Sentinel Node Biopsy in N0 Squamous Cell Carcinoma of the Oral Cavity and Oropharynx in Patients Previously Treated With Surgery or Radiation Therapy

A Pilot Study

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Objectives: To assess the feasibility of sentinel lymph node (SLN) localization and to determine the predictive value of SLN biopsy for occult neck metastases in patients previously treated with surgery or radiation therapy and with N0 squamous cell carcinoma of the oral cavity or oropharynx.

Design: Prospective case series.

Setting: Tertiary academic hospital.

Patients: Eleven patients with T1 to T4 N0 squamous cell carcinoma of the oral cavity or oropharynx.

Interventions: Patients underwent preoperative peritumoral injection of technetium Tc 99m sulfur colloid followed by dynamic lymphoscintigraphy and operative localization of the SLN(s) with the use of a handheld gamma probe.

Main Outcome Measures: The presence or absence of metastatic disease in N0 squamous cell carcinoma of the oral cavity and oropharynx in patients previously treated with surgery or radiation therapy as identified by SLN biopsy findings.

Results: In each of the 11 patients, 1 to 3 SLNs were identified by lymphoscintigraphy. All SLNs identified by lymphoscintigraphy were successfully identified and removed with the use of an intraoperative gamma probe. In 10 of the 11 patients, the biopsy findings from the SLN(s) accurately predicted the presence or absence of occult neck metastasis. There was 1 instance of a negative SLN with a positive neck dissection. The overall negative predictive value of the study was 91%. No aberrant lymphatic drainage patterns were observed in this study.

Conclusion: In patients previously treated with surgery or radiation therapy, SLN biopsy was as effective as in previously untreated patients according to published reports and warrants inclusion of this patient group into larger studies.

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Quamous Cell Carcinoma (SCC) is the most common malignancy of the upper aerodigestive tract. The presence of malignant cells in the lymph nodes is a major prognostic factor for patient outcome; lymph node metastasis decreases the chance of survival by at least 50%. Therefore, a critical role in the care of the patient with head and neck disease is the determination of whether the disease has metastasized to the neck.

Since Cabanas' first described the theory in 1977, the use of sentinel lymph node (SLN) biopsy to predict locoregional metastases has considerably expanded. The use of SLN biopsy is standard care in the treatment of cutaneous melanoma and breast cancer and is gaining acceptance in the treatment of oral and oropharyngeal SCC. Multiple authors have described this technique and its use for oral and oropharyngeal SCC. The published results of a recent international conference on SLN biopsy in mucosal head and neck cancer found the negative predictive value of a negative SLN to be 96%.

Despite the clear efficacy of SLN biopsy as a prognostic indicator of oral and oropharyngeal SCC, most previously published studies on this topic, including a previous study from our group, either excluded patients previously treated with surgery or radiation therapy or failed to differentiate them from the remainder of the cohort. Pitman et al reviewed the cases of 5 previously treated patients with recurrence or new primary SCC, but all of these patients had undergone prior neck dissection (selective or radical) on the ip-
bilateral side. This patient population represents a considerable proportion of all patients with head and neck cancer. Thus, the goal of the present study was to assess the feasibility of SLN localization using lymphoscintigraphy and gamma-probe radiolocalization in patients previously treated with surgery or radiation therapy and to determine the effectiveness of SLN biopsy in predicting the status of the clinically node negative (N0) neck in this subset of patients. This study demonstrates that SLN biopsy can be successfully used in previously treated patients to reliably predict metastases in the remainder of the neck with a negative predictive value of 91%, indicating that this treatment option should be presented to patients with recurrent SCC.

**METHODS**

Patients with biopsy-proven SCC of the oral cavity or oropharynx with no clinical or radiological (computed tomographic) evidence of cervical lymph node involvement and who had received previous treatment for SCC were eligible for this prospective study. No patients had prior surgery in the neck. Patients presenting to the Nova Scotia Cancer Center (Halifax), with T1 to T4 N0 SCC of the oral cavity and oropharynx were assessed by an interdisciplinary tumor board. Those for whom surgical treatment was recommended, including resection of the primary tumor as well as neck dissection, were offered enrollment in the study.

Eleven adult patients were enrolled in the study from February 2003 to March 2004. The Queen Elizabeth II Health Sciences Centre (Halifax) research ethics committee approved the protocol of this study, and appropriate written consent was obtained from all patients.

Patients underwent lymphoscintigraphy the day before surgery. Unfiltered technetium Tc 99m sulfur colloid was used as the radioactive tracer. After the patient had received topical anesthesia, the tracer (18.5-37.0 MBq in 0.5-1.0 mL) was injected submucosally around the circumference of the tumor (to convert millicuries to megabecquerels, multiply by 37). A non-alcoholic mouthwash was used immediately after the injection to minimize the possibility that the patient might swallow residual radioactive material.

Imaging using a standard large field-of-view gamma camera (GE Starcam; GE Medical Systems, Haifa, Israel) was then performed for 10 minutes in dynamic mode (4 frames per minute). Static images were taken for up to 2 hours after injection until the nodes were localized. Images of the radioactive nodes were taken in the anterior-posterior and lateral planes. Using the gamma camera, the location of the node(s) was marked directly on the overlying skin with indelible ink, providing a lymphatic map.

Patients received general anesthesia and were prepared for surgery in the standard fashion the following morning. The primary tumor was excised first to decrease the background radiation. A total of 19 SLNs were removed from the 11 patients and sent for histopathologic analysis. The histopathologic analysis of the SLN was then compared with the remainder of the lymphadenectomy specimen. The SLN(s) and the remainder of the lymphadenectomy specimens were submitted separately to the pathology department for histopathologic evaluation. The SLN(s) was measured and serially sectioned at 2- to 3-mm intervals along its long axis and submitted in toto in 1 or more cassettes. Each layer was stained with hematoxylin-eosin and cytokeratin and subsequently evaluated by the same pathologist (M.B.) for the presence of metastatic disease. The remaining lymphadenectomy specimens were oriented using sutures and labeled as to the lymph node groups they represented (according to the standard numerical designation of lymph node groups in the neck). The lymph nodes from these specimens were measured, submitted in toto (whole, bisected, or serially sectioned, depending on size) in 1 or more cassettes, and stratified as to which level they represented. The lymphadenectomy specimen was then examined in a standard fashion by the reference pathologist. The report included the number of lymph nodes from each group, the number of involved nodes and the level at which they were located, the size of the largest metastatic focus, and the presence or absence of extracapsular spread. The histopathologic analysis of the SLN was then compared with the remainder of the lymphadenectomy specimen.

**RESULTS**

Of the 11 patients who completed the study, 6 were men and 5 were women (mean age, 61.6 years [range, 36-80 years]). The location (number) of the primary tumors were the buccal mucosa (4), oral tongue (3), floor of mouth (3), and tonsillar fossa (1). Tumors at presentation were staged as follows: T1 in 3 patients, T2 in 3 patients, T3 in 2 patients, and T4 in 3 patients. All lesions were staged N0 by clinical examination and computed tomography. All 11 patients had received prior treatment for oral or oropharyngeal SCC. Eight of them had single modality surgery as treatment, whereas 2 had undergone primary radiation therapy as treatment, and 1 patient undergone radiation therapy with concurrent chemotherapy (Table).

Lymphoscintigraphy was performed in all 11 patients, and findings revealed 1 or more SLNs in each subject. In 4 patients, 2 SLNs were identified; and in 2 patients, 3 SLNs were identified. The remaining 5 patients had only 1 SLN identified during lymphoscintigraphy (Table). All SLNs detected by lymphoscintigraphy prior to surgery were identified by the handheld gamma probe through the intact skin and in the open lymphatic bed after elevation of subplatysmal neck flaps. A total of 19 SLNs were removed from the 11 patients and sent for histopathologic analysis (Table).

On histopathologic examination, the SLNs of 11 patients were negative; in 10 of the patients, all nodes from the remainder of the neck were also negative (Table). In 1 patient, 2 positive lymph nodes (Figure) were reported to be stuck to the primary tumor resection specimen, but no other lymph nodes were positive (including the SLNs). Although the positive nodes were located in a region that is not included in a standard neck dissection, these nodes were not identified by lymphoscintigraphy, and for this reason the result was considered to be false negative. Therefore, the overall negative predictive value of SLN biopsy was 91% in the patients examined in this study who were previously treated with surgery or radiation therapy.
Patients with recurrent SCC disease of the oral cavity and oropharynx unfortunately comprise a large proportion of cases of head and neck cancer. However, the population of previously treated patients has been systematically excluded from SLN biopsy trials. Some authors feel that prior surgery or radiation therapy may alter the head and neck lymphatic flow and lead to higher false-negative rates. Altered lymphatic patterns after surgery and radiation therapy have been observed in patients with breast cancer with prior axillary dissection; however, SLN biopsy has been successful in these patients, despite the demonstration of alternative lymphatic pathways. This study examined the efficacy of SLN biopsy in 11 patients with recurrent SCC disease of the oral cavity and oropharynx, none of whom had undergone prior neck dissection. Our results indicate that SLN biopsy in the previously treated patient is as effective as in the previously untreated patient, with an overall negative predictive value of the SLN of 91%.

All 11 patients enrolled in this study had undergone previous surgery, radiation therapy, or chemotherapy for treatment of SCC. Of the 3 patients who received prior radiation therapy, 1 (patient 9) received ipsilateral radiation, whereas the other 2 (patients 1 and 11) had bilateral radiation (Table). Despite these previous treatments, we successfully identified 1 or more SLNs on lymphoscintigraphy, and these were successfully removed intraoperatively. Although the lymphatic channels in these patients were likely disrupted or altered at the microscopic level, the SLN biopsy procedure worked as well as in a previous study of untreated patients. There were no instances of seriously altered lymphatic flow as demonstrated by lymphoscintigraphy. Of the 11 patients, 10 had only negative nodes, whereas 1 had a negative SLN biopsy but 2 positive nodes elsewhere (Table). Interestingly, the 2 positive nodes identified were stuck to the primary resection specimen and were not contained within the standard neck dissection specimen. We postulate that the nodes were not identified on lympho-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumor Site</th>
<th>Tumor Stage</th>
<th>Previous Treatment</th>
<th>SLN Location, Level</th>
<th>Histopathologic Status of Neck Dissection (No. of Nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Floor of mouth</td>
<td>T4</td>
<td>XRT/Chemo</td>
<td>2</td>
<td>Positive (2/29)</td>
</tr>
<tr>
<td>2</td>
<td>Buccal mucosa</td>
<td>T4</td>
<td>Surg</td>
<td>1</td>
<td>Negative (0/5)</td>
</tr>
<tr>
<td>3</td>
<td>Lateral tongue</td>
<td>T2</td>
<td>Surg</td>
<td>2</td>
<td>Negative (0/49)</td>
</tr>
<tr>
<td>4</td>
<td>Lateral tongue</td>
<td>T3</td>
<td>Surg</td>
<td>2</td>
<td>Negative (0/47)</td>
</tr>
<tr>
<td>5</td>
<td>Tonsillar fossa</td>
<td>T1</td>
<td>Surg</td>
<td>1</td>
<td>Negative (0/15)</td>
</tr>
<tr>
<td>6</td>
<td>Buccal mucosa</td>
<td>T1</td>
<td>Surg</td>
<td>1</td>
<td>Negative (0/40)</td>
</tr>
<tr>
<td>7</td>
<td>Floor of mouth</td>
<td>T3</td>
<td>Surg</td>
<td>2</td>
<td>Negative (0/13)</td>
</tr>
<tr>
<td>8</td>
<td>Buccal mucosa</td>
<td>T2</td>
<td>Surg</td>
<td>2</td>
<td>Negative (0/45)</td>
</tr>
<tr>
<td>9</td>
<td>Buccal mucosa</td>
<td>T1</td>
<td>XRT</td>
<td>1</td>
<td>Negative (0/5)</td>
</tr>
<tr>
<td>10</td>
<td>Floor of mouth</td>
<td>T2</td>
<td>Surg</td>
<td>2</td>
<td>Negative (0/21)</td>
</tr>
<tr>
<td>11</td>
<td>Lateral tongue</td>
<td>T4</td>
<td>XRT</td>
<td>2</td>
<td>Negative (0/13)</td>
</tr>
</tbody>
</table>

Abbreviations: Chemo, chemotherapy; SLN, sentinel lymph node; surg, surgery; XRT, radiation therapy.

a Histopathologic status of all SLNs was negative.
b Excluding the SLN(s).

Figure. Image of patient 1. The large white area represents the anterior floor-of-mouth primary tumor with considerable background radioactivity. The 3 sentinel lymph nodes can be identified in the right neck (circled in red).
scintigraphy secondary to the considerable background radiation given off by the primary tumor after injection. In essence, the 2 nodes were hidden in the radioactivity of the primary tumor. Although the positive nodes were resected with the primary tumor and were not part of the neck dissection, we felt they represented a false-negative finding and deserved to be reported as such. We noted that this particular patient was the only one to have received prior chemotherapy. It is possible that this treatment, alone or in combination with radiation therapy, influenced the efficacy of SLN biopsy in this situation. However, with only 1 example, it is impossible to draw any conclusion without considerable further study.

The treatment of the clinically N0 neck in patients with SCC of the head and neck continues to be controversial. Although most institutions advocate treatment of the neck by surgery or radiation therapy if the likelihood of occult metastasis is greater than 15% to 20%, these numbers imply that 80% to 85% of patients with N0 SCC of the head and neck experience the unnecessary morbidity of irradiation or neck dissection. The use of SLN biopsy in oral and oropharyngeal SCC was initiated in an attempt to avoid this unnecessary treatment and has expanded greatly over the past decade. The negative predictive value of the SLN biopsy in previously published studies3-10 of N0 SCC of the oral cavity and oropharynx has ranged from 90% to 100%, thereby indicating that SLN biopsy is a successful means of predicting metastatic outcome in the head and neck region. Indeed, a report11 from a consensus conference in 2005 indicated that with the findings reported in the current literature, SLN biopsy for oral and oropharyngeal cancer is sufficiently validated. To our knowledge, the present study expands the patient population that can benefit from the predictive value of SLN biopsy by demonstrating, for the first time, the efficacy of this technique (a negative predictive value of 91%) in predicting the metastatic outcome of previously treated patients with SCC. Although SLN biopsy is fast becoming the standard of care in the treatment of both newly identified and recurrent SCC disease of the oral cavity and oropharynx, observational trials with longer periods of follow-up will solidify its important predictive role in the treatment of head and neck cancer.

In conclusion, SLN biopsy obviously has the potential to decrease the need for neck dissection in cases of the N0 neck, thereby reducing patient morbidity and institutional costs. To our knowledge, this study demonstrates for the first time that SLN biopsy in patients previously treated with surgery or radiation therapy, a considerable proportion of all patients with head and neck cancer, seems as effective as in previously untreated patients, as described in published reports. Based on our results, we recommend that previously treated patients should be included in future SLN biopsy studies because they may potentially benefit from the procedure as much as the untreated cohort.

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Author Contributions: Drs Hart, Henry, Nasser, Trites, Taylor, Bullock, and Barnes 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: Hart, Nasser, Bullock, and Barnes. Acquisition of data: Hart, Henry, Nasser, Trites, Taylor, Bullock, and Barnes. Analysis and interpretation of data: Hart, Henry, Trites, Taylor, and Bullock. Drafting of the manuscript: Hart, Henry, Nasser, Trites, Taylor, Bullock, and Barnes. Critical revision of the manuscript for important intellectual content: Hart, Henry, Trites, Taylor, Bullock, and Barnes. Administrative, technical, and material support: Hart, Henry, Nasser, Trites, Taylor, Bullock, and Barnes. Study supervision: Nasser, Taylor, Bullock, and Barnes.

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REFERENCES