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Unilateral Neck Therapy in the Human Papillomavirus-Era: Virus Association does not Alter Accepted Regional Spread Patterns

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Abstract

Background—To determine whether the incidence of bilateral neck disease tonsil cancer is rising.

Methods—We reviewed tonsil cancer incidence data from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute.

Results—The annual incidence of advanced neck disease (N2) with small primary tonsil cancer is increasing (annual percent change (APC), $p < 0.05$) during two evaluable time frames (1988–2003 and 2004–2008). The increase for small primary tonsil cancer from 2004–2008 is associated with increased ipsilateral disease (ie, T1-2N2ab, APC 10.6%, $p < 0.05$) rather than bilateral neck disease (T1-2N2c, APC 5.9%, APC = NS). The increase in bilateral neck disease is less than the overall rise in T1-2 tonsil cancer (APC 7.2%, $p < 0.05$).

Conclusions—In the HPV era bilateral neck disease is increasingly common. This appears to be a consequence of increasing incidence of tonsil cancer rather than a new biologic behavior.

Keywords

Tonsil; SEER; HPV; Unilateral Therapy; Stage Migration

Introduction

Elective radiation of the contralateral, radiographically negative neck contributes to head and neck radiotherapy treatment toxicity. Prior to the advent of intensity modulated radiation therapy (IMRT), radiation of the contralateral neck required the administration of significant dose to the major contralateral salivary glands (parotid and submandibular). With IMRT, the dose to the salivary glands can be reduced, and although a corresponding improvement in the parotid salivary flow rate can be measured, a patient reported improvement in

xerostomia-related quality of life is not always detectable (1,2). Although many factors contribute to symptomatic xerostomia, it appears that dose to the contralateral salivary apparatus is a continuous variable, so that minimizing the dose further than accepted dosimetric constraints (3) may be expected to provide enhanced symptom relief (4–7). Limiting radiation to the ipsilateral side of the neck is a highly effective means to reduce damage to the contralateral salivary apparatus. In addition, unilateral neck radiotherapy can reduce dose to the pharynx, which is proposed to be an independent predictor of treatment-related dysphagia (8, 9).

Unilateral neck radiotherapy in patients with selected lateralized tonsil cancer has been practiced safely for decades (10–12). Ideal candidates appear to have primary tumors with no greater than minimal involvement of an adjacent structure that drains to the bilateral neck (base of tongue, soft palate) (13). The potential increased risk of contralateral neck metastases secondary to advanced ipsilateral regional disease is difficult to characterize, since in the past most patients with advanced regional disease tended to have larger primary tumors. In the most oft-quoted analysis (10) no patient with ipsilateral treatment of N2–N3 disease developed a contralateral recurrence. However, it is noteworthy that there were few N2–N3 patients in that report because bilateral therapy was delivered to almost all due to concern that bulky ipsilateral nodal involvement precipitates aberrant, contralateral nodal drainage (14).

The clinical rationale for unilateral neck radiotherapy is based upon patients treated from 1970–1991. Since the early 1990s, rates of tobacco use in the United States have decreased (15). There has been a corresponding decrease in most cancers of the upper aerodigestive tract, with the exception of a rise in tumors of the oropharynx (16). This parallels an increasing incidence of human papillomavirus (HPV)-associated cancers that are most prevalent in the oropharynx (17). HPV-related oropharynx cancer has a different presentation from HPV-negative oropharynx cancer—characterized by smaller T-classification by comparison to the N-classification (18).

The emergence of a new type of squamous cell cancer of the oropharynx with more advanced nodal stage relative to a given T-classification warrants reexamination of the question of unilateral radiotherapy. This manuscript addresses the incidence trends of bilateral adenopathy in tonsil cancer from 1988 – 2008 to determine whether bilateral nodal involvement has become more common in tonsil cancer as the proportion of HPV associated cancers has increased and whether unilateral neck radiotherapy remains appropriate for HPV associated oropharynx cancer.

Materials and Methods

We obtained incidence data from the SEER program of the National Cancer Institute for the years 1988 – 2008. We queried the SEER 9 registries. The SEER registries report data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis and treatment. The SEER registries were strategically selected to maximize representation of the overall US population, reflecting approximately 28% of US individuals (19).

The SEER database was interrogated for cases of tonsil and oropharynx cancer. Because of a coding change that occurred during the study period, it was necessary to divide the time frame into two separate intervals. For the years 1988–2003, SEER reports the American Joint Committee on Cancer (AJCC) 3rd edition stage, based primarily on the Extent of Disease (EOD) 10 Extension, Nodes, and Tumor size variables (20). We chose tonsil cancers coded as ‘invasive cancer confined to one of the following sub sites: anterior wall (including vallecula and lingual (anterior) surface of the epiglottis), one lateral wall, one posterior wall’ and ‘localized, NOS’ as those that could potentially be amenable to unilateral therapy. For the years 2004–2008, SEER includes tumor, nodal and metastasis (TNM) staging according to the AJCC 6th edition, and we evaluated T1 and T2 tumors as those that were potentially amenable to unilateral therapy.

Cases per 1,000,000 were calculated using SEER*Stat software (<http://seer.stat.gov/seerstat/index.html>) and age adjusted to the US 2000 population. The annual percent change (APC) was estimated for all instances using the weighted least squares method in the SEER*Stat software, version 7.0.4. The 95% confidence intervals for the APC were calculated to assess the precision of the obtained estimates using the Tiwari modification.

Results

There has been a significant increase in the incidence of oropharynx cancer from 1988–2008 (Percentage change (PC) 32%, APC 1.1%, $p < 0.05$). The corresponding increased incidence of tonsil cancer from during the same time period has been profound (PC 54%, APC 1.7%, $p < 0.05$).

Primary Tumor Size Trends

The number of primary tonsil tumors potentially amenable to unilateral therapy increased in both time frames evaluated (1988–2003: APC 3.6%, $p < 0.05$ and 2004–2008: APC 7.2%, $p < 0.05$). Tonsil cancers thought to be advanced decreased in incidence from 1988–2003 (APC = -0.5%, $p < 0.05$) while advanced tumors from 2004–2008 increased, albeit at a rate that does not reach statistical significance (APC 1.2%, $p = \text{NS}$). When tonsil cancer primary tumor stage is evaluated separately in the 2004–2008 time frame, it appears as if T2 (APC 7.1%, $p < 0.05$) and T3 (APC 11.8%, $p < 0.05$) tonsil cancers are increasing in incidence, while T1 (APC 7.2%, $p = \text{NS}$) and T4 (-1.9%, $p = \text{NS}$) tonsil cancers are not (Tables 1 and 2).

Regional Disease Trends

In both time frames evaluated, the incidence of lymph node negative tonsil cancer is decreasing: 1988–2003, APC -1.6%, $p < 0.05$ and 2004–2008, APC -0.3%, $p = \text{NS}$. The incidence of N1 necks increased from both 1988–2003 (APC 4.5%, $p < 0.05$) and 2004–2008 (APC 1.5%, $p = \text{NS}$). The incidence of N2 demonstrated a significant increase from both 1988–2003 (APC 3.6%, $p < 0.05$) and 2004–2008 (5.7%, $p < 0.05$). Analysis of the significantly increased incidence of N2 neck disease suggests that it is due to a rising incidence of advanced ipsilateral disease (N2aN2b) rather than bilateral/contralateral disease

(N2c), because the overall incidence of advanced ipsilateral disease is five times that of bilateral disease with an increased APC (2004–2008: 6.2% v 3.4%) (Figure 1).

Small Primary Tonsil Cancer Trends

The incidence of small primary tonsil cancer without regional disease (the most common presentation in 1988), has been relatively stable (1988–2003: APC 0%, 2004–2008: APC 3.6%, $p = \text{NS}$). The incidence of N1 tonsil cancer has been increasing, but it remains relatively rare. The most pronounced trend has been an increase in incidence of N2 cancers (1988–2003: APC 7.2%, $p < 0.05$ and 2004–2008: 10.9%, $p < 0.05$), currently the most common presentation with a small primary tonsil cancer. When divided between advanced ipsilateral disease and advanced bilateral regional disease (i.e. N2a- N2b vs. N2c), the incidence of advanced ipsilateral regional disease (i.e., N2a or N2b) is increasing at a rate similar to that of N2 disease in general (1988–2003: APC 7.0%, $p < 0.05$, 2004–2008: APC 10.6%, $p < 0.05$) while small primary tonsil cancers with bilateral neck nodes remain relatively rare. Their incidence is changing at a pace that is not statistically significant (1988–2003: 6.9%, $p = \text{NS}$, 2004–2008: 5.9%, $p = \text{NS}$) (Figure 2).

Discussion

Survival for HPV associated oropharynx cancers is far superior to that of non-HPV associated oropharynx cancers (17, 18, 21, 22). Current cooperative group trials are restricted by HPV status and efforts to reduce long term toxicity are a major objective of these studies (23). One approach to minimizing the toxicity of treatment for head and neck cancers is to define patterns of nodal spread and the safety of unilateral neck radiation. Since HPV-related tonsil cancer represents a distinct clinicopathologic entity from “traditional risk factor tonsil cancer (24),” the possibility that the nodal disease of these lesions more often spreads to the contralateral side of the the neck warrants consideration.

The SEER data presented in this manuscript and others (16, 18) demonstrates that the incidence and staging of oropharynx cancer is changing in the HPV-era. Advanced regional disease among all T-stages is increasing. Small primary tonsil cancer with advanced regional spread (e.g..N2 neck) is rising from 7.2% to almost 11% on an annual basis. The cumulative increase over decades signifies that tonsil cancer with advanced regional node disease is twice as common as it was fewer than 25 years ago. Analysis confined to small primary tonsil tumors with advanced node metastases demonstrates that their current incidence is three to four times that of 1988.

All examined regional stage variables are increasing as a consequence of the general trend of rising incidence of oropharynx and tonsil cancer. These increases may critically affect locoregional treatment decisions. The increasing incidence of N2 neck disease reflects an increase in ipsilateral neck disease that is more pronounced than that of contralateral neck disease (N2aN2b APC 10.6% vs. N2c APC 5.9%). We chose to report the incidence (per 1,000,000 patients) at the first and last year of each time period, (rather than the percentage change) to demonstrate that the increased ipsilateral APC is magnified by the increased incidence in general. This shows that, despite the annual percentage change, the incidence of

small primary tonsil cancer with bilateral neck adenopathy is still less than 1 per 1,000,000 in 2008, as it was in 1988.

This approach is subject to typical SEER limitations including underrepresentation of minorities and regions, data entry error/incompleteness, and variations in data reporting. The SEER database was not intended to address such a nuanced issue, and it does not provide treatment information. Thus, some inferences are subject to a degree of uncertainty. There are certainly oropharynx cancers limited to one subsite that could be either midline or close to midline and not representative of patients classically receiving unilateral therapy. There are also tonsil cancers that involve two subsites (which might be suitable for unilateral therapy). In addition, the coding change that necessitated a split of the years 1998–2008 into two unequal groups renders the analysis more cumbersome than one might prefer. However, important information may be derived.

The data do not support the contention that HPV-related cancers show a higher rate of contralateral nodes than tumors caused by tobacco and alcohol abuse. Since the incidence of bilateral neck nodal disease is not increasing at a disproportionate rate from that of 20 years ago, adopting a policy of bilateral neck radiation in all tonsil cancer patients in the era of HPV-related cancers does not seem justified.

Conclusion

The incidence of advanced regional disease in small primary tonsil cancer is increasing. This analysis of available population-based data supports the previously validated finding that small primary, lateralized tonsil cancer is rarely associated with contralateral adenopathy. While contralateral adenopathy in small primary tonsil cancer is increasing in prevalence, it appears to be a consequence of the rising rate of tonsil cancer, rather than a special feature of HPV-related tumors. There is no current justification to alter the previously proposed indications for unilateral neck radiotherapy for lateralized tonsil cancer.

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Figure 1.
Incidence of N Stage of Tonsil Cancer and all stage Tonsil Cancer (1988–2008)

Figure 2.
SEER incidence of Small Primary Tonsil Cancer by N-Stage, 1988–2008

Table 1

T-Stage and N-Stage Trends for Oropharynx Cancer

	1988 – 2003			2004 – 2008		
	Incidence in referenced year [†]	APC	Incidence in referenced year [†]	Incidence in referenced year [†]	AF	
<i>T Stage</i>						
T1–T2	1988	9.4	1.9%*	2004	15.2	6.7%*
	2003	13.1		2008	20.4	
T3–T4	1988	15.3	0.3%	2004	10.4	2.3%
	2003	16.0		2008	11.3	
<i>N Stage</i>						
N0	1998	10.5	−0.1%	2004	9.2	0.8%
	2003	10.6		2008	9.7	
N1	1988	2.2	3.1%*	2004	7.6	2.7%
	2003	3.7		2008	8.3	
N2	1988	10.1	3.0%*	2004	14.6	6.2%*
	2003	15.8		2008	18.4	
N2a–N2b	1988	8.1	2.6%*	2004	10.5	6.3%*
	2003	12.0		2008	13.0	
N2c	1988	2.0	5.0%*	2004	3.6	6.7%*
	2003	3.9		2008	4.9	
N3	1988	0.8	−0.7%	2004	2.3	−5.2%
	2003	0.6		2008	1.9	
<i>Localized Tonsil Cancer</i>						
T1–T2N0	1988	4.3	−0.5%	2004	4.7	1.9%
	2003	4.3		2008	5.6	
T1–T2N1	1988	0.5	7.1%*	2004	3.4	3.9%
	2003	1.4		2008	4.2	
T1–T2N2	1988	1.9	7.1%*	2004	6.4	11.7%*

	1988 – 2003		2004 – 2008		AF
	Incidence in referenced year [†]	APC	Incidence in referenced year [†]		
T1-T2N2a-N2b	2003	5.9	2008	9.7	
	1988	1.7	2004	5.1	11.2% *
	2003	5.2	2008	7.6	
T1-T2N2c	1988	0.2	2004	1.1	14.2% *
	2003	0.7	2008	2.0	
	1988	0.1	2004	0.6	
T1-T2N3	2003	0.2	2008	0.7	3.9%

* p < 0.05

[†] per 1,000,000

Table 2

T-Stage and N-Stage Trends for Tonsil Cancer

	1988 – 2003			2004 – 2008		
	Incidence in referenced year [†]	APC	Incidence in referenced year [†]	Incidence in referenced year [†]	AF	
<i>T Stage</i>						
T1–T2	1988	3.1		2004	6.5	
	2003	6.6	3.6%*	2008	8.7	7.2%*
T3–T4	1988	6.6		2004	4.8	
	2003	6.0	–0.5%	2008	5.2	1.2%
<i>N Stage</i>						
N0	1988	3.8		2004	3.4	
	2003	3.1	–1.6%*	2008	3.4	–0.3%
N1	1988	0.7		2004	3.5	
	2003	1.6	4.5%*	2008	3.6	1.6%
N2	1988	3.7		2004	6.9	
	2003	7.3	3.6%*	2008	8.7	5.7%*
N2a–N2b	1988	3.3		2004	5.2	
	2003	6.1	3.3%*	2008	6.9	6.2%*
N2c	1988	0.6		2004	1.4	
	2003	1.2	5.1%*	2008	1.6	3.4%
N3	1988	0.3		2004	0.9	
	2003	0.2	–1.4%	2008	1.0	3.5%
<i>Localized Tonsil Cancer</i>						
T1–T2N0	1988	1.5		2004	1.4	
	2003	1.5	0.0%	2008	1.9	3.6%
T1–T2N1	1988	0.2		2004	1.6	
	2003	0.9	9.5%*	2008	1.8	2.8%
T1–T2N2	1988	0.7	7.2%*	2004	3.0	10.9%*

	1988 – 2003		2004 – 2008		AF	
	Incidence in referenced year [†]	APC	Incidence in referenced year [†]			
T1-T2N2a-N2b	2003	3.6	2008	4.5		
	1988	0.7	2004	2.6		
	2003	3.3	7.0%*	2008	4.0	10.6%*
T1-T2N2c	1988	0.6	2004	0.4		
	2003	1.2	6.9%	2008	0.4	5.9%
	1988	0.3	-	2004	0.2	
T1-T2N3	2003	0.2	-	2008	0.3	20.1%

* p < 0.05
[†] per 1,000,000