Predicting Residual Neck Disease in Patients With Oropharyngeal Squamous Cell Carcinoma Treated With Radiation Therapy

Utility of p16 Status

David C. Shonka Jr, MD; Asal N. Shoushtari, MD; Christopher Y. Thomas, MD; Christopher Moskaluk, MD, PhD; Paul W. Read, MD, PhD; James F. Reibel, MD; Paul A. Levine, MD; Mark J. Jameson, MD, PhD

Objective: To identify factors that predict complete response of cervical nodal disease to radiation therapy (RT) in patients with oropharyngeal squamous cell carcinoma (OP-SCCA).

Design: Histologic analysis of prospectively collected specimens and retrospective medical chart review.

Setting: Tertiary referral center.


Intervention: Definitive RT, with or without chemotherapy and with or without neck dissection (ND).

Main Outcome Measure: Presence of a viable tumor in post-RT ND specimen.

Results: Tissue specimens from 69 patients with OP-SCCA treated primarily with RT, with or without chemotherapy, were evaluated. Of these, 47 (68.1%) were strongly and diffusely positive for p16 expression by immunohistochemical analysis, signifying human papillomavirus positivity. Patients with p16-positive and p16-negative tumors (hereinafter, p16+ and p16−, respectively) had similarly sized primary tumors on presentation, but p16+ primary tumors were associated with more advanced neck disease (nodal stages N2c-N3; 31.9% vs 4.5% for p16− tumors) and more contralateral nodes (27.7% vs 4.5% for p16− tumors). Forty-seven patients (59.0%) underwent planned posttreatment ND (a total of 55 NDs). The NDs performed for p16− tumors were significantly more likely to have viable tumor in the specimen (50.0% vs 18.0% for p16+ tumors; P = .02). In addition, p16+ necks with residual viable cancer were characterized by incomplete response on post-RT imaging, tobacco and alcohol use, and extracapsular spread on pretreatment imaging.

Conclusions: In conjunction with other clinical parameters, p16 status can help predict the need for post-RT ND in patients with OP-SCCA. Although close observation may be warranted in selected patients with p16+ tumors, patients with p16− tumors are at much higher risk for residual neck disease, even when initial nodal disease is less advanced.


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overexpress p16. This is a reflection of the mechanism of malignant transformation of HPV-associated tumors. Malignant transformation of HPV-associated tumors occurs when the E6 and E7 oncoprotein pathways inactivate 2 tumor-suppressor proteins, p53 and pRb, resulting in unchecked cellular proliferation. In addition to its role in tumor suppression, pRb acts as an inhibitor of p16 transcription. Inactivation of pRb results in a decreased level of P16 protein expression.8 Protein p16 has been studied for its prognostic significance in head and neck (HN) malignant disease. Patients with p16-positive (herein, p16+ ) tumors exhibit better response to induction chemotherapy and RT, with better disease-free and overall survival compared with patients with p16-negative (herein, p16− ) tumors.6,7 Given these findings, it is anticipated that p16 positivity identifies a subset of patients who are more likely to have their regional disease controlled with RT or RT/chemotherapy alone, without the addition of a post-RT ND. The purpose of this study was to determine if p16 status, in conjunction with other tumor and patient characteristics, can be used to predict complete cervical nodal response to RT in patients with OP-SCCA and thus assist with the decision to perform post-RT ND.

In the present study, we assess the pathologic status of ND specimens obtained from patients with OP-SCCA in whom RT was used with or without chemotherapy as the definitive treatment modality. Moderately conservative criteria were used to select patients for post-RT ND, irrespective of p16 status. We also evaluate the outcome for observed necks (ie, regional recurrence) and correlate these findings with p16 status. We use these data in conjunction with other tumor characteristics to identify subgroups of patients in whom post-RT ND can safely be avoided and in whom the risk of residual disease is high enough to warrant surgical intervention.

METHODS

A retrospective medical chart review was performed of patients with OP-SCCA treated with RT alone or RT/ chemotherapy from January 1, 2002, through June 1, 2008. The study was approved by the University of Virginia institutional review board. Patients who underwent RT or surgery at an outside institution were excluded from the study.

Patient demographic information was collected, including age, sex, and tobacco and alcohol use. Patients were documented to be alcohol and tobacco users if they admitted to current use during their initial history and physical examination or if they had greater than a 3-pack-year history. All patients underwent staging endoscopy with diagnostic biopsy; specimens collected were used to confirm a diagnosis of SCCA and were evaluated for histologic grade. During the time frame that the cohort underwent staging endoscopy, p16 evaluation by immunohistochemical (IHC) analysis became standard for all initial HN SCCA biopsy specimens. Thus, the p16 status of some tumors was identified on the diagnostic biopsy. For the remaining tumors, a tissue microarray was prepared using archived tumor specimens. Tissue microarray technology has been shown to be a rapid and efficient method for retrospective analysis of protein expression.8

We determined p16 status by IHC analysis per Reimers et al.9 Cells were considered positive for p16 when strong, diffuse nuclear and cytoplasmic staining were noted. Specimens were considered p16+ when more than 60% of the tumor cells were stained.

The TNM stage was determined using findings from physical examination, pretreatment computed tomographic (CT) scan, and staging endoscopy. Location of cervical nodal disease was recorded as presence of extracapsular spread (ECS) on pretreatment CT. Post-RT ND was performed for N2+ disease at initial staging, for the presence of ECS on pretreatment evaluation (any N stage), or for evidence of residual pathologic adenopathy on post-RT neck CT (any N stage). Some patients with N2a disease with a less than 4-cm node without ECS that exhibited a complete response were observed. The decision to perform post-RT ND was made without knowledge of p16 status. Neck dissections were performed at 4 to 8 weeks after completion of RT. Neck dissection specimens were evaluated for the presence of residual viable tumor cells. Patients who did not meet criteria for post-RT ND were followed with serial physical examinations every 8 to 10 weeks for the first year and every 3 months thereafter.

The statistical significance of differences between patients with p16+ vs p16− OP-SCCA was determined using t test, χ2 test, or Fisher exact test, as appropriate. These analyses were performed using standard statistical functions in Microsoft Excel 2003 (Redmond, Washington). In order to determine the predictive value of tumor characteristics for cervical nodal response, univariate and multivariate analyses were performed using SPSS statistical software (version 16.0.1 for Windows; SPSS Inc, Chicago, Illinois). Results were considered significant at P ≤ .05.

RESULTS

Sixty-nine patients who were treated with definitive RT with or without chemotherapy at the University of Virginia from January 1, 2002, through June 1, 2008, for OP-SCCA were identified as having cervical metastases at diagnosis (N+ disease). Of these patients, 56 (81.2%) were male and 13 (18.8%) were female. Their average age was 58.3 years. Of the tissue specimens collected from these 69 patients, 47 (68.1%) were strongly and diffusely positive for p16 expression by IHC analysis, signifying HPV positivity.

Patient characteristics are shown in Table 1. Patients with p16+ and p16− tumors were similar in their sex distribution, but patients with p16− tumors tended to be older, male, nonalcohol users, and non-smokers.

Table 1. Patient Characteristicsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>p16-Negative</th>
<th>p16-Positive</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>69</td>
<td>22 (31.9)</td>
<td>47 (68.1)</td>
<td>.05b</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>58.5</td>
<td>62.5</td>
<td>56.7</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (18.8)</td>
<td>6 (27.3)</td>
<td>7 (14.9)</td>
<td>.26c</td>
</tr>
<tr>
<td>Male</td>
<td>56 (81.2)</td>
<td>16 (72.7)</td>
<td>40 (85.1)</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>User</td>
<td>52 (75.4)</td>
<td>22 (100)</td>
<td>30 (63.8)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Nonuser</td>
<td>17 (24.6)</td>
<td>0</td>
<td>17 (36.2)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>User</td>
<td>40 (58.0)</td>
<td>18 (81.8)</td>
<td>22 (46.8)</td>
<td></td>
</tr>
<tr>
<td>Nonuser</td>
<td>29 (42.0)</td>
<td>4 (18.2)</td>
<td>25 (53.2)</td>
<td>.006c</td>
</tr>
</tbody>
</table>

aData are presented as number (percentage) except where indicated.

bT Test.
cFisher exact test.

aPositive correlations were noted between p16 status and presence of ECS (P = .001).

bPositive correlations were noted between p16 status and initial histologic grade (P = .05).

cPositive correlations were noted between p16 status and tobacco use (P = .001).

cPositive correlations were noted between p16 status and alcohol use (P = .001).
to be older (average age, 62.5 years, vs 56.7 years for those with p16+ tumors; \( P = .05 \)), and were more likely to use tobacco and alcohol (Table 1). All patients with p16− tumors were smokers, and 81.8% drank alcohol, compared with only 63.8% and 46.8% in patients with p16+ tumors (\( P < .001 \) and \( P = .006 \), respectively).

Table 2 summarizes tumor characteristics. The p16+ primary tumors were fairly evenly distributed between base of tongue and tonsil (51.1% and 48.9%, respectively), but p16− primary tumors were predominantly tonsillar (63.6% vs 27.3% base of tongue; \( P = .03 \)). The 2 groups had similarly sized primary tumors on presentation, but p16+ primaries were associated with more advanced neck disease (N2c-N3; 31.9% vs 4.5% for p16− tumors; \( P = .01 \)) and more contralateral nodes (27.7% vs 4.5% for p16− tumors; \( P = .03 \)). Histologically, p16+ tumors were similarly distributed between well, moderately, and poorly differentiated tumors when basaloid tumors were excluded. Of the 13 basaloid tumors, all were p16− tumors; \( \chi^2 \) Test.

The ND complication rates are also shown in Table 4. The results of univariate and multivariate analyses of the variables described in this section are shown in Table 5. The outcome measure used was the presence of viable tumor in the ND specimen or recurrence of disease in observed necks. No observed neck developed clinically or radiologically identified recurrence within the follow-up period (average follow-up period, 41.0 months; range, 3-60 months).

On univariate analysis, p16 negativity, tobacco use, alcohol use, and treatment without chemotherapy were significantly correlated with the presence of residual disease. All of these factors were included in the multivariate model, with the exception of chemotherapy, because it is a subjective treatment decision already based on patient and tumor characteristics. In this model, p16 negativity and alcohol use remained clear independent
pathologic characteristics, we reassessed the data for a reliable algorithm that would allow us to reduce the number of post-RT NDs, particularly in patients with p16+ tumors. With 1 exception, all patients with p16+ tumors and residual viable tumor tissue found on ND were tobacco and alcohol users who did not demonstrate a radiologic complete response (CR) after RT. The exception was a 48-year-old male nonsmoker, nondrinker with a T1N1 tonsil cancer who demonstrated a radiologic complete response after RT/chemotherapy but underwent post-RT ND because of pretreatment ECS. If we had performed ND on necks in patients with tobacco and alcohol use (section symbol), 5 had viable tumor; 12 of 25 necks with a complete response (CR) (dagger), none had viable tumor; 12 of 16 necks with a partial response (PR) in nonsmoking/nondrinking patients (double dagger), none had viable tumor; and 10 of 13 necks in patients with tobacco and alcohol use (section symbol), 5 had viable tumor. The total number of NDs was 39. Using this proposed algorithm, 18 NDs would have been performed, and all 7 necks with residual viable tumor would have undergone ND.

is applied to p16+ tumors and the standard algorithm is applied to p16- patients, the overall sensitivity and specificity for residual cervical disease are 100% and 71.6%, respectively.

Table 4. Neck Dissection Characteristics

<table>
<thead>
<tr>
<th>p16 Status</th>
<th>All</th>
<th>p16-Negative</th>
<th>p16-Positive</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N+ necks</td>
<td>82</td>
<td>23 (28.0)</td>
<td>59 (72.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Neck treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck dissection</td>
<td>55</td>
<td>16 (69.6)</td>
<td>39 (66.1)</td>
<td>.49b</td>
</tr>
<tr>
<td>Observation</td>
<td>27</td>
<td>7 (30.4)</td>
<td>20 (33.9)</td>
<td></td>
</tr>
<tr>
<td>Neck dissection type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective</td>
<td>25</td>
<td>7 (43.8)</td>
<td>18 (46.2)</td>
<td>.78c</td>
</tr>
<tr>
<td>Modified radical</td>
<td>22</td>
<td>6 (37.5)</td>
<td>16 (41.0)</td>
<td></td>
</tr>
<tr>
<td>Radical</td>
<td>8</td>
<td>3 (18.8)</td>
<td>5 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Pathologic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No viable tumor present</td>
<td>40</td>
<td>8 (50.0)</td>
<td>32 (82.1)</td>
<td>.02b</td>
</tr>
<tr>
<td>Viable tumor present</td>
<td>15</td>
<td>8 (50.0)</td>
<td>7 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>Any complication</td>
<td>22</td>
<td>9 (56.3)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Complication types, No.</td>
<td>Perioral weakness</td>
<td>6</td>
<td>2</td>
<td>4 NC</td>
</tr>
<tr>
<td>Shoulder weakness</td>
<td>13</td>
<td>3</td>
<td>10 NC</td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td>2</td>
<td>0</td>
<td>2 NC</td>
<td></td>
</tr>
<tr>
<td>Wound infection/ dehiscence</td>
<td>4</td>
<td>2</td>
<td>2 NC</td>
<td></td>
</tr>
<tr>
<td>Chyle leak</td>
<td>2</td>
<td>2</td>
<td>0 NC</td>
<td></td>
</tr>
<tr>
<td>Seroma</td>
<td>1</td>
<td>1</td>
<td>0 NC</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NC, not calculated.

a Data are presented as number (percentage) except where indicated.

b Fisher exact test.
c $\chi^2$ Test.

Figure. Based on the standard treatment protocol described in the "Methods" section, the following neck dissections (NDs) were performed: 5 of 5 necks with extracapsular spread (ECS) (asterisk), 2 had viable tumor; 12 of 25 necks with a complete response (CR) (dagger), none had viable tumor; 12 of 16 necks with a partial response (PR) in nonsmoking/nondrinking patients (double dagger), none had viable tumor; and 10 of 13 necks in patients with tobacco and alcohol use (section symbol), 5 had viable tumor. The total number of NDs was 39. Using this proposed algorithm, 18 NDs would have been performed, and all 7 necks with viable tumor would have undergone ND.

Several studies have demonstrated the prognostic significance of the p16 protein in HN malignant disease. Interestingly, p16 overexpression has been associated with more advanced TNM stage and higher histologic...
grade at the time of diagnosis. For p16+ tumors, our data indicate a trend toward more advanced cervical disease with more contralateral adenopathy at the time of diagnosis compared with p16– tumors, as well as a higher incidence of basaloïd histologic classification (which is almost exclusively p16+), which has traditionally been thought to represent a more aggressive form of OP-SCCA. Despite these features, patients with p16+ tumors exhibit better response to induction chemotherapy and RT, with better rates of disease-free and overall survival.6,7,10,11 The present study demonstrates that p16+ tumors are also associated with a high rate of complete pathologic response of cervical nodal disease to RT alone or RT/chemotherapy; patients with p16+ tumors are significantly less likely to have persistent viable tumor in their posttreatment ND specimens compared with patients with p16– tumors (P = .02). When one considers the apparently more extensive disease on presentation in the p16+ group, this finding is even more compelling.

Other tumor markers have been evaluated for their prognostic significance in HN malignant disease. Licitra et al12 showed that p53 status was not prognostic for overall survival, incidence of tumor relapse, or incidence of second tumor. Epidermal growth factor receptor (EGFR) expression, current or former smoking behavior, and female sex were associated with poor response to RT and poor survival in a multivariate analysis.13 High EGFR expression, combined with low p53/high Bcl-xL expression, female sex, and smoking were associated with a poor response to chemotherapy and RT.7 Aeberson et al14 showed that tumor levels of transforming growth factor α (TGF-α), EGFR, and platelet-derived growth factor AB in OP-SCCA are not predictive of response to RT. In a study15 of oral cavity and OP-SCCA, EGFR overexpression was significantly related to decreased overall survival. In addition to p16, EGFR was evaluated in the present study but was not correlated with control of cervical metastatic disease (data not shown). Given the well-demonstrated importance of EGFR in HN SCCA and other epithelial cancers, the lack of correlation in this study may result from the methodology used to assess EGFR expression. Alternatively, as with other growth factor receptors involved in cancer, while the role of the EGFR may be central to the development and growth of OP-SCCA, expression level may not be the appropriate method to assess its involvement in a given tumor; hence the less than perfect correlation between outcomes and EGFR expression level noted in the literature. Interestingly, the role of EGFR may be minor in HPV-positive tumors, and EGFR-outcome associations in prior studies may have been confounded by a variable inclusion rate of HPV-positive tumors.

The present study assumes that the presence or absence of viable tumor on pathologic assessment of an ND specimen correctly identifies patients who would or would not have gone on to develop regional recurrence had the ND not been performed. Obviously, this postulate is reasonable but difficult to prove and certainly cannot be assessed within the confines of the present study. We also did not evaluate the impact of the type of ND performed on long-term regional control. The majority of the NDs performed in this study were selective or modified radical with sparing of the spinal accessory nerve. In general, the goal was to remove all levels that were known to have disease present on initial evaluation, even if a CR was noted at those levels after RT. One study15 demonstrated a low false-negative rate for CT evaluation of cervical nodal response to radiation therapy for OP-SCCA, particularly in levels I and V. This study concluded that it is reasonable to spare levels I and V in patients without radiologic and clinical evidence of positive nodes in these locations and that the extent of ND for patients with nodal disease associated with oropharyngeal cancer treated with RT should include levels II to IV. Another study16 demonstrated no change in the disease-specific and overall survival regardless of the extent of ND. However, Arghiris et al17 demonstrated that ND improves neck control for patients with clinically residual disease or N3 neck cancer but has no significant impact on the outcome of patients who are clinically disease-free after treatment with chemotherapy and RT. In this context and in light of the findings of the present study, it seems likely that the current standard approach to post-RT ND results in an excessive number of NDs being performed, particularly in patients with p16+ tumors.

Other methods of predicting response of cervical disease after RT or RT/chemotherapy have been discussed in the literature. A recent study11 concluded that it is not yet clear whether fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) can reliably avoid planned ND when a residual mass persists in the neck after chemotherapy and RT. The most reliable scoring criteria and the optimal timing between completion of radiation and FDG-PET still have to be determined.17,18 Also, it is clear that, while centers that perform a high volume of FDG-PET/CT assessments of patients with HN SCCA can develop a high level of expertise and stringent predictive criteria on residual cervical disease, many institutions cannot be as accurate with their present level of experience. While high cost is still an important downside to routine use of PET/CT, a more concerning issue is the delay of 8 to 12 weeks before being able to accurately ascertain the status of a posttreatment neck. In this time frame, post-RT ND becomes more challenging due to increased tissue fibrosis, and presumably the delay in treatment presents at least a small risk of tumor progression, although to our knowledge this has not been demonstrated.

It is worthwhile to identify methods of limiting the number of NDs performed when no viable tumor remains after RT. While the mortality rate remains low with ND regardless of the extent of dissection, morbidity remains an issue. One recent study19 showed marginal mandibular nerve injury in 23% of the necks dissected. Additionally, modified nerve-sparing NDs are associated with temporary shoulder dysfunction that is reversible with appropriate postoperative physical therapy.20 Better shoulder outcomes are noted with selective ND but shoulder morbidity remains a risk even with more limited surgery.21,22 Our patients ultimately exhibited excellent outcomes with resolution of shoulder weakness, except when undergoing radical ND. It is unclear why the p16– group had a higher...
complication rate; this may be related to specific patterns of nodal spread, which we did not assess, or to their older age and tobacco- or ethanol-associated comorbidities. However, the small number of complications limits our ability to adequately assess this issue.

Overall, it is clearly a reasonable goal to reduce the number of NDs, but this must occur with a high level of confidence that recurrence rates will not increase. It is interesting to note that, while the stage and grade of tumor have been associated with survival, they are less tightly bound in our study to control of regional metastasis. We found that p16 negativity was actually the best predictor of residual cervical disease after RT or RT/chemotherapy in our patients, which occurs markedly less frequently in patients with p16+ tumors. Given this finding, we sought to find predictors that would better isolate the “at-risk” patients with p16+ tumors. Those with p16+ tumors who have a history of tobacco and alcohol use are at much higher risk, and virtually all patients with p16+ tumors in our study without these habits could be spared a ND. Thus, we propose an algorithm for further evaluation that involves selecting patients with p16+ tumors for post-RT ND by imaging (eliminate patients with a radiologic CR) and then tobacco and alcohol use history (include patients with positive histories). In our study, this would have left 1 neck with residual disease undissected. This was clearly a rare case—small-volume disease with a radiologic CR. However, this patient was noted to have ECS on his pretreatment imaging; we would anticipate this would increase the risk of failure to control cervical metastatic disease but need to confirm this in a larger series. We noted that, if ECS is added as a criterion to perform an ND even in an otherwise low-risk patient with a p16+ tumor, all patients with residual cancer would have been treated without significantly increasing the number of unnecessary NDs. Implementing our suggested algorithm would have considerably reduced the number of NDs performed and the related patient morbidity. An obvious limitation of the proposed approach is the lack of detail regarding the risk of tobacco and alcohol use (eg, how much risk is incurred by light vs heavy use). A more detailed study is warranted.

For patients with p16− tumors, 50% of our ND specimens contained viable tumor, while none of our observed necks went on to develop recurrence. Thus, we recommend continued aggressiveness in performing NDs in these patients whenever concerning characteristics are present (large or multiple positive nodes, ECS, lack of CR after RT, inability to use appropriate adjuvant chemotherapy). The algorithm proposed for p16+ tumors would have actually yielded poorer results in patients with p16− tumors, leaving several necks with residual disease undissected. This again reiterates the unique nature of p16+, and thus of HPV-positive OP-SCCA.

In conclusion, this study has demonstrated the distinct nature of HPV-positive OP-SCCA, as determined by p16 expression status, in terms of its response to RT/chemotherapy. Determining the p16 status of each patient with OP-SCCA has clear utility in predicting the need for posttreatment ND. The p16 status was a more reliable predictor of response to RT or RT/chemotherapy than predictors of survival such as stage and grade. The routine use of biomarkers, such as p16 status and others, may be of great value due to low cost and consistent interpretability. In the future, the predictive value of these markers will need to be assessed against other modalities such as FDG-PET.

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Correspondence: Mark J. Jameson, MD, PhD, Department of Otolaryngology–Head and Neck Surgery, University of Virginia Health System, Box 800713, Charlottesville, VA 22908 (mjjj4e@virginia.edu).

Author Contributions: All of the authors 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: Shonka, Read, Reibel, Levine, and Jameson. Acquisition of data: Shonka, Shoushtari, Thomas, Moskaluk, Levine, and Jameson. Analysis and interpretation of data: Shonka, Thomas, Read, and Jameson. Drafting of the manuscript: Shonka, Read, and Jameson. Critical revision of the manuscript for important intellectual content: Shonka, Shoushtari, Moskaluk, Reibel, Levine, and Jameson. Statistical analysis: Jameson. Administrative, technical, and material support: Shoushtari, Thomas, Moskaluk, Read, Levine, and Jameson. Study supervision: Thomas, Read, Reibel, Levine, and Jameson.

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REFERENCES


**Correction**

Error in Figure. In the Original Article titled “Oropharyngoplasty With Template-Based Reconstruction of Oropharyngnx Defects” by Chepeha et al, published in the September 2009 issue of the Archives (2009;135[9]:887-894), Figure 3 was mistakenly reversed on page 889. The correct version of Figure 3 is reprinted below.

*Figure 3.* Revascularized free tissue L-shaped transfer template. BOT indicates base of the tongue; NP, nasal palate; and RMT, retromolar trigone.