Exploration for an Algorithm for Deintensification to Exclude the Retropharyngeal Site From Advanced Oropharyngeal Squamous Cell Carcinoma Treatment

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IMPORTANCE Understanding the drainage patterns to the retropharyngeal lymph nodes is an important consideration in oropharyngeal squamous cell carcinoma (OPSCC) because treatment of these nodes is related to increased morbidity. Prediction of these drainage patterns could not only help minimize treatment morbidity but also prevent failures in at-risk patients as deintensification trials are under way for this disease.

OBJECTIVE To evaluate the prevalence of pathologic retropharyngeal adenopathy (RPA) in OPSCC relative to involvement of the oropharyngeal subsite, number of metastatic neck nodes, T classification, and N classification.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective review from January 1, 2003, through December 31, 2010, at an academic referral center of 205 previously untreated patients with pathologically confirmed, advanced-stage (III, IV) OPSCC. Data analysis was performed from January 1, 2013, through June 30, 2015.

EXPOSURE Concurrent chemoradiotherapy.

MAIN OUTCOMES AND MEASURES Radiologic evidence of pathologic RPA was tabulated and related to involvement of the oropharyngeal subsite, number of metastatic neck nodes, T classification, and N classification.

RESULTS Of the 205 previously untreated patients (183 men; mean age, 56.1 years), pathologic RPA was identified in 37 (18.0%) of the 205 patients. Pathologic retropharyngeal lymph nodes were found in 12 (13.5%) of 89 patients with base of tongue cancers, 24 (22.0%) of 109 patients with tonsil cancers, and 1 (14.3%) of 7 patients with other oropharyngeal subsite cancers. Increasing prevalence of RPA was positively correlated with closer proximity to the posterior tonsillar pillar. A multivariable logistic regression model using the oropharyngeal subsite, involvement of the posterior tonsillar pillar, number of metastatic neck nodes, T classification, and N classification revealed that the number of metastatic neck nodes was statistically significant (odds ratio, 1.44; 95% CI, 1.20-1.71; \( P < .001 \)).

CONCLUSIONS AND RELEVANCE The prevalence of pathologic RPA in this cohort was 18.0%, and patients with multiple nodes had the highest risk of pathologic RPA, followed by involvement of the posterior tonsillar pillar. However, these data suggest that there is no clear algorithm that can be used for deintensification to exclude the retropharyngeal site from the treatment volume using extent of disease gathered from pretreatment imaging for patients with advanced-stage OPSCC.
During the past decade, advanced-stage oropharyngeal squamous cell carcinoma (OPSCC) has been treated with concurrent chemoradiotherapy. Surgery followed by adjuvant therapy has seen a resurgence because of technological advances with robotic surgery.1,2 Performing surgery first may avoid the use of 2 modalities or may reduce the short- and long-term toxic effects associated with concurrent high-dose chemoradiotherapy. To try to decrease the toxic effects associated with multiple modalities, trials are ongoing to decrease the overall dose of adjuvant radiotherapy or completely avoid radiotherapy.3

An important consideration when determining the extent of treatment is the decision to include the retropharyngeal lymph nodes in the surgical or radiation field. Lymphatic drainage to the retropharyngeal lymph nodes has been described by Rouvière.4 The prevalence of retropharyngeal lymph nodes in OPSCC is reported to be 12% to 18%, but these reports do not always stratify the prevalence by subsite, and many of the reports were made before the human papillomavirus (HPV) era.5-7 The prevalence of retropharyngeal lymph node involvement may not be fully appreciated in patients with advanced-stage OPSCC who are treated with primary chemoradiotherapy or surgery followed by adjuvant therapies because the radiotherapy volume includes the ipsilateral and many times bilateral retropharyngeal lymph nodes.5,8 With the increasing interest in surgery alone or deintensification of radiotherapy in patients with OPSCC, it is important to know the prevalence of pathologic retropharyngeal adenopathy (RPA) and to understand the drainage patterns so that they can be addressed and incorporated into the treatment plan. The purpose of this study was to evaluate the prevalence of pathologic RPA relative to involvement of the oropharyngeal subsite, number of metastatic neck nodes, T classification, and N classification to better understand whether there is an algorithm that can be used for deintensification to exclude the retropharyngeal site from the treatment volume using extent of disease gathered from pretreatment imaging for patients with advanced-stage OPSCC.

Methods

Study Population

All patients were treated under a uniform clinical protocol that consisted of weekly concomitant carboplatin, paclitaxel, and intensity-modulated radiation therapy from January 1, 2003, through December 31, 2010. Data analysis was performed from January 1, 2013, through June 30, 2015. Patients were offered this regimen if they presented with pathologically confirmed, previously untreated, advanced-stage (III, IV) OPSCC. Staging was reevaluated and performed in accordance with the 2013 American Joint Committee on Cancer (AJCC) staging system with clinical examination, direct laryngoscopy in the operating room, and computed tomography (CT) and/or CT and positron emission tomography (PET).9 Patients were excluded if they had undergone previous surgery or radiotherapy to the upper aerodigestive tract or neck or imaging was not performed within 4 weeks of the initiation of treatment.

Table 1. Baseline Characteristics of the Entire Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding (N = 205)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>56.1</td>
</tr>
<tr>
<td>Subsite</td>
<td></td>
</tr>
<tr>
<td>BOT</td>
<td>89 (43.3)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>109 (53.2)</td>
</tr>
<tr>
<td>Other subsiteb</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Overall stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22 (10.7)</td>
</tr>
<tr>
<td>IV</td>
<td>183 (89.3)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>36 (17.6)</td>
</tr>
<tr>
<td>T2</td>
<td>65 (31.7)</td>
</tr>
<tr>
<td>T3</td>
<td>37 (18.0)</td>
</tr>
<tr>
<td>T4</td>
<td>67 (32.7)</td>
</tr>
<tr>
<td>N stage</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>14 (6.8)</td>
</tr>
<tr>
<td>N1</td>
<td>15 (7.3)</td>
</tr>
<tr>
<td>N2a</td>
<td>17 (8.3)</td>
</tr>
<tr>
<td>N2b</td>
<td>79 (38.5)</td>
</tr>
<tr>
<td>N2c</td>
<td>51 (24.9)</td>
</tr>
<tr>
<td>N3</td>
<td>29 (14.1)</td>
</tr>
<tr>
<td>HPV status</td>
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<tr>
<td>Positive</td>
<td>171 (83.4)</td>
</tr>
<tr>
<td>Negative</td>
<td>15 (7.3)</td>
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<tr>
<td>Missing</td>
<td>19 (9.3)</td>
</tr>
<tr>
<td>Tobacco status</td>
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</tr>
<tr>
<td>Never</td>
<td>61 (29.8)</td>
</tr>
<tr>
<td>Prior</td>
<td>72 (35.1)</td>
</tr>
<tr>
<td>Current</td>
<td>72 (35.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BOT, base of tongue; HPV, human papillomavirus.

* Data are presented as number (percentage) of patients unless otherwise indicated.

b Other subsite includes glossotonsillar sulcus, posterior pharyngeal wall, and soft palate.

Population Characteristics

A total of 215 patients met the criteria for this study. Ten patients were excluded because pretreatment imaging was unavailable for review or they had undergone excisional lymph node biopsies before referral and definitive CT findings. A total of 205 previously untreated patients (183 men; mean age, 56.1 years) were identified, and baseline characteristics are listed in Table 1. Of the 205 patients, 109 (53.2%) had tonsil cancer, 89 (43.4%) had base of tongue cancer, 3 (1.5%) had glossotonsillar sulcus cancer, 3 (1.5%) had posterior pharyngeal wall cancer, and 1 (0.5%) had soft palate cancer. Because of the low frequency of glossotonsillar sulcus, posterior pharyngeal wall, and soft palate involvement, these cancers were subsequently classified as other oropharyngeal subsites. Of the 205 patients, 67 (32.7%) had T4 tumors, and 183 (89.3%) had stage IV cancer. The HPV status was determined by immunohistochemical analysis and/or polymerase chain reaction using a previously described method.10 Patients were considered to have HPV if p16 or polymerase chain reaction test results were positive. The HPV status was known for 186 (90.7%) of 205 patients. Tobacco status...
was defined categorically as never, prior (quit >6 months before diagnosis), or current use of cigarettes, cigars, pipe, chewing tobacco, snuff, or snus. There were 61 never tobacco users, 72 prior tobacco users, and 72 current tobacco users.

Treatment Protocol
Radiotherapy was administered 5 days per week. The prescribed doses were 70 Gy at 2.0 Gy per fraction to gross disease and 59 to 63 Gy at 1.7 to 1.8 Gy per fraction to low-risk and high-risk subclinical regions, respectively, administered concomitantly according to published methods. Radiation fields covered the ipsilateral and contralateral retropharyngeal lymph nodes in all patients. Chemotherapy consisted of weekly intravenous carboplatin (area under the curve, 1) administered for 30 minutes and 30 mg/m² of intravenous paclitaxel administered for 1 hour. Hydration and an antiemetic were administered according to the standard of care.

Pretreatment Imaging
Pretreatment CT or CT/PET scans within 4 weeks of starting therapy were reviewed by a neuroradiologist (M.I.). Primary and secondary tumor site and size, distance of the primary tumor from the midline, involvement of the posterior tonsillar pillar, and encasement of the carotid artery by the primary tumor were recorded. The size (largest 2 dimensions) and distribution (levels I-V) of each lymph node were recorded for each level of the neck. We defined AJCC N3 disease as a lymph node or group of lymph nodes greater than 6 cm. A total of 150 patients who underwent CT and 55 patients who underwent CT/PET had their scans reviewed. Figure 1 shows an example of CT evidence of pathologic RPA. Retropharyngeal lymph nodes were considered pathologic if they met any of the following criteria as determined by the neuroradiologist (M.I.): enlarged (>1 cm), fluodeoxyglucose (FDG) avid on CT/PET with anatomical correlation less than 1 cm, cystic or necrotic component if less than 1 cm, or evidence of extracapsular spread if less than 1 cm. The RPA cases that met these criteria were included as positive nodes per the AJCC staging criteria. Table 2 lists all patients with pathologic RPA stratified by type of imaging obtained and radiologic criteria.

Statistical Analysis
Bivariate associations among clinical variables were tested with nonparametric tests (ie, Fisher exact test, χ² test with Monte Carlo estimates for error terms) or the Spearman rank correlation method. A multivariable logistic regression model was performed using the oropharyngeal subsite, involvement of the posterior tonsillar pillar, number of metastatic neck nodes, T classification, and N classification. An R package (OptimalCutpoints, version 1.1-3) was used to try to determine whether there was a clinically relevant cut point for the total number of metastatic neck nodes that predicted RPA. All patients provided written informed consent to participate in the University of Michigan Specialized Program of Research Excellence, which was approved by the Institutional Review Board for Human Experimentation at the University of Michigan.

Results
Pathologic RPA was identified in 37 patients (18.0%); 23 (11.2%) tested positive on CT, and 14 (6.8%) tested positive on CT/PET. When stratifying by subsite, pathologic RPA was found in 24 (22.0%) of 109 tonsil cancers, 12 (13.5%) of 89 base of tongue cancers, and 1 (14.3%) of 7 other oropharyngeal subsite cancers (the patient with soft palate cancer) (Figure 2). Although pathologic RPA was more commonly observed for patients with tonsil subsite cancers, the prevalence of the base of tongue cancers was higher than expected, although the difference was not statistically significant (P > .14).

The description of lymphatic drainage to the retropharyngeal node by Rouvière suggests that involvement of the posterior tonsillar pillar should be associated with the highest prevalence of RPA. To evaluate this association, we categorized the involvement of the oropharynx by stratifying the location of the edge of the primary tumor to the posterior tonsillar pillar into
3 categories. First, tumors of the base of the tongue that had no involvement of the glossotonsillar sulcus were considered to have no involvement with the posterior tonsillar pillar. Second, tumors of the tongue base with involvement of the glossotonsillar sulcus or tumors of the tonsil were considered to be adjacent to the posterior tonsillar pillar. Third, tumors of the tongue base or the tonsil were considered to involve the posterior tonsillar pillar. Figure 2 shows involvement of oropharyngeal subsites and the posterior tonsillar pillar with the associated prevalence of retropharyngeal lymph nodes. A positive correlation was found between involvement of the posterior tonsillar pillar and the presence of RPA ($P = .05$).

The prevalence of pathologic RPA also increases when stratified by the total number of metastatic neck nodes ($P < .001$; Figure 3). Of the 37 patients with pathologic RPA, 35 patients (94.6%) had pathologic RPA with other lymph node involvement. Of these 35 patients, 30 (85.7%) had single additional metastatic lymph node. An R package was then used to determine whether there was a clinically relevant cut point for the number of metastatic neck nodes. This analysis identified 3 or more nodes as the cut point. The prevalence of RPA with 3 or more nodes was 32.0% (31 of 97 patients) compared with a prevalence of 5.6% (6 of 108 patients) with 2 or fewer nodes ($P < .001$).

The number of patients with pathologic RPA when stratified by T classification was 5 (14%) of 36 with T1 disease, 11 (16.9%) of 65 with T2 disease, 7 (18.9%) of 37 with T3 disease, and 14 (20.9%) of 67 with T4 disease (Figure 2). Although the prevalence of pathologic RPA appears to be increasing with advancing T classification, this finding was not statistically significant ($P > .15$). The number of patients with pathologic RPA when stratified by N classification was 0 of 14 with N0 disease, 2 (13.3%) of 15 with N1 disease (these 2 patients are classified as having N1 disease because of the retropharyngeal lymph node), 31 (21.1%) of 147 with N2 disease, and 4 (13.8%) of 29 with N3 disease (Figure 2). No significant differences were found in the prevalence of pathologic RPA when stratified by N classification ($P > .11$). These data suggest that the presence of RPA is not associated with T classification or N classification.

Two patients presented with isolated pathologic RPA without evidence of other nodal involvement and are of specific...
interest. These patients presented with advanced T classification (T3, T4) base of tongue cancer. Both patients had tumors that extended into the glossotonsillar sulcus and were current smokers at the time of diagnosis. One patient tested HPV positive and the other tested HPV negative, and neither patient developed a locoregional recurrence.

A multivariable logistic regression model using the oropharyngeal subsite, involvement of the posterior tonsillar pillar, number of metastatic neck nodes, T classification, and N classification was performed. Only the number of metastatic neck nodes was a statistically significant predictor of a retropharyngeal node (odds ratio, 1.44; 95% CI, 1.20-1.71; P < .001).

Discussion

Pathologic RPA was seen in all oropharyngeal subsites and occurred in all T classifications and N classifications. As a result, an algorithm could not be developed that would facilitate exclusion of the retropharyngeal site from the treatment volume for patients with advanced-stage OPSCC.

To further understand the lymphatic drainage pattern to the retropharyngeal nodes, the original descriptions by Rouvière of the primary lymphatic drainage of the oropharynx were evaluated and used for our analysis of the primary tumor extent in relation to the posterior tonsillar pillar. Rouvière first separated his description into drainage of the lateral pharynx and palate (soft palate, palate tonsil, palse arches) from drainage of the tongue base. The anterior and middle collecting vessels of the soft palate ran to the subdigastric nodes, but the posterior collecting vessels of the soft palate ran through the posterior tonsillar pillar and superior constrictor and drained into the retropharyngeal nodes. We were able to identify involvement of the posterior tonsillar pillar on CT. Tumors that involved the posterior tonsillar pillar could gain access to the retropharyngeal lymph node basin through vessels that pierce the constrictor from the soft palate system. At the outset of this study, we sought to describe a systematic pattern that would predict pathologic RPA. Lymphatic drainage patterns were thought to be a key anatomical factor that would help predict RPA. Although we have found a correlation with posterior tonsillar pillar involvement, this was not significant in our multivariable analysis. Consequently, we cannot develop a clear cut point that would suggest that there is an opportunity to spare patients from treatment of the retropharyngeal lymph nodal basin.

For this study, a categorical classification in relation to the posterior tonsillar pillar (no involvement with the posterior tonsillar pillar, adjacent to the posterior tonsillar pillar, involved the posterior tonsillar pillar) was developed, and we found an increasing prevalence of pathologic RPA. This finding may have treatment implications for surgeons and radiation oncologists. For patients who undergo surgery alone, dissection of the retropharyngeal lymph nodal basin vs close follow-up with serial imaging may be important to adequately stage disease. For patients undergoing radiotherapy, data reveal improved quality of life in patients in whom the retropharyngeal lymph nodal basin is spared from radiotherapy. Although this study involved multiple head and neck cancer subsites other than the oropharynx, involvement of the posterior tonsillar pillar may be a contraindication for this radiation-sparing technique. At the University of Michigan, since 2002, the radiotherapy volumes consistently include the ipsilateral and contralateral retropharyngeal lymph nodes. This change occurred because of 3 contralateral retropharyngeal lymph node recurrences at the skull base, with 2 patients having no evidence of nodal disease at presentation. In this study, RPA was found in 6 (5.6%) of 108 patients who had 2 or fewer metastatic nodes. This frequency is thought to be unacceptably high to exclude the retropharyngeal site from the treatment volume because of the difficulty with surgical salvage and or additional radiotherapy of the retropharyngeal site.

The high prevalence of pathologic RPA with base of the tongue cancers, which was not significantly different from that of tonsil cancers, was also surprising. In the description by Rouvière, the tongue base was drained primarily by the basal lymphatic vessels, which were divided into the median and lateral basal trunks. The median basal trunk ran along the median glossoepiglottic fold, turned laterally, and met with the lateral basal trunks at the level of the inferior palatine tonsil (via the glossotonsillar sulcus). Although most lymphatic drainage from the inferior tonsillar pole terminated in the subdigastric nodes, it was in this area that the lymphatics could pierce the superior constrictor and enter into the retropharyngeal lymph nodal basin. This finding may explain the observation of pathologic RPA from tumors that involve the tongue base when compared with lateral pharyngeal sites (Figure 2). In our cohort, patients who presented with a base of tongue cancer without other subsite involvement had an RPA prevalence of 11.1% (4 of 36 patients). In patients with a base of tongue cancer with glossotonsillar sulcus involvement, the prevalence of pathologic RPA was 16.7% (8 of 48 patients).

This study used radiographic evidence of retropharyngeal lymph node metastasis without histologic conformation. Our radiologic criteria used to detect retropharyngeal metastasis (FDG avid on CT/PET, enlarged [>1-cm], cystic or necrotic component, evidence of extracapsular spread) are well-established criteria in the literature. The confirmation of tumors in retropharyngeal lymph node metastasis that are FDG avid on CT/PET has been performed in a small series of patients treated at the Mayo Clinic. All patients who had FDG-avid nodes on CT/PET had histologic confirmation of their metastasis, but they also found that patients with no radiographic evidence of RPA had micrometastasis in these lymph nodes on surgical sampling. These patients with occult N0 disease present a therapeutic dilemma because patients treated with surgery alone without retropharyngeal lymph node dissection may harbor microscopic disease that goes untreated. Patients with posterior pillar involvement may be at even greater risk of treatment failure with this paradigm and should be considered for lymph node dissection or serial imaging. It is likely that the involvement of retropharyngeal lymph nodes is higher than suggested by imaging. Given the descriptions by Rouvière, it is likely that microscopic involvement of the retropharyngeal lymph nodes is higher if the posterior tonsillar pillar is involved. Further analysis of a larger cohort, including patients with early-stage disease, will be nec-
necessary to understand whether involvement of the posterior tonsillar pillar remains important in OPSCC. Like most cancer models, there also seems to be a biological component because when more lymph nodes are involved there is an increased likelihood of retropharyngeal lymph node involvement. From this work, it seems that for patients with advanced-stage OPSCC, the presence of RPA is more closely related to a regional metastatic phenotype rather than a specific lymphatic drainage pattern from the posterior tonsillar pillar. However, for patients with less advanced disease with lower nodal burden, the involvement of the posterior tonsillar pillar may become more important and indicate that the retropharyngeal lymph nodal basin should be included in the treatment plan.

Conclusions

The prevalence of radiologic evidence of pathologic RPA in this cohort was 18.0%. There was a correlation in a univariable analysis with involvement of the posterior tonsillar pillar and RPA. The multivariable analysis revealed that patients with multiple nodes had the highest risk of pathologic RPA. However, these data suggest that there is no clear algorithm that can be used to exclude the retropharyngeal site from the treatment volume using extent of disease gathered from pretreatment imaging for patients with advanced-stage OPSCC.

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Author Contributions: Dr Chepeha had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Spector, Chinn, Chepeha. Acquisition, analysis, or interpretation of data: Spector, Bellile, Gallagher, Kang, Moyer, Prince, Wolf, Bradford, McHugh, Carey, Worden, Eisbruch, Ibrahim, Chepeha. Drafting of the manuscript: Spector, Bellile, Chepeha. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Chinn, Bellile, Chepeha. Administrative, technical, or material support: Spector, Chinn, Gallagher, Moyer, Wolf, Carey, Eisbruch, Chepeha. Study supervision: Spector, Kang, Wolf, Worden, Prince, Chepeha.

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REFERENCES