Sentinel Node Localization in Oral Cavity and Oropharynx Squamous Cell Cancer

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Objective: To evaluate the feasibility and predictive ability of the sentinel node localization technique for patients with squamous cell carcinoma of the oral cavity or oropharynx and clinically negative necks.

Design: Prospective, efficacy study comparing the histopathologic status of the sentinel node with that of the remaining neck dissection specimen.

Setting: Tertiary referral center.

Patients: Patients with T1 or T2 disease and clinically negative necks were eligible for the study. Nine previously untreated patients with oral cavity or oropharyngeal squamous cell carcinoma were enrolled in the study.

Interventions: Ulnofiltered technetium Tc 99m sulfur colloid injections of the primary tumor and lymphoscintigraphy were performed on the day before surgery. Intraoperatively, the sentinel node(s) was localized with a gamma probe and removed after tumor resection and before neck dissection.

Main Outcome Measures: The primary outcome was the negative predictive value of the histopathologic status of the sentinel node for predicting cervical metastases.

Results: Sentinel nodes were identified in 9 previously untreated patients. In 5 patients, there were no positive nodes. In 4 patients, the sentinel nodes were the only histopathologically positive nodes. In previously untreated patients, the sentinel node technique had a negative predictive value of 100% for cervical metastasis.

Conclusions: Our preliminary investigation shows that sentinel node localization is technically feasible in head and neck surgery and is predictive of cervical metastasis. The sentinel node technique has the potential to decrease the number of neck dissections performed in clinically negative necks, thus reducing the associated morbidity for patients in this group.


For patients with head and neck cancer, the histopathologic status of cervical lymph nodes is an important prognostic factor. Thus, accurate staging of the cervical lymph nodes is important for the treatment of this population. Even when patients have clinically negative lymph nodes, there is still a significant chance that they may harbor occult metastases. For patients with head and neck cancer who are treated surgically, management of the clinically negative neck usually involves an elective neck dissection. Unfortunately, the performance of an elective neck dissection may frequently leave an aesthetic and functional impairment. Cosmetic deformities due to neck dissection procedures may result from the lengthy scar and the ensuing asymmetry of the neck. Furthermore, acute and chronic shoulder dysfunction can be important sequelae of neck dissections. If sentinel node localization can predict which patient requires a neck dissection, then neck dissection may be avoided in patients with negative sentinel nodes, thus reducing the associated cosmetic deformities and shoulder dysfunction.

Noninvasive evaluations, such as clinical examination, radiographic studies, and ultrasonography, are very useful but still are not sufficiently sensitive or specific to serve as stand-alone, staging modalities for predicting the histopatho-
PATIENTS AND METHODS

PATIENTS

The eligibility criteria for this prospective study included patients with previously untreated oral cavity or oropharyngeal SCC (American Joint Committee on Cancer stage I and II disease) and excluded patients who had previously undergone neck surgery or radiation therapy of the head and neck or who had a history of any noncutaneous malignancy. For midline tumors, sentinel node localization and neck dissection were performed bilaterally. When the primary tumor treatment involved surgery, our approach was to perform a neck dissection for primary tumor depth of greater than 2 mm. Primary sites other than the oral cavity and pharynx were excluded because of the inaccessibility for precision injection of the primary site. Informed consent was obtained for all participating patients. The institutional review board of the University of Michigan, Ann Arbor, approved the protocol.

From October 1998 to January 2000, we enrolled 9 previously untreated patients (4 men and 5 women; mean age, 61.9 years; age range, 22-80 years), including 7 with unilateral lesions and 2 with bilateral lesions. All but 1 of the primary lesions were oral cavity SCCs (oral tongue and floor of the mouth); the remaining lesion was oropharyngeal (tonsil). The tumor stage in all patients was American Joint Committee on Cancer stage II (T2 N0). Two patients had midline lesions; consequently, the sentinel nodes were identified and localized bilaterally. Thus, the sentinel node localization technique was used for 11 necks among 9 patients.

Two patients were excluded from analysis for eligibility or protocol violations. One patient was excluded when it was discovered that he had a remote history of radiation therapy for a previous SCC of the oral cavity. The second patient was excluded because of a previous noncutaneous malignancy: he had a tonsillar lymphoma, which was treated with chemotherapy.

Approximately two thirds of the patients who were approached for enrollment in the protocol elected to participate. Those patients who declined enrollment reported concern regarding spending the additional time required to participate in a clinical study. Some patients also expressed concern regarding pain associated with tumor injection.

MATERIALS

On the afternoon before surgery, the patients arrived at the nuclear medicine suite for tumor injection with 3 mCi of unfiltered technetium Tc 99m sulfur colloid radiotracer. At least 1 member from the Department of Otolaryngology and 1 from the Department of Nuclear Medicine were present at the time of each injection. A total volume of 0.20 mL was prepared from a commercially available sulfur colloid kit (CIS-US Inc, Bedford, Mass). Because the injections elicited a painful, burning sensation in the patients, 2% tetracaine hydrochloride (Pontocaine) solution was used as topical anesthetic. Four injections of equal volume (0.05 mL) were meticulously placed submucosally at 4 equidistant points within 2 mm of the peripheral tumor margin.

We elected to perform tumor injection on the afternoon before surgery, with a first case start in the operating room the following morning, so that a reliable time between tumor injection and surgery could be established. The time elapsed between tumor injection and surgery was approximately 16 hours.

Immediately after the injection, the patients were taken for scintigraphic imaging. Anterior and lateral images were obtained with a single-head gamma camera (E CAM; Siemens’s Medical System Inc, Hoffman Estates, Ill). Serial images were obtained with the patients supine and in an upright position in a prone position. Images were obtained approximately 16 hours after injection.

RESULTS

For each of the 9 eligible patients, the sentinel node was successfully localized and removed. For all previously untreated patients, the sentinel node technique had a negative predictive value of 100% for the absence of cervical metastasis. For our 9 patients demonstrated cervical metastasis on permanent pathologic analysis; in each instance, the sentinel node(s) was the only node(s) identified that harbored metastasis. The Table provides data on the location of the primary tumors and sentinel nodes as well as the histopathologic status of both the sentinel nodes and the remainder of the neck dissection specimens. When assessing the size of the sentinel nodes, we found no statistical difference between histologically positive and negative sentinel nodes. The mean size of the positive and negative sentinel nodes was 1.86 and 1.52 cm (P = .66), respectively.

The 2 patients who were enrolled but excluded from the analysis owing to treatment for previous head and neck malignancies did not demonstrate sentinel
images were taken up to 1 hour after injection and once again the following morning before surgery. During imaging, the primary injection site was lead shielded so that the sentinel nodes could be more easily identified. The lymphoscintigrams were used to provide preoperative information on the general location and number of sentinel nodes, rather than specific detailed anatomical data. For patients with unilateral, nonmidline lesions that were found to have contralateral radiotracer uptake on the lymphoscintigrams, we did not pursue localization of the contralateral node and contralateral neck dissection because bilateral neck dissection for unilateral, nonmidline primary tumors in clinically negative necks is not the current standard of care. A senior staff nuclear medicine physician provided lymphoscintigraphic interpretations before surgery.

INTROPERATIVE IDENTIFICATION

Preoperatively, lymphoscintigraphic scans were examined to aid in identification of the sentinel node. The procedure began with an attempt to transcutaneously identify the sentinel node with a gamma probe (Navigator Gamma Guidance System; Auto Suture Co, Norwalk, Conn); however, the “shine-through” effect of the primary tumor frequently made this difficult. The higher radioactivity from the injection site, termed the shine-through artifact, obscures localization of the sentinel nodes in the first echelon. Therefore, extirpation of the primary tumor site was always performed before sentinel node localization and neck dissection. The sentinel node was then assessed transcutaneously. A neck dissection incision was made, and the sentinel nodes were identified with the aid of the gamma probe and individually dissected and removed. After the removal of the sentinel nodes, the tissue bed was reevaluated to confirm the removal of all sentinel nodes. Subsequently, a selective neck dissection (levels I-IV) was performed.

PROCESSING OF SPECIMENS

After removal of the sentinel nodes and completion of the neck dissection, the entire surgical specimen was stored in the Department of Nuclear Medicine for 48 hours to allow decay of the radioisotope to background levels. At our institution, the Department of Pathology does not receive any tissue specimen that has been exposed to radioactivity for at least 48 hours, regardless of the amount of radioactivity. Therefore, primary tumor margins could not be evaluated routinely at the time of surgery. There is ongoing dialogue between the Departments of Otolaryngology, Pathology, Nuclear Medicine, and Radiation Safety at our institution regarding this issue. Both the Department of Nuclear Medicine and the Department of Radiation Safety have stated clearly that the level of radioactivity used in this protocol is safe for intraoperative use for both the patient and the surgeon, requiring no special precautions. We are optimistic that with the growing popularity of this technique and its established safety, this problem will be resolved at our institution in the near future. This potentially problematic scenario is addressed in our informed consent process before patient enrollment in the study.

After the 48-hour period, the neck dissection specimens were grossly evaluated and processed according to standard protocol at our institution. Each of the 4 levels of the neck dissection specimen was submitted separately for permanent analysis. Lymph nodes were identified by palpation and visual inspection and then bisected. A single representative cross section of each lymph node was histologically examined by an attending pathologist to evaluate for cervical metastasis. The sentinel nodes were processed and examined in an identical fashion to the nodes from the neck dissection specimens. Afterward, the histopathologic status of the sentinel nodes was compared with that of the remainder of the neck dissection specimens.

nodes. No radiotracer uptake was elicited in the cervical lymphatics of the patient who had previously undergone radiation therapy to the oral cavity and cervical region for an oral cavity SCC. He was not found to have cervical metastasis after neck dissection. The second patient, who had been previously treated with chemotherapy for tonsillar lymphoma, had radiotracer uptake, but the sentinel node was not identified intraoperatively. In the latter patient, cervical metastases were subsequently discovered after neck dissection.

One patient was found to have a positive microscopic primary tumor margin, which was reported on permanent pathological analysis. This patient subsequently underwent postoperative radiation therapy because of cervical metastasis. No complications occurred in association with the sentinel node localization technique. This patient is presently free of disease.

The lymphoscintigrams demonstrated cervical lymph node radiotracer uptake and served as a guide for the number and location of sentinel nodes. In 6 of the 7 patients with unilateral lesions, the number of sentinel nodes determined by lymphoscintigraphy correlated with the number of sentinel nodes identified intraoperatively in the ipsilateral neck area. Two of the 7 patients with unilateral primary lesions also demonstrated lymphoscintigraphic uptake on the opposite side of the neck. According to protocol, no attempts were made intraoperatively to locate the nodes on the opposite side of the neck. Neither of the 2 patients with unilateral primary lesions and bilateral uptake has subsequently developed contralateral cervical metastasis. The 2 patients with midline primary lesions who underwent bilateral neck dissections demonstrated multiple bilateral nodes on the lymphoscintigrams. For both of these patients, 1 sentinel node was identified intraoperatively in each side of the neck.

Additional operative time was used for patients undergoing sentinel node localization. Time spent for data recording and locating sentinel nodes added approximately 45 minutes to the operative time. Also, some delays were encountered in operating room start time because of difficulty in coordinating the second lymphoscintigraphic scan performed in the nuclear medicine suite on the morning of surgery.
Data on Primary Tumor and Sentinel Node Location as Well as Histopathologic Status of Both the Sentinel Nodes and the Remaining Neck Dissection Specimen(s)*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumor Site</th>
<th>Type of Neck Dissection</th>
<th>Location (No. of Nodes)</th>
<th>Sentinel Node Largest Dimension, cm</th>
<th>Histopathologic Status† (No. of Positive Nodes)</th>
<th>Histopathologic Status of the Remainder of the Neck Dissection Specimen(s) (No. of Nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lateral oral tongue</td>
<td>Unilateral</td>
<td>Level II (2)</td>
<td>3.0 and 0.5</td>
<td>Positive (1)</td>
<td>Negative (0/30)</td>
</tr>
<tr>
<td>2</td>
<td>Retromolar trigone</td>
<td>Unilateral</td>
<td>Level II (2)</td>
<td>1.3 and 1.2</td>
<td>Negative</td>
<td>Negative (0/38)</td>
</tr>
<tr>
<td>3</td>
<td>Lateral oral tongue</td>
<td>Unilateral</td>
<td>Level II (2)</td>
<td>1.0 and 1.0</td>
<td>Negative</td>
<td>Negative (0/27)</td>
</tr>
<tr>
<td>4</td>
<td>Posterolateral floor of the mouth</td>
<td>Unilateral</td>
<td>Level II (1)</td>
<td>2.5</td>
<td>Negative</td>
<td>Negative (0/17)</td>
</tr>
<tr>
<td>5</td>
<td>Tonsil</td>
<td>Unilateral</td>
<td>Level II (1)</td>
<td>2.0</td>
<td>Positive (1)</td>
<td>Negative (0/34)</td>
</tr>
<tr>
<td>6</td>
<td>Posterolateral floor of the mouth</td>
<td>Unilateral</td>
<td>Level II and level III (2)</td>
<td>0.8 and 2.0</td>
<td>Positive (2)</td>
<td>Negative (0/28)</td>
</tr>
<tr>
<td>7</td>
<td>Anterior floor of the mouth</td>
<td>Bilateral</td>
<td>R level II (2); L level II (2)</td>
<td>2.5 and 2.0; 1.5 and 1.0</td>
<td>Negative</td>
<td>Negative, R (0/32) and L (0/13)</td>
</tr>
<tr>
<td>8</td>
<td>Anterior floor of the mouth</td>
<td>Bilateral</td>
<td>R level I (1); L level II (1)</td>
<td>1.5; 2.5</td>
<td>Positive, R level I (1)</td>
<td>Negative, R (0/31) and L (0/32)</td>
</tr>
<tr>
<td>9</td>
<td>Lateral oral tongue</td>
<td>Unilateral</td>
<td>Level I (1); level III (1)</td>
<td>1.2; 0.6</td>
<td>Negative</td>
<td>Negative (0/45)</td>
</tr>
</tbody>
</table>

*The sentinel node was predictive of cervical metastasis in all 9 cases. R indicates right; L, left.

Our preliminary results provide promising evidence that sentinel node localization is technically feasible for oral cavity and oropharyngeal SCC and is predictive of cervical metastasis. Although previous efforts using sentinel node localization in patients with head and neck cancer have enjoyed limited success, we believe that there are several technical issues that contributed to the successful implementation of this technique in this study. Close collaboration between the otolaryngologist and the nuclear medicine physician was critical. Because of the difficulty associated with oral cavity injection, it was essential that an otolaryngologist be involved in the tumor injection process. Similarly, the presence of the nuclear medicine physician was key to issues relating to the handling of the radioisotopes and lymphoscintigraphic image acquisition. Another important distinction in our study was the use of 3 mCi of unfiltered technetium Tc 99m sulfur colloid, as opposed to 1 mCi used in previous studies. We think that the higher activity that we used facilitated detection of the deep lymphatics in the head and neck many hours after tumor injection. Furthermore, we believe that it is essential to place the injections meticulously within the submucosal region at the margin of the tumor and to use small, precise volumes of radiotracer so that there would be greater likelihood that the lymphatics that drain the primary tumor would be accessed instead of having radiotracer diffuse more widely to involve adjacent lymphatics that were not directly draining the primary site. Finally, removing the primary tumor first is essential to intraoperative localization of the sentinel node so that the shine through of the primary tumor does not impede identification of the sentinel node.

In our study, we elected to include patients with early disease (American Joint Committee on Cancer stages I and II) and clinically negative necks, because it is this targeted group of patients in whom the potential of avoiding an elective neck dissection and its associated morbidity is most practical. This approach is consistent with the paradigm that has been established with breast and cutaneous melanoma sentinel node surgery.

Our initial experience also underscores the importance of careful patient selection and adherence to eligibility criteria. The sentinel node localization technique may not be reliable for patients who have been previously treated. Therefore, the results of this study may only be applicable to previously untreated patients.

We have discovered with our initial efforts that, while there is reason for enthusiasm with the sentinel node localization technique, there is a learning curve with this technique. There are many technical fine points regarding tumor injection and imaging as well as intraoperative localization and specimen processing. The inability to assess frozen-section margins was an obstacle during this study. Because of the current policy at our institution regarding the handling of specimens that have been exposed to radioisotopes, we were unable to send intraoperative specimens to our pathology department for frozen-section analysis. Consequently, 1 patient was found to have a positive microscopic margin on permanent analysis. This patient proceeded to undergo postoperative radiation therapy for cervical metastasis.

Our early results show the promise that sentinel node localization may have in head and neck oncological surgery for previously untreated patients with clinically negative regional disease. If successful, patients with negative sentinel nodes would be spared a neck dissection and the associated morbidity. Thus far, we have shown the technique to be logistically feasible, with a negative predictive value of 100% in the...
untreated population. We are continuing to accrue patients to provide the sample size necessary to determine if this technique provides sufficient specificity and predictive value to serve as a staging technique in this population.

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REFERENCES