Pathologically Determined Tumor Volume vs Pathologic T Stage in the Prediction of Outcome After Surgical Treatment of Oropharyngeal Squamous Cell Carcinoma

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**IMPORTANCE** Traditional prognostic models for squamous cell carcinoma of the head and neck are based on the TNM staging system. However, there is growing evidence that tumor volume (TV) may be a more accurate predictor of outcome.

**OBJECTIVE** To determine whether pathologic TV (pTV) in patients with oropharyngeal squamous cell carcinoma treated surgically is a more significant predictor of outcome compared with pathologic tumor (pT) stage.

**DESIGN, SETTING, AND PARTICIPANTS** Review of patients whose treatment was managed between January 1, 1985, and December 2005 at a US tertiary referral cancer center. The participants included 159 patients who had undergone primary surgery for oropharyngeal squamous cell carcinoma and had 3 dimensions reported on histopathologic testing.

**MAIN OUTCOMES AND MEASURES** The pTV was calculated as the product of the 3 dimensions expressed in cubic centimeters. For comparison of pT stage with pTV in outcome prediction, concordance indexes were generated using the bootstrap method (n = 1000) to quantify the predictive accuracy of recurrence and survival outcomes. Concordance indexes were then compared and a significant difference was considered when \( P < .05 \).

**RESULTS** The median age of the patients was 59 years (range, 22-84 years) and 106 were male (67%). Sites of the tumors were base of the tongue (86 patients [54%]), tonsil (48 [30%]), soft palate (24 [15%]), and posterior pharyngeal wall (1 [1%]). The median follow-up time was 64 months (range, 1-272 months). The median tumor volume was 6.8 cm\(^3\) (range, 0.1-162.5 cm\(^3\)). Pathologic TV was a significant predictor of disease-specific mortality. Unlike pT stage, pTV was a significant predictor of local recurrence, regional recurrence, and distant recurrence. Comparison of concordance indexes showed that pTV was a significantly better predictor of disease-specific mortality, local recurrence, and distant recurrence (all \( P < .05 \)).

**CONCLUSIONS AND RELEVANCE** Pathologic TV outperforms pT stage in the prediction of outcome following surgical treatment of oropharyngeal cancer. Tumor volume should be considered in the design of prospective surgical trials.

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The current combined American Joint Committee on Cancer and Union for International Cancer Control staging manual uses the anatomic descriptions of tumor (T), nodal (N), and distant metastases (M) to predict outcome in a validated model. Radiologic estimated tumor volume (TV) has been shown to be a reliable predictor of outcome in squamous cell carcinoma of the larynx, hypopharynx, and nasopharynx. The role of TV in predicting outcome for patients with oropharyngeal squamous cell carcinoma (OPC) is less clear, with several groups reporting little influence on outcome. In contrast to this, a recent review of outcomes from Memorial Sloan-Kettering Cancer Center suggested that radiologic TV was of prognostic significance in patients who received intensity-modulated radiotherapy. This is in keeping with the findings of a surgical series that included OPC as its largest subsite. The aim of our study was to determine whether radiologic TV was of prognostic significance in patients with oropharyngeal cancer who underwent surgical resection is also prognostic of outcome. We also wanted to determine whether pTV outperformed pathologic tumor (pT) stage in predicting outcome.

Methods

With institutional review board approval, 159 consecutive patients who had primary surgical resection of OPC and had 3 dimensions reported on histopathologic testing within Memorial Sloan-Kettering Cancer Center between 1985 and 2005 were identified from our institutional database. Data extracted included patient demographics, surgical procedure, histopathologic report, adjuvant therapy, and outcome. The pTV was calculated as the product of the 3 dimensions expressed in cubic centimeters. Oncologic outcomes were determined using the Kaplan-Meier method except for disease-specific death, which was estimated by cumulative incidence functions after treating death from other causes as competing risks. The outcomes assessed included overall mortality, disease-specific mortality (DSM), local recurrence (LR), regional recurrence (RR), locoregional recurrence, and distant recurrence (DR). The relationship between pT stage and outcomes was evaluated using the log-rank test or the nonparametric Gray test for DSM. The relationship between pTV and outcome was based on univariable analysis by treating the volume as a continuous predictor with splines to accommodate nonlinear relation without categorization. For comparison of pT stage with pTV in outcome prediction, concordance indexes were generated using the bootstrap method (n = 1000) to quantify predictive accuracy.

Concordance indexes were then compared and a significant difference was considered when \( P < .05 \).

Statistical analysis was carried out using commercial software (JMP, version 4.0, SAS Institute Inc; and SPSS, version 19.0; IBM). Open-source statistical software R-2.14.2 (www.r-project.org) was also used.

Results

The descriptive statistics of the group overall are reported in Table 1. The median age of the cohort was 59 years (range, 22-84 years). There were 106 men (67%) and 53 women (33%). Sites of the tumors were base of the tongue (86 patients [54%]), tonsil (48 [30%]), soft palate (24 [15%]), and posterior pharyngeal wall (1 [1%]). Pathologic T-stage categories were pT1 (20 patients [13%]), pT2 (64 [40%]), pT3 (37 [23%]), and pT4 (38 [24%]). Pathologic N-stage categories were pN0 (34 patients [21%]), pN1 (24 [15%]), pN2 (90 [57%]), and pN3 (2 [1%]). Tissue was available for human papilloma virus (HPV) analysis using p16 immunohistochemistry in 122 patients. Sixty-six of the tissue samples (42%) were p16 positive. Tumor dimensions ranged from 0.1 cm to 8 cm, corresponding to a median calculated volume of 6.8 cm\(^3\) (range, 0.1-162.5 cm\(^3\)).

Eight patients underwent surgery on the primary lesion alone (5%); 6 of these patients had pT1 disease, 1 patient had pT2 disease, and 1 had pT3 disease. Two patients underwent...
surgery for the primary lesion and received postoperative radiotherapy to the pharynx and neck. Treatment in 46 patients (29%) was managed with surgery for the primary site and neck without postoperative radiotherapy, and the remaining 103 patients (65%) had surgery to both the primary lesion and neck with postoperative radiotherapy. No patients received postoperative chemotherapy, as this was not standard care during the period studied.

With a median follow-up of 64 months (range, 1-272 months), the 5-year DSM, LR, RR, and DR were 23%, 16%, 13%, and 17%, respectively. Pathologic T stage was a significant predictor of 5-year DSM; 5-year DSM for pT1 was 6%; pT2, 12%; pT3, 25%; and pT4, 46% (P < .001). However, pT stage did not predict LR, RR, or DR (pT1, 2, 3, and 4: 5-year LR, 16%, 8%, 17%, and 29%, respectively [P = .09]; 5-year RR, 11%, 6%, 19%, and 20%, respectively [P = .055]; and 5-year DR, 6%, 14%, 20%, and 23%, respectively [P = .18]).

On univariate analysis, pTV was a significant predictor of DSM. However, unlike pT stage, pTV was also a significant predictor of LR, RR, and DR. On comparison with pT stage, pTV was a significantly better predictor of DSM, LR, and DR (P < .05) (Table 2 and Figure).

Discussion

Current internationally recognized staging systems in head and neck cancer are based on anatomic details of tumor, as well as nodal and distant metastases.1-3 In the case of OPC, categories T1 to T3 are based on the single largest dimension, with T4 reserved for locally invasive disease. The system's use of a single measurement fails to capture data in 3 dimensions. Cross-sectional imaging has given clinicians a way of calculating the 3-dimensional tumor volume prior to definitive therapy, leading to interest in its use as a predictor of outcome. Many groups have analyzed the impact of primary radiologic TV across multiple subsites of head and neck cancer, with reproducibly favorable results.3-7 For example, Hermans et al14 demonstrated that radiologic TV calculated on pretreatment computed tomographic scanning of glottic carcinomas could be correlated with rates of local recurrence. The same finding was reported by Mancuso et al3 and Kraas et al9 for lesions of the supraglottis, again using pretreatment computed tomographic scans. The value of radiologic TV in lesions of the hypopharynx has been reported by Fameijer et al17 and Chen et al16 in early- and late-stage tumors of the hypopharynx.

The volume of disease in regional nodes and its influence on outcome has also been studied but found to be less predictive than primary TV.14,16 The vast majority of these TV studies rely on radiologic measurements, with few groups reporting volumes calculated using surgical specimens.5,17

In the setting of OPC, there is conflicting evidence of the predictive power of radiologic TV on outcome. Some groups have demonstrated a strong link between primary radiologic TV and outcome.14-16,18 Groups from Europe and America have demonstrated that gross radiologic TV predicts recurrence and survival following treatment with intensity-modulated radiotherapy. Others have found radiologic TV to be of little or no use.5,13,14 Nathu et al,13 Mendenhall et al,9 and Been et al13 found that radiologic T stage was more useful in outcome prediction in patients with OPC than was TV. Keberle et al18 showed that, although volume had a minor influence on recurrence rates, the effect of tumors crossing the midline was more significant. The reasons for the differences in these findings are unclear and may include potential treatment biases,14 limitations in imaging, confounding factors such as HPV, or the lack of a correlation.

In the present study, we selected only patients who received primary surgical resection. We limited the cohort to patients who had all 3 dimensions recorded in the histopathologic report to allow volume calculation. This method avoided any limitations of dental amalgam or swallowing artifact that could bias imaging-based studies. We report on 159 patients who were monitored for a median of more than 5 years, giving ample time to detect failure and death due to disease. As expected, most patients had disease involving the base of the...
As expected, pT stage was predictive of disease-specific survival. However, when compared with pTV as a predictor, pT stage performed less well in the prediction of local and distant failure as well as disease-specific death. Our data therefore suggest pTV to be a significant predictor of outcome. As the American Joint Committee on Cancer moves from the traditional TNM system to more advanced modular staging systems,19 it is important that variables that predict outcome are identified and refined. In a time when the pendulum of treatment has swung toward chemotherapy plus radiotherapy and seems likely to return to the direction of surgical management of OPC,20,21 it is increasingly relevant to analyze oncologic outcomes for patients who undergo surgical treatment for this disease. Encompassing pathologic or radiologic TV into these staging systems will improve the prognostic value of such systems. In addition, recent studies22 suggest that the current staging system for OPC is inadequate and in need of improvement. This highlights the need for critical analysis of factors prognostic for outcome in this group, such as the use of pTV measurements.

In conclusion, our data add weight to the growing consensus that pTV outperforms traditional pT stage in the prediction of outcome following treatment of OPC. Its use should therefore be considered in modifications of the staging system for this increasingly prevalent disease.

Table 2. C-Index for pTV vs pT Stage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>pTV C-Index</th>
<th>pT Stage C-Index</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.617</td>
<td>0.629</td>
<td>−0.012</td>
<td>.65</td>
</tr>
<tr>
<td>Disease-specific</td>
<td>0.676</td>
<td>0.577</td>
<td>0.099</td>
<td>.01</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>0.607</td>
<td>0.504</td>
<td>0.103</td>
<td>.004</td>
</tr>
<tr>
<td>Distant</td>
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<td>0.470</td>
<td>0.153</td>
<td>.01</td>
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<tr>
<td>Locoregional</td>
<td>0.611</td>
<td>0.528</td>
<td>0.082</td>
<td>.06</td>
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<tr>
<td>Regional</td>
<td>0.569</td>
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<td>0.058</td>
<td>.29</td>
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<tr>
<td>Local</td>
<td>0.618</td>
<td>0.472</td>
<td>0.146</td>
<td>.006</td>
</tr>
</tbody>
</table>

Abbreviations: C-index, concordance index; pT, pathologic tumor; pTV, pathologic tumor volume.

Figure. Comparison of Pathologic Tumor Volume vs Pathologic T Stage in Outcome Prediction

DO indicates disease outcome; DSS, disease-specific survival; LR, local recurrence; LRR, locoregional recurrence; and OS, overall survival.

ARTICLE INFORMATION

Submitted for Publication: February 19, 2013; final revision received June 5, 2013; accepted July 19, 2013.


Author Contributions: Drs Nixon and Ganly had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Nixon, Palmer, Ganly. Acquisition of data: Nixon, Palmer, Ganly. Analysis and interpretation of data. All authors. Drafting of the manuscript: Nixon, Lakin, Kattan, Lee, Ganly. Critical revision of the manuscript for important intellectual content: Palmer, Kattan, Ganly. Statistical analysis: Nixon, Palmer, Lakin. Administrative, technical, and material support: Palmer. Study supervision: Ganly.

Conflict of Interest Disclosures: None reported.

Previous Presentation: This study was presented at the American Head and Neck Society 2013 Annual Meeting; April 11, 2013; Orlando, Florida.

REFERENCES

Pathologic Tumor Volume vs T Stage Prediction


