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Tumor volume as a predictor of survival in HPV positive oropharyngeal cancer

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Abstract

Background—Increasing evidence exists that tumor volume may be a superior prognostic model than traditional TNM staging. It has been observed that OPSCC in the setting of human papillomavirus (HPV) positivity have a greater propensity for cystic nodal metastases, and thus presumably larger volume with relatively smaller primary tumors. The influence of HPV status on the predictive value of tumor volume is unknown.

Methods—Fifty-three patients with HPV-positive OPSCC were treated with definitive chemotherapy and intensity-modulated radiation therapy (IMRT).

Results—The estimated 2-year overall survival (OS) and disease-free survival (DFS) was 92.2% and 83.6%, respectively. Nodal classification did not predict OS ($p=0.096$) or DFS ($p=0.170$). Similarly, T classification did not predict OS ($p=0.057$) or DFS ($p=0.309$). Lower nodal volume was associated with greater DFS ($p=0.001$).

Conclusions—Nodal tumor volume was found to be predictive of DFS. DFS was best predicted by nodal gross tumor volume at 24 months.

Keywords

oropharyngeal cancer; neoplasm staging; tumor burden; human papillomavirus; IMRT

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Introduction

The ability to obtain precise measurements of gross tumor volume (GTV) in head and neck squamous cell carcinoma (HNSCC) has prompted clinicians to investigate its utility as a potential prognostic marker in the clinical setting [1–4]. Retrospective studies regarding GTV in HNSCC, and specifically oropharyngeal cancer, have proposed an increased risk of recurrence and poorer survival among patients with a higher GTV [4–8]. This information is biologically plausible, as GTV may be a surrogate marker for overall tumor burden.

HPV positive cancers in the head and neck have well-established gross characteristics which differ from HPV negative cancers. For instance, HPV positive oropharyngeal cancer (HPV+ OPSCC) is characterized as having smaller primary tumors. Cystic nodal metastases (CLN), of presumably larger volume, is also strongly associated with HPV+ OPSCC [9]. CLN invariably increases the GTV. However, the actual burden of tumorigenic cells within HPV positive primary tumors and CLN is unknown.

The tumor node metastasis (TNM) is the most commonly used staging system to describe HNSCC. Like other generic staging systems, TMN is not fully comprehensive of all key prognostic variables, including HPV status and volumetric measures of disease. In HPV+ OPSCC, TNM data have been used to establish high-risk groups, as well as other clinicopathologic information such as smoking history. T4 disease and N2c/N3 nodal staging are risk factors for poor survival, whereas extracapsular spread may be less prognostic than in HPV-HNSCC [10–12]. Given the dramatic increase in HPV+ OPSCC and the well-established superior survival versus HPV-HNSCC [9–14], we sought to evaluate the utility of GTV in predicting oncologic outcome for HPV+ OPSCC. Our hypothesis was two-fold: 1) high-risk groups (TNM) will be associated with poorer survival versus low-risk groups, as previously described in the literature; 2) the volume of tumor burden will not be predictive of oncologic outcome in HPV+ patients treated with curative-intent IMRT, as larger tumor volume may not be correlative with a large percentage of malignant cells.

Materials and Methods

All patients were treated at the University of Pittsburgh Cancer Institute and signed written informed consent for treatment. Patient information was obtained from an institutional database, the Head & Neck Organ-Specific Database, with appropriate Institutional Review Board approval.

Patients

Patients with locally advanced (stage III–IV), biopsy-proven OPSCC were obtained from the University of Pittsburgh Cancer Institute (UPCI) prospective head and neck cancer database between October 2006 and September 2012 were studied. Inclusion criteria included HPV positivity confirmed at our institution by either p16 (p16 was positive if there was more than 80% staining seen on immunohistochemistry) or HPV in-situ hybridization; treatment with curative-intent IMRT; and documented, reproducible treatment plan. Exclusion criteria included distant metastasis, treatment delivery at a satellite location (limited ability to

manipulate the original treatment plan and calculate GTV), insufficient follow up, and previous head and neck cancer or radiation. 53 patients were included in the final cohort.

Definitive treatment was defined as initiation of radiotherapy within 6 weeks of diagnosis with curative intent. Per standard institutional protocol, all patients underwent a complete history and physical examination, direct flexible fiberoptic endoscopy, complete blood counts, and liver function tests. Chest X-ray (CXR), computed tomography (CT) scans of the chest and abdomen, and positron emission tomography (PET) scans were obtained per the treating physician and/or study protocol before initiating treatment.

Classification of high-risk and low-risk groups

Tumors were staged according to the 2002 American Joint Committee on Cancer (AJCC) system, using the clinical data obtained from physical examination, direct laryngoscopy under anesthesia and contemporaneous imaging. Secondary to number of patients with advanced T classification, patients were classified as T1–T2 (low-risk) versus T3–T4 (high-risk). With regard to nodal classification, patients were classified as N0–N2b (low-risk) versus N2c–N3 (high-risk), based on previous literature [10–14].

Determination of gross tumor volume and treated lymph node volume

Candidates for IMRT were treated using a Varian Clinac Ex (Varian Medical Systems, Palo Alto, CA) at the University of Pittsburgh Cancer Institute, Shadyside Campus. The primary gross tumor volume (pGTV) and metastatic nodal volume (nGTV) were initially delineated per institutional protocol which is based on clinical examination, including endoscopy, and all available imaging. To standardize, all volumes were re-calculated for the purpose of this study from the initial planning contours of the clinical radiation treatment plan (Eclipse, Varian MS, Palo Alto, CA) by a single attending-level head and neck radiation oncologist (DAL). Overall tumor volume (GTV) was determined by the addition of pGTV and nGTV, unless otherwise stated.

Chemotherapy

Of the 53 eligible patients, 52 received concurrent platinum-based chemotherapy or systemic biologic agent per institutional algorithms and/or study protocols. The 1 patient not receiving therapy had an adverse reaction to chemotherapy early in the treatment course.

Statistical analysis

Primary outcomes included 2-year disease free survival (DFS), and overall survival. Two-year DFS was defined as total and persistent elimination of disease from the primary tumor and regional lymph nodes following primary chemoradiation. Follow-up was defined as the time between the date of diagnosis and most recent follow up appointment or date of death. All data regarding primary endpoints was available.

Two-year DFS and OS was calculated by the Kaplan-Meier method, and compared using log rank tests. Cox regression hazards models evaluating DFS and OS were used for the continuous tumor volume measurements. Concordance index was calculated to compare the predictive ability of the models. Significance was chosen at a p -value <0.05 level, and p -

values were two-sided. Statistical analyses were conducted at the University of Pittsburgh Clinical and Translational Science Institute and supported by the National Institutes of Health through Grant Number UL1-TR-000005.

Results

Patient and tumor characteristics

Fifty-three patients met our inclusion criteria and were included in this study. 52 patients completed their prescribed systemic therapy. All patients completed radiation therapy (6600–7400 Gy). Most patients were male (n=50, 94.3%); the average age was 55 years (39–81 years). There was a nearly even breakdown of never, former, and current smokers. The patient and tumor demographics are summarized in Table 1. Overall, only 1 patient presented with T4 disease. 49.1% (n=26) of tumors had cervical metastases classified as N2b (N0=3, N1=7, N2a=7, N2c=7, N3=7). The mean follow-up was 29 months (4–76 months).

Cohort experienced high OS and DFS and a wide range of tumor volume

Across all patients, the overall survival and DFS were 92.2% and 86.3% respectively. The mean tumor volumes were as follows: primary tumor 18.8 cm³ (SD 21.02 cm³), nodal metastasis 26.75 cm³ (SD 38.12 cm³), and overall gross tumor volume 44.49 cm³ (SD 45.0 cm³). Although the event of treatment failure was fortunately rare, there were 8 patients with recurrent disease, usually this was distant metastatic disease. Failure patterns are summarized in Table 2.

Association of T and N classification with survival

When dichotomized into high-risk (T3–T4) versus low-risk T classification (T1–T2), there was a trend toward decreased overall survival with high-risk T classification (p=0.057). However, there was no association of decreased overall survival with high-risk N classification (p=0.309). Kaplan-Meier analysis of OS and DFS by T classification and by N classification are presented in Figure 1.

Lower nGTV is associated with greater DFS

Nodal gross tumor volume (nGTV) has a weak association with OS (p=0.097), but lower nodal volume was strongly associated with greater DFS (p=0.002) by Cox regression modeling. However, primary gross tumor volume (pGTV) was not associated with differences in OS or DFS. These data are presented in Table 3.

nGTV is more predictive of DFS at 12 and 24 months than pGTV and TNM staging

Using a rank-based concordance index, the relative ability of each variable to predict DFS was determined. At time 12 months, a two-variable model containing both pGTV and nGTV as separate predictors was best for predicting DFS (c-index = 87.6%). However, by time 24 months, the predictive ability of the two-variable model (c-index=77.8%) was outperformed by nGTV alone (c-index=82.8%). At both 12 and 24 months, nGTV was a superior predictor

for DFS than T classification or N classification, when T classification and N classification were dichotomized to high-risk versus low-risk groups.

Discussion

Epidemiologic data has shown that the incidence of OPSCC is increasing over the past 3 decades, mirroring the increasing prevalence of HPV during the same period [14–16]. The clinical relevance of this observation is that HPV⁺ OPSCC has been shown to have a distinct biological behavior which portends a better prognosis [11–17].

Given the favorable prognosis of HPV⁺ OPSCC, studies have sought to evaluate if standard chemoradiation approaches, though highly effective in these cancers, may be deescalated to minimize complications from chemoradiation (CRT) and hopefully improve the quality of life in these patients [18, 19]. Identification of HPV⁺ OPSCC patients which are at a relatively increased risk of poor outcome is paramount to patient selection regarding de-escalation, as these patients may be poor candidates for such protocols.

GTV has been proposed as a potential biomarker for HNSCC given that it could be a surrogate marker to measure the extent of disease load in these patients [7,8]. Studies have indicated that patients with larger GTV may need to be treated with a higher radiation dose for better tumor control [1]. However, this concept has not been validated in HPV⁺ OPSCC, in whom de-intensified therapy is currently controversial.

In this study, neither of our hypotheses were confirmed. High-risk/low-risk patient groups based on TNM staging were not associated with OS or DFS following treatment with CRT. This finding is similar to a recent report by Nixon et al concluding pathologic tumor volume was superior to pathologic T classification in predicting disease-specific mortality following surgical treatment of OPSCC [20], suggesting tumor volume may be superior to traditional TNM staging in predicting oncologic outcome regardless of treatment modality. Notably, we observed very few patients with truly advanced T classification, described as T4 in the HPV⁺ OPSCC patients [10]. As such, we artificially created the high-risk T classification group of T3–T4. Even then, the sample size was small, and we expect that with increased patient numbers the trends observed would likely be significant. Furthermore, given the crossed Kaplan-Meier curves, it is improper to use cox proportional hazards for more detailed analysis of TNM data.

Secondarily, tumor volume—specifically nodal volume—was associated with survival by cox regression analysis. In our cohort of HPV⁺ OPSCC patients, we identified nodal tumor volume (nGTV) as a possible pretreatment metric to predict disease-free survival. When evaluated within this cohort, nGTV was a better predictor of DFS than pGTV, T classification, or N classification at both 12 months and 24 months. The hazard ratios presented are for a one-unit (cm³, cubic centimeter) increase in nGTV. To make this more clinically meaningful, this can be converted by exponentiation of the hazard ratio, such that a 5cm³ increase in nGTV results in a hazard ratio of 1.112; that is, for 5cc increase in nGTV, the patient's relative risk of recurrence increases 11%.

This result poses several clinical questions. Perhaps there may be differences between high-volume N2c disease and low-volume N2c disease. While underpowered to analyze the current cohort, there were 7 patients with N2c disease (mean nGTV 37.53 89.63 cm³). Anecdotally, 1 of these patients had recurrence (oligometastatic disease) with nGTV of 89.63 cm³.

Understanding the biologic and molecular basis for different phenotypes of nodal disease—matted, cystic, extensive, etc—is the true aim of seeking to quantify gross characteristics to predict tumor and tumor-host responses to treatment. Raguert et al reported cystic change to be present at a microscopic level in as many as 50% of metastases from a primary SCC in Waldeyer's ring [21]. CLN are merely surrogates for the underlying pathology (i.e. HPV status), and perhaps gross tumor volume is not an effective measure.

This study has several limitations beyond those associated with a retrospective review and small sample size, as previously described. There was a low incidence of recurrence and death in the cohort, as highlighted in Table 2. This limits the ability to interpret the presented results, as well as resample the data and perform meaningful bootstrap analysis of concordance index modeling; therefore, our results are likely an optimistic estimate. Furthermore, there are 2 obvious areas of selection bias: exclusion of community cancer center patients and exclusion of OPSCC patients were treated with upfront surgery. At our institution, we have begun to selectively treat p16⁺ OPSCC patients with transoral robotic surgery (TORS) on a prospective clinical trial, NCI-2013-00814. These patients are selected if the primary tumor is small (T1-2) and is easily exposed transorally for resection for TORS. The exclusion of these patients may potentially bias our results. Lastly, smoking history was inconsistently recorded, limiting our ability to incorporate smoking into the predictive model herein. As smoking history is thought to be the most important factor after HPV-status, and ideal model to predict patient outcome would include a patient's smoking status [14].

In conclusion, for HPV+ OPSCC, high-risk groups (TNM) were not associated with poorer DFS or OS versus low-risk groups in this sampling of limited events. Nodal tumor volume may be predictive of DFS in HPV+ OPSCC. The estimated risk of recurrence increases 1.11 times for every 5cm³ of nGTV. At 24 months, nodal volume may more predictive of recurrence than pGTV, T classification, or N classification; there is a similar predictive ability at 12 months. In a disease in which most patients present as T2N2b, tumor volume may be a more informative and robust predictor of disease-free survival. HPV+ OPSCC patients with high nodal tumor volume may be poor candidates for de-escalation protocols.

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Figure 1.

Overall survival and disease-free survival by T classification and N classification: When dichotomized into high-risk (T3–T4) versus low-risk T classification (T1–T2), there was a trend toward decreased overall survival with high-risk T classification ($p=0.057$). However, there was no association of decreased overall survival with high-risk N classification ($p=0.309$).

Cox regression model fitted to disease-free survival					
	Regression coefficient (b)	Standard error SE(b)	p-value	Hazard ratio**	95% CI for hazard ratio
pGTV	0.002	0.016	0.922	1.002	0.971-1.033
nGTV	0.021	0.007	0.001	1.021	1.008-1.035

Figure 2.

Lower nodal volume is associated with greater disease-free survival: Nodal gross tumor volume has a weak association with OS ($p=0.097$), but lower nodal volume was strongly associated with greater disease-free survival ($p=0.002$). However, primary gross tumor volume was not associated with differences in overall survival or disease free survival. The hazard ratios presented are for a one-unit (cm^3 , cubic centimeter) increase in nodal gross tumor volume. To make this more clinically meaningful, this can be converted by exponentiation of the hazard ratio, such that a 5cm^3 increase in nodal gross tumor volume results in a hazard ratio of 1.112; that is, for 5cc increase in nodal gross tumor volume, the patient's relative risk of recurrence increases 11%.

Table 1

Patient and Tumor Demographics : Fifty-three patients comprised the cohort. All patients completed radiation therapy (6600–7400 Gy). Most patients were male (n=50, 94.3%); the average age was 55 years (39–81 years). There was a roughly even breakdown of never, former, and current smokers. Over 94% of patients presents with clinical evidence of cervical metastasis. Overall, only 1 patient presented with T4 disease.

Patient Demographics			Tumor Characteristics		
	No. Patients	%		No. Patients	%
<u>Gender</u>			<u>T Classification</u>		
male	50	94.3	TX	2	3.8
female	3	5.7	T1	18	34
			T2	25	47.2
			T3	7	13.2
<u>Age</u>			T4	1	1.9
mean	55.43 years				
range	39–81 years		<u>N Classification</u>		
			N0	3	5.7
			N1	7	13.2
			N2a	7	13.2
<u>Smoking</u>			N2b	26	49.1
never	21	39.6	N2c	7	13.2
former	16	30.2	N3	3	5.7
current	16	30.2			

Table 2

HPV+ OPSCC Failure Patterns: Eight of 53 patients (15.1%) suffered disease following primary treatment. Most often, this was distant metastatic disease. In the 5 patients with progression to distant disease the mean volume of nodal disease at presentation was 95.49 cm³, as compared to 26.75 cm³ across the entire cohort.

Characteristics of Patients with Recurrence				
	pattern	smoking	TNM	nodal volume (cc)
1	local	never	T2N0	0
2	neck	never	T1N2b	97.21
3	neck	current	T4N2b	11.55
4	distant	current	T2N3	131.45
5	distant	never	T2N2a	25.33
6	distant	former	T1N2b	157.29
7	distant	current	T2N2c	89.63
8	distant	current	T2N3	73.75