 status, N (%)				.5433[a]
p16+	104 (90.4%)	55 (88.7%)	49 (92.5%)	
p16−	11 (9.57%)	7 (11.3%)	4 (7.5%)	
Tonsillectomy status, N (%)				<.0001[a]
Prior tonsillectomy	32 (27.8%)	4 (6.5%)	28 (52.8%)	
Intact tonsils	83 (72.2%)	58 (93.5%)	25 (47.2%)	
Stage grouping, N (%)				.2608[a]
Stage I	2 (1.74%)	1 (1.6%)	1 (1.9%)	
Stage II	5 (4.35%)	2 (3.2%)	3 (5.7%)	
Stage III	12 (10.4%)	6 (9.7%)	6 (11.3%)	
Stage IVA	91 (79.1%)	48 (77.4%)	43 (81.1%)	
Stage IVB	5 (4.4%)	5 (8.1%)	0 (0%)	
Age at diagnosis (mean ± *SD*)	56.2 ± 9.3	55.2 ± 9.9	57.5 ± 8.4	.1427[b]
Smoking pack-years (mean ± *SD*)	16.2 ± 21.8	18.3 ± 22.3	13.9 ± 21.1	.1138[b]

[a]*P* value calculated using Fisher's exact test.
[b]*P* value calculated using Wilcoxon rank sum test.

P values < .05 deemed statistically significant. TNM staging information was retroactively assessed and patients assigned prognostic staging categories per AJCC 7th Edition cancer staging guidelines.[17] Multivariate logistic analysis (MVA) was performed on all univariately significant variables (*P* < .1) utilizing stepwise model building. Odds ratios (OR), *P* values, and 95% Wald confidence limits were calculated for all UVA and MVA analyses.

3 | RESULTS

From 280 eligible candidates, 115 patients with a history of OPSCC were successfully interviewed yielding a response rate of 41%. Failures to response were most often due to noncurrent phone information (eg, disconnected numbers) or candidates and widowed family members declining participation.

Aggregate patient characteristics and tests for association by tumor location are shown in Table 1. Prior tonsillectomy was performed in 32 (27.8%) of patients, and was significantly (*P* < .0001) associated with tumor location. Of patients with prior tonsillectomy, 12.5% had palatine tonsil tumors while the other 87.5% had non-tonsil tumors. Approximately half (49.6%) of all patients had prior smoking history. A statistically significant relationship existed between tumor location and smoking status (*P* = .0249), with 59.7% of tonsil patients having smoking history compared to 37.7% of non-tonsil patients having prior smoking history. To further analyze patients with smoking history, we implemented as subgroup analysis for patients with a smoking history (Table 2). Among prior and current smokers, there was no significant difference in age of diagnosis, mean pack-years, sex, race, p16 status, or prognostic stage grouping between tonsil and non-tonsil patients. Prior tonsillectomy remained significant in this subgroup analysis as 25% patients with prior tonsillectomy had tonsil tumors, while 75% had non-tonsil tumors.

Patients were predominantly HPV positive, with 104 (90%) having p16 positive tumors and 11 (10%) having p16 negative tumors. Within the p16 positive group, there were 55 (53%) patients with tonsil tumors, and 49 (47%) patients with non-tonsil tumors. Of the patients with non-tonsil tumors, 44 (90%) had tumors located at the base of tongue, with the remaining 5 (10%) in the following locations: floor of mouth (1), soft palate (2), oropharyngeal wall (1), and right glossopharyngeal sulcus (1). Within the p16 negative group, there were 7 (64%) tonsil tumors and 4 (36%) non-tonsil tumors.

TABLE 2 Patient age and pack years for patients with smoking history

Patient characteristic	All patients	Tonsil tumors	Non-tonsil tumors	*P* value
N	**57**	**37**	**20**	
Location of tumor, N (%)				
Tonsil	37 (64.9%)	37 (100%)		
Base of tongue	17 (29.8%)		17 (85.0%)	
Other	3 (5.3%)		3 (15.0%)	
Sex, N (%)				.2862[a]
Male	4 (7.0%)	4 (10.8%)	0 (0%)	
Female	53 (93.0%)	33 (89.2%)	20 (100%)	
Race, N (%)				.6542[a]
Black	6 (10.5%)	3 (8.1%)	3 (15.0%)	
White	51 (89.47%)	34 (91.9%)	17 (85.0%)	
P16 status, N (%)				.9949[a]
p16+	47 (82.5%)	30 (81.1%)	17 (85.0%)	
p16−	10 (17.5%)	7 (18.9%)	3 (15.0%)	
Tonsillectomy status, N (%)				.0020[a]
Prior tonsillectomy	12 (21.1%)	3 (8.1%)	9 (45.0%)	
Intact tonsils	45 (78.9%)	34 (91.9%)	11 (55.0%)	
Stage grouping, N (%)				.4419[a]
Stage I	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Stage II	4 (7.0%)	2 (5.4%)	2 (10.0%)	
Stage III	6 (10.5%)	3 (8.1%)	3 (15.0%)	
Stage IVA	43 (75.5%)	28 (75.7%)	15 (75.0%)	
Stage IVB	4 (7.0%)	4 (10.8%)	0 (0.0%)	
Age at diagnosis (mean ± *SD*)	56.7 ± 9.7	55.1 ± 9.9	59.6 ± 8.7	.1193[b]
Smoking pack-years (mean ± *SD*)	32.8 ± 20.3	30.6 ± 21.4	36.8 ± 18.1	.1053[b]

[a]*P* value calculated using Fisher's exact test.
[b]*P* value calculated using Wilcoxon rank sum test.

TABLE 3 Tonsillectomy effect on tumor location for P16+ patients

HPV status	Patient characteristic	Tonsil tumors	Non-tonsil tumors	*P* value
	N	**55**	**49**	
P16+	**Tonsillectomy status, N (%)**			<.0001[a]
N = 104	Prior tonsillectomy	4 (7.3%)	27 (55.1%)	
	Intact tonsils	51 (92.73%)	22 (44.9%)	

Abbreviation: HPV, human papillomavirus.
[a]*P* value calculated using Fisher's exact test.

TABLE 4 Univariate and multivariate logistic regression of patients with tonsil tumors

Parameter	UVA OR	UVA 95% CI	*P*[a]	MVA OR	MVA 95% CI	*P*[a]
Gender (Female)	3.57	(0.946-13.699)	.0603	4.16	(0.902-19.138)	.0675
Race (White)	1.85	(0.493-6.946)	.3614			
Prior smoker	2.44	(1.151-5.181)	.02	2.61	(1.061-6.408)	.0367
P16+	0.64	(0.177-2.324)	.499			
Intact tonsils	16.67	(5.154-50.000)	<.0001	15.16	(4.623-49.691)	<.0001
Early stage (I or II)	0.62	(0.133-2.916)	.5476			
Age at diagnosis	0.97	(0.935-1.014)	.1909			
Smoking pack-years	1.01	(0.992-1.027)	.2837			

Abbreviations: CI, confidence interval; MVA, multivariate logistic analysis; OR, odds ratios; UVA, univariate logistic analysis.
[a]*P* values based on Wald chi-square test, parameters with $P < .1$ were kept in MVA models.

We also observed statistically significant difference in tumor location among those patients with p16 positive tumors (Table 3). Of the 55 patients within the p16 positive tonsil cancer group, only 4 patients (7.3%) had had a previous tonsillectomy ($P < .001$). Conversely, within the p16+ non-tonsil cancer group, 27 patients (55.1%) had a previous tonsillectomy. For the p16 negative patients, 1 patient (14.3%) with tonsil carcinoma had had a tonsillectomy vs 2 (50%) of the non-tonsil carcinoma patients, which was not statistically significantly different ($P = .4909$), likely due to small sample size (N = 10).

To model the effect of these patient clinical and demographic variables on tumor location, we conducted UVA and MVA logistic regression. Table 4 presents these analyses along with OR and 95% confidence intervals (CIs). In UVA analysis, there was significant association with tonsil tumor locations based on prior smoking history (OR = 2.4, $P = .0200$) and lack of previous tonsillectomy (OR = 16.7, $P < .0001$). Female gender was also associated (OR = 3.6, $P = .0603$) with a higher rate of tonsil cancers and was included in MVA analysis. In MVA analysis, female gender (OR = 4.16, $P = .0675$), prior smoking history (OR = 2.6, $P = .0367$), and intact tonsils (OR = 15.2, $P < .0001$), demonstrating that prior tonsillectomy is an independent predictor of tumor location after adjusting for gender and prior smoking history.

4 | DISCUSSION

Our data suggest that prior tonsillectomy is associated with a change in the distribution of HPV-related primary tonsil OPSCC. In patients with p16+ squamous cell carcinoma of the tonsils, we observed a preponderance (91%) of intact tonsils. Conversely, in patients with p16 + squamous cell carcinoma elsewhere (usually the base of tongue), we observed approximately a 50% chance of tonsillectomy status. This suggests that tonsillectomy may confer a protective effect in developing HPV-related primary tonsil OPSCC. Interestingly, a small number of patients with prior tonsillectomy still developed tonsil cancer, likely due to incomplete removal of the tonsil. Tonsillectomy techniques have evolved over the study period, including microdebrider, laser, coblation, and electrocautery partial tonsillectomy and cold dissection, coblation, and electrocautery total tonsillectomy.[18] Without knowing the extent of tonsillectomy and amount of residual tissue, it is impossible to know if this population is indeed a uniform one. In our OPSCC patient cohort, multivariate analysis showed that patients without tonsillectomies were more than 15 times likely to be diagnosed with tonsil cancer than patients with tonsillectomies.

The growing incidence of HPV-related OPSCC has been suggested to be partially explained by the decline in tonsillectomy rates over the last 50 years.[19] Our data support this concept. The number of tonsillectomies performed on children <15 years old has declined from 970 000 in (years) to 289 000 in 2010.[20,21] We hypothesize that one reason for the increased proportion of HPV positive to HPV negative cancers, aside from the decline in smoking rates, may also be partially explained by this trend. If true, we would expect a further increase in incidence of HPV positive tonsil cancers to continue to increase over the next few decades, as more individuals enter into their 40s and 50s with intact tonsils. However, future analysis would

also need to account for the changing prevalence of oropharyngeal HPV, which could be influenced by trends in vaccination rates, changes in sexual practices, and novel antiviral treatments.

A nation-wide study from Sweden (1970-2009) observed that tonsillectomies (N = 225 718) were associated with reduced risk of tonsil cancers (standardized incidence ratios [SIRs] 1+ years post-tonsillectomy = 0.31; 95% CI = 0.08-0.79 and 5+ years post-tonsillectomy = 0.17; 95% CI = 0.02-0.62), but unrelated to other oropharyngeal or other head and neck cancers (SIRs 1+ years post-tonsillectomy = 1.61; 95% CI = 0.77-2.95 and 0.92; 95% CI = 0.64-1.27, respectively).[22] The authors did not believe tonsillectomies should be considered as a secondary prevention strategy for tonsil cancers or other oropharyngeal cancers at this time. Some of the reasons were that: tonsillectomies did not alter risk of non-tonsil oropharyngeal cancers, and the mortality due to tonsillectomy outnumbers the incidence of oropharynx cancers. Other obstacles were inadequate risk stratification for the identification of high-risk individuals, inadequate identification and location of premalignant lesions, and lack of low-morbidity, cost-effective treatments for premalignant lesions.[22]

The study from Sweden and this study raise a number of important questions. Do tonsillectomies decrease the incidence of tonsil cancer, the distribution of tonsil cancer or both? If the development of HPV-related tonsil cancer requires both tonsillar tissue and HPV exposure, consequently the complete removal of the tonsillar tissue (total, not partial, tonsillectomy) should result in a decreased incidence HPV-related tonsil cancer and altered distribution of HPV-related OPSCC, which is consistent with the observations of the Swedish study and our study, respectively. However, total tonsillectomies are unlikely to affect the incidence of non-tonsil HPV-related OPSCC and unlikely reduce the overall incidence of OPSCC. For this reason, tonsillectomies as a public health policy to reduce HPV-related OPSCC is flawed. Furthermore, tonsillectomy is an invasive surgical procedure that carries risks.

Vaccination against high-risk serotypes of HPV has been implemented nationally in Denmark and Australia and has been shown to be a cost-effective preventative intervention.[23] However, the incidence of OPSCC in Eastern Denmark has continued to rise with 62% of cases including HPV+, implying that the effects still remain to take effect and that there still exists a high HPV prevalence.[24] We continue to recommend use of vaccination against HPV as well as public health efforts toward patient sexual education, smoking cessation, and alcohol abuse control to decrease the risk of OPSCC.[25]

A limitation of our current study is its retrospective nature of analysis. We used the AJCC 7th edition for staging the tumors as this was the staging employed to classify this retrospective patient population. Incomplete medical records, sometimes devoid of tonsillectomy status, were partially circumvented by the telephone interview. Our inability to successfully contact a majority of eligible patients could contribute to a selection bias, particularly one which underrepresents the deceased, those without a phone or who changed phone numbers. No educational resources were provided to participants during the phone interview, so we cannot eliminate potential self-reporting errors of tonsillectomy status. Furthermore, due to a much smaller pool of p16 negative patients, our study is unable to draw conclusions regarding tonsillectomy and HPV negative tonsil cancers. Given the higher mortality associated with HPV negative OPSCC, p16 negative patients were more likely to be deceased and thus unable to be contacted and included in this study.

5 | CONCLUSIONS

We found that patients with p16 positive OPSCC at a non-tonsil site were much more likely to have had prior tonsillectomy vs those arising within the tonsil. Nevertheless, we do not advocate tonsillectomies as a public health policy to reduce HPV-related OPSCC.

ACKNOWLEDGMENT

We thank Daniel Przybysz, MD for feedback in an earlier version of the manuscript and facilitating communication with the statistician.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Altenhofen B, DeWees TA, Ahn JW, et al. Childhood tonsillectomy alters the primary distribution of HPV-related oropharyngeal squamous cell carcinoma. *Laryngoscope Investigative Otolaryngology*. 2020;5:210–216. https://doi.org/10.1002/lio2.342