Management of Cervical Metastases in Advanced Squamous Cell Carcinoma of the Base of Tongue

Steven D. Pletcher, MD; Michael J. Kaplan, MD; David W. Eisele, MD; Mark I. Singer, MD; Jeanne M. Quivey, MD; Nancy Lee, MD

Objective: To clarify the role of neck dissection following primary radiotherapy for treatment of squamous cell carcinoma of the base of tongue.

Design: Case series.

Setting: Academic, tertiary care medical center.

Patients or Other Participants: A consecutive series of 45 patients with biopsy-proven squamous cell carcinoma of the base of tongue and cervical metastases treated with primary radiotherapy at The University of California, San Francisco, was examined. Patients with a prior history of neck irradiation, neck dissection, or head and neck cancer within 5 years were excluded.

Main Outcome Measures: Overall survival and regional control.

Results: Of the 45 patients treated with definitive radiotherapy, 25 (56%) achieved a complete response, 13 (29%) achieved a partial response, 4 (9%) were nonresponders, and 3 (7%) did not complete radiotherapy. Two thirds of the complete responders had N2 or N3 disease; 3 had recurrences in the neck, 1 of which was an isolated neck recurrence. Of the 13 partial responders, 5 had isolated persistence of disease, with 4 undergoing neck dissections. The only long-term survivors among the partial responders were those 4 who underwent a neck dissection. Overall survival was 50% at 3 years and 32% at 5 years. Regional control for complete responders was 84% at 5 years.

Conclusions: The low rate of isolated regional recurrence in patients with a complete response to radiotherapy supports the practice of surveillance alone in such patients. Patients with less than a complete response appear to benefit from prompt surgical salvage.


Locally advanced squamous cell carcinoma (SCC) of the base of tongue (BOT) can be treated with surgical resection followed by radiotherapy or with definitive radiotherapy with or without chemotherapy. Although cure and recurrence rates are similar with these 2 approaches, in general, the morbidity is considered to be less with radiotherapy. Therefore, in recent years, many centers have preferred to treat SCC of the BOT with radiotherapy, reserving surgery for salvage treatment.

This shift in treatment approach has raised the issue of how to effectively address cervical metastases in patients with cancer involving the BOT. For patients with multiple or bulky (>3 cm) cervical metastases, controversy exists regarding whether a planned neck dissection is required following radiotherapy. With the goal of avoiding the potential morbidity of a neck dissection in a previously irradiated field, some centers choose to clinically follow up patients who have demonstrated a complete response to radiotherapy. This approach, however, is complicated by the potential unreliability of clinical and imaging examinations to detect persistent or recurrent neck disease following primary radiotherapy, as well as a low rate of surgical salvage for neck recurrence once recurrence becomes apparent.

At The University of California, San Francisco, patients with SCC of the BOT and cervical metastases who achieve a complete response to radiotherapy have been observed regardless of pretreatment nodal staging. In this study, we review our treatment outcomes with this approach during 15 years.

METHODS

From the Departments of Otolaryngology—Head and Neck Surgery (Drs Pletcher, Kaplan, Eisele, and Singer) and Radiation Oncology (Drs Quivey and Lee), The University of California, San Francisco. The authors have no relevant financial interest in this article.
tion criteria for the study were presentation within the stated timeline, biopsy-proven SCC of the BOT, and the presence of pathologic cervical nodes on clinical examination or by imaging studies. Patients were excluded if they were initially irradiated at outside institutions, treated with a primary surgical approach, treated with palliative intent, had a prior history of neck irradiation or neck dissection, or had a history of head and neck cancer within 5 years before presentation.

The age at presentation of our study patients ranged from 36 to 85 years (median age, 57 years). Each patient was staged according to the 1997 American Joint Committee on Cancer staging criteria (Table 1).

Radiotherapy was delivered using several different methods: once- or twice-daily fractionation to a total dosage between 70 and 74 Gy (0.70 and 0.74 rad) (28 patients); concomitant boost, an accelerated fractionation technique (9 patients); combined external beam radiotherapy 50 Gy (0.50 rad) and brachytherapy 20 Gy (0.20 rad) (7 patients); or intensity-modulated radiotherapy (1 patient). Twenty patients were treated with combined cisplatin-based chemotherapy and radiotherapy.

Response to radiotherapy was assessed at 6 to 8 weeks after completion of treatment. Patients who had no evidence of disease at this time were considered to have had a complete response. Patients with a decrease in size but not complete resolution of neck metastases or primary tumor were deemed to have a partial response. Lack of clinical response or progression of disease defined the nonresponder group. Complete responders were observed with clinical examinations and imaging studies; computed tomographic scans were used more recently. Partial responders and nonresponders were considered for salvage surgery.

Overall survival and regional control were calculated using Kaplan-Meier curves. All regional control and survival times were measured from the date of diagnosis until death or last follow-up.

The study design was reviewed and approved by The University of California, San Francisco, Committee on Human Research. No informed consent was obtained, in accord with committee guidelines.

### RESULTS

Of the 45 patients treated with definitive radiotherapy, 25 (56%) achieved a complete response to radiotherapy, 13 (29%) achieved a partial response, and 4 (9%) were nonresponders. In 3 patients (7%), the response to radiotherapy could not be assessed. Two patients died during radiation treatment, and 1 patient underwent a neck dissection while undergoing emergency external carotid artery ligation for control of oropharyngeal hemorrhage. Histologic grade was available for 34 of the 45 patients. Of these, 14 (41%) were poorly differentiated, 15 (44%) were moderately well differentiated, and 5 (15%) were well differentiated. Three patients had excisional biopsies of metastatic nodes before radiotherapy at outside institutions. These 3 patients were subsequently referred to our institution, found to have a primary SCC of the BOT, and treated with primary radiotherapy. Overall survival at 3 and 5 years was 50% and 32%, respectively (Figure 1).

### COMPLETE RESPONDERS

Of the 25 complete responders, 16 (64%) remained disease free for the duration of follow-up (median, 40 months). All of the 9 patients (36%) who had recurrences subsequent to a complete response died of recurrent disease. Mean and median times to recurrence were 19 and 21 months, respectively; mean and median survival was 27 months (Table 2).

Three patients developed recurrent neck disease, 1 with isolated neck recurrence. This patient underwent a salvage neck dissection. Intraoperatively, the patient was noted to have tumor adherent to the carotid artery, and gross tumor resection was performed. The patient underwent further radiotherapy, developed a second recurrence in the ipsilateral neck 20 months after salvage surgery, and eventually died of uncontrolled neck disease. One of the 2 remaining patients with isolated locoregional recurrence was not a surgical candidate because of the extent of disease; the other declined surgical salvage. Regional control for complete responders at 3 and 5 years was 84% (Figure 2).

### Table 1. T and N Staging of Patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>T2</td>
<td>4</td>
<td>9</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>T4</td>
<td>5</td>
<td>8</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>27</td>
<td>8</td>
<td>45</td>
</tr>
</tbody>
</table>

### Table 2. Pattern of Failure for Complete Responders

<table>
<thead>
<tr>
<th>Stage</th>
<th>Location of Failure</th>
<th>Time to Failure, mo</th>
<th>Status at Last Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 N2c</td>
<td>L, R, M</td>
<td>6</td>
<td>Died in 9</td>
</tr>
<tr>
<td>T4 N1</td>
<td>M</td>
<td>31</td>
<td>Died in 40</td>
</tr>
<tr>
<td>T2 N2c</td>
<td>M</td>
<td>25</td>
<td>Died in 27</td>
</tr>
<tr>
<td>T4 N1</td>
<td>L, R</td>
<td>12</td>
<td>Died in 19</td>
</tr>
<tr>
<td>T2 N1</td>
<td>M</td>
<td>21</td>
<td>Died in 25</td>
</tr>
<tr>
<td>T3 N1*</td>
<td>R</td>
<td>13</td>
<td>Died in 39</td>
</tr>
<tr>
<td>T4 N3</td>
<td>L</td>
<td>10</td>
<td>Died in 24</td>
</tr>
<tr>
<td>T4 N2b</td>
<td>M</td>
<td>23</td>
<td>Died in 29</td>
</tr>
<tr>
<td>T4 N3</td>
<td>M</td>
<td>29</td>
<td>Died in 33</td>
</tr>
</tbody>
</table>

Abbreviations: L, local (base of tongue) recurrence; M, distant metastases; R, regional (neck) recurrence.

*Patient had salvage surgery.
PARTIAL RESPONDERS

Thirteen patients achieved a partial response to radiotherapy. Five patients had isolated failure in the neck; 4 of these underwent salvage surgical procedures (Table 3). Three patients had radical neck dissections, and 1 had a modified radical neck dissection sparing the spinal accessory nerve. All 4 patients are long-term disease-free survivors, with a median follow-up of 47 months. Pathology reports from all 4 patients revealed necrotic tumor.

NONRESPONDERS

Of the 4 patients who failed to respond to radiotherapy, 3 died within 5 months of diagnosis; the remaining patient was lost to follow-up at 10 months with progressive disease.

COMPLICATIONS OF RADIOTHERAPY

Nine patients (20%) experienced 10 complications. Three patients developed osteoradionecrosis of the mandible. This complication resolved with conservative treatment in 1 patient; 1 patient required a single surgical debridement, and 1 patient underwent multiple surgical debridements and iliac crest bone grafting. The latter patient also required percutaneous endoscopic gastrostomy placement for long-term enteral feeding. Two patients died during radiotherapy, 1 of an aspiration pneumonia and 1 of an unknown cause. Other complications included severe dysphagia requiring percutaneous endoscopic gastrostomy placement (3 patients), oropharyngeal bleed (1 patient), and submental abscess (1 patient).

COMMENT

The role of neck dissection after primary radiotherapy for advanced cervical metastases is unclear. In the final analysis, a planned neck dissection should be performed if a definable group of patients will benefit from surgery at an interval following radiotherapy, as opposed to when persistent or recurrent disease is detected.

In our study, 3 of 25 patients developed recurrent neck disease after a complete response to radiotherapy. Two of these patients had concurrent local recurrence; thus, a planned neck dissection alone for these 2 patients would not have cured their disease. One patient, however, may have derived significant benefit from a planned neck dissection. The unlikely event of developing an isolated recurrence of regional disease following a complete response to radiotherapy supports the practice of observing patients who achieve a complete response to radiotherapy for SCC of the BOT.

Based on their excellent 5-year survival and regional control rates using a planned neck dissection approach, Lee et al argue for planned neck dissections for all patients with cervical metastases. In their study, 100 patients with SCC of the BOT were treated with external beam radiation, brachytherapy, and planned neck dissections. The neck dissections were performed 3 weeks after completion of the external beam radiotherapy in conjunction with iodine 192 implant placement. The authors noted a 5-year survival of 87% and a regional control of 96%. Although these results are excellent, the burden of disease for these patients is much less than that of the patients in the present study. Only 3% of patients from their study had T4 disease, while in the present study 40% of patients had T4 disease. The nodal staging also varied between the 2 groups. Lee et al included N0 patients in their study, and 50% of their patient population had N0 or N1 nodal staging. Only 22% of patients in our study had N1 disease, and N0 patients were excluded. Therefore, the difference in overall survival and regional control may be related to the difference in patient population, specifically lower-staged patients, rather than the addition of a planned neck dissection.

In a recent study of patients with BOT or tonsillar fossa SCC, Roy et al also support the practice of planned neck dissections. These investigators compared the clinical and radiographic assessment of patients with the pathologic assessment of neck dissection specimens performed 6 to 8 weeks after completion of radiotherapy. They concluded that planned neck dissections were warranted for patients with N2 or N3 cervical disease regardless of the response to radiotherapy, based on their observation that clinical and radiographic assessment of a complete response did not always correlate with pathologic findings in neck dissection specimens. In their study, 3 of 9 patients with a complete response on physical ex-
amination and computed tomographic scan 6 weeks after completion of radiotherapy had neck dissection specimens that revealed persistent tumor cells on pathologic examination. The question not answered by their study, however, is whether pathologic findings in a neck dissection correlate with the subsequent clinical course.

Evidence of the tendency of routine pathologic analysis to overestimate the reproducibility of recently irradiated tumor cells comes from Strasser et al, who compared routine histopathologic preparations of postirradiation neck dissection specimens with specimens prepared using Ki67 immunohistochemical staining, looking for the proliferative capability of tumor cells. In their study, the interval between completion of radiotherapy and neck dissection ranged from 16 to 95 days (median, 27 days). Strasser et al found positive histopathologic specimens in 11 of 17 specimens, but only 3 of 17 showed Ki67 positivity. These results suggest that nearly 1 in 4 pathologically “positive” specimens in this setting lack reproductive capability.

This proposed incongruity between histopathologic examination findings and morphologic behavior may explain the discrepancy between the rate of pathologically positive necks reported by Roy et al (33%) and the rate of regional recurrence in our study (12%). This assertion is further supported by comparing the results of Peters et al, who found an 11% rate of recurrent neck disease in complete responders, with those of Lee et al, who found that 33% of complete responders had positive pathologic neck dissection specimens. Therefore, the argument that planned neck dissections are necessary because of a high rate of positive pathologic specimens must be tempered by this incongruity between positive pathologic specimens and clinical outcome. Furthermore, patients with regional recurrence may have persistent local disease or distant metastases and hence would not derive curative benefit from a neck dissection alone.

Our finding that only 4% of complete responders developed isolated neck recurrence is consistent with the studies in the literature in which patients with a complete response were observed. Peters et al found a 5% (3/62) rate of isolated neck recurrence for complete responders in a study of patients with primary oropharyngeal carcinoma. In a review of primary radiotherapy for supraglottic carcinoma, Chan et al found a 7.5% (6/80) rate of isolated neck recurrence in complete responders who did not have planned neck dissections. Both groups recommend observation following a complete response to radiotherapy, based on these data.

In our series, patients with local recurrence or persistence had poor outcomes. No surgical salvage procedures were attempted in these patients, primarily because the patients were unwilling to assume the added morbidity of a glossectomy. A clear understanding of the role and necessary extent of salvage surgery before initiation of treatment, combined with close follow-up with a head and neck surgeon following completion of radiotherapy, may allow increased opportunity for surgical salvage.

The excellent clinical outcomes of patients with a partial response to radiotherapy who undergo surgical salvage with early neck dissections emphasize the importance of close surveillance for patients with a complete response. Early detection and intervention in complete responders with neck recurrence may allow surgical efficacy in these patients to approach that of partial responders with neck disease persistence. Encouraging reports of the early detection capabilities of positron emission tomographic scans for recurrence after radiotherapy may lead to improved surgical salvage rates resulting from earlier disease detection.

The low rate of isolated regional recurrence in patients with a complete response to radiotherapy supports the practice of surveillance alone in such patients. Patients with less than a complete response require prompt surgical evaluation and, if surgical candidates, prompt surgical salvage. Patients with a complete response to radiotherapy require close surveillance using imaging and clinical examination.

Submitted for publication November 8, 2002; accepted December 16, 2002.

This study was presented in part as a poster at the American Academy of Otolaryngology—Head and Neck Surgery annual meeting; September 23, 2002; San Diego, Calif.

We thank Vivien K. Weinberg, PhD, for her assistance with the statistical analysis.

Corresponding author and reprints: Steven D. Pletcher, MD, Department of Otolaryngology—Head and Neck Surgery, The University of California, San Francisco, 400 Parnassus Ave, Room A728, Campus Box 0342, San Francisco, CA 94143 (e-mail: spletcher@ohns.ucsf.edu).

REFERENCES