Sentinel Lymph Node Biopsy in N0 Squamous Cell Carcinoma of the Oral Cavity and Oropharynx

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Objectives: To ascertain the feasibility of sentinel lymph node (SLN) localization by preoperative lymphoscintigraphy and intraoperative gamma probe radiolocalization and to determine the predictive value of the SLN for occult metastasis of the neck in N0 squamous cell carcinoma of the oral cavity and oropharynx.

Design: A prospective study of 20 consecutive patients with N0 squamous cell carcinoma of the head and neck who underwent lymphoscintigraphy and SLN biopsy.

Interventions: On the day before surgery, each patient who completed the study underwent a submucosal peritumoral injection of unfiltered technetium 99m sulfur colloid followed by lymphoscintigraphy. Focal areas of radioactivity were marked on the overlying skin. The following day, the patients underwent resection of the primary tumor, elevation of subplatysmal flaps, identification and removal of the SLNs as identified by gamma probe, and complete neck dissections.

Results: Lymphoscintigraphy and gamma probe radiolocalization accurately identified 1 or more SLNs in all 20 patients. In 4 (20%) of the 20 patients, the SLN correctly identified metastatic disease. In no instance was the SLN negative when the lymphadenectomy specimen was positive.

Conclusions: In this study, the SLN had a negative predictive value of 100%. Sentinel lymph node biopsy is feasible and appears to accurately predict the presence of occult metastatic disease. Although further study is warranted, SLN biopsy could potentially guide head and neck oncologists to the patient with N0 disease who would benefit most from selective neck dissection and prevent the morbidity of unnecessary neck dissection.


QUAMOUS CELL CARCINOMA (SCC) is the most common malignancy of the upper aerodigestive tract. Head and neck SCC typically metastasizes into the regional cervical lymph nodes before spreading to distant organs. The presence of malignant cells in the lymph nodes is a major prognostic factor for patient outcome, as the presence of lymph node metastasis has been shown to decrease survival by 50%. The determination of whether or not the disease has metastasized to the neck is therefore of critical significance.

Based on the findings of clinical examination, many patients who present with SCC of the upper aerodigestive tract have no neck nodes of concern; ie, they have clinically negative or N0 necks. Imaging modalities such as ultrasound, computed tomography, and magnetic resonance imaging have been used in this context in an effort to identify patients with occult nodal disease. These techniques are based primarily on size criteria, with nodes smaller than 10 mm not generally considered suspicious. However, nodes as small as 2.0 mm can contain micrometastatic disease. Other factors, such as the size, site, and depth of invasion of the primary tumor, as well as the presence of perineural invasion, have also been implicated in predicting regional metastasis. These techniques, though helpful, have not proved to be completely reliable, and there is still a 20% to 30% incidence of occult nodal metastasis in necks categorized as N0.

In SCC of the oral cavity and oropharynx, the main options for treatment of the N0 neck are elective neck dissection (lymphadenectomy), radiation therapy, or a combination of the two. The traditional “watchful waiting” approach to avoid the morbidity of prophylactic neck dissection or radiotherapy has not been supported by recent literature. A method that accurately identifies metastatic disease in the N0 neck is highly desirable. It would minimize the number of unnecessary neck dissections and courses of radiotherapy for those necks that...
are truly N0. More importantly, it would minimize the number of N0 necks that are inappropriately observed because they actually harbor micrometastatic disease.

Our goals were to assess the feasibility of sentinel lymph node (SLN) localization using preoperative lymphoscintigraphy and intraoperative gamma probe radiolocalization and to determine the utility of SLN biopsy in diagnosing occult metastasis in the neck in patients with N0 SCC of the oral cavity and oropharynx.

**METHODS**

Patients with biopsy-proved SCC of the oral cavity and oropharynx with no clinical or radiologic (computed tomographic) evidence of cervical lymph node involvement were eligible for this prospective study. Patients who presented 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. Twenty-one adult patients were enrolled in the study from February 2003 to March 2004. The QEII HSC 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. The area surrounding the tumor was topically anesthetized with 4% viscous lidocaine mouth rinse and 10% lidocaine spray. Unfiltered technetium 99m sulfur colloid was used as the radioactive tracer. After the patient was topically anesthetized, the tracer (0.5-1.0 mCi in 0.5-1.0 mL) was injected submucosally around the circumference of the tumor. A nonalcohol mouthwash was used immediately after the injection to minimize the risk of residual radioactive material being swallowed.

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). Multiple 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 anteroposterior and lateral planes (Figure 1). Using the gamma camera, the location of the node(s) was marked directly on the overlying skin with indelible ink, providing a lymphatic map. A senior staff nuclear medicine radiologist interpreted the lymphoscintigraphic images before surgery. One patient was excluded from the study as a result of an erroneously short time under lymphoscintigraphy.

Patients were admitted to the hospital and taken to the operating room the following morning. They were placed under general anesthesia and prepared for surgery in the standard fashion. The primary tumor was excised first to decrease the background radioactivity. A neck dissection incision was made, with subsequent elevation of subplatysmal flaps, and the SLN(s) was identified with the use of a handheld gamma probe (Figure 2) (Navigator GPS; United States Surgical Corporation, Norwalk, Conn) combined with the images from the static lymphoscintigraphy. Once identified, the SLN(s) was individually excised, with precautions being taken to avoid disruption of the node.

The significance of a given emission measurement from the gamma probe was derived from the Poisson distribution, which relates the SD to the mean number of disintegrations according to the following formula:

$$\text{SD} = \sqrt{N_1}$$

where $N_1$ indicates the counts of the hot SLN and $N_x$ the mean counts of the adjacent tissue of the lymphatic bed after biopsy of the SLN.

To achieve an emission measurement precision of 98%, the counts for an SLN must be greater than the background counts by 3 SDs. The following gamma count measurements were taken: (1) the hot spot/node in vivo; (2) the hot spot/node alone ex vivo (Figure 3); (3) the lymphatic bed after the hot spot/node was removed; and (4) the operating room background. The level of the SLN was recorded and the elective neck dissection was performed.

The SLN(s) and the rest of the lymphadenectomy specimens were submitted separately to the pathology department.
Of the 20 patients who completed the study, 13 were male and 7 were female. Their ages ranged from 35 to 83 years, with a mean age of 62.75 years. The locations of the primary tumors were as follows: buccal mucosa (n = 7), oral tongue (n = 4), floor of the mouth (n = 4), retromolar trigone (n = 1), oral vestibule (inner lower lip) (n = 1), tonsillar fossa (n = 1), lateral tongue base (n = 1), and alveolar ridge (n = 1). The tumor stage at presentation was T1 in 3 patients, T2 in 11 patients, T3 in 4 patients, and T4 in 2 patients. The disease in all patients was staged N0 by clinical examination and computed tomography (Table).

Lymphoscintigraphy was performed in all cases and revealed 1 or more SLNs in all 20 patients. Two hot spots were identified in 7 patients, and 4 hot spots were identified in 1 patient. In these 8 patients, it was likely that the radioactive tracer spread distal to the SLN; however, the hot spots were considered as possible SLNs for the purposes of this study, and all were removed separately. The remaining 12 patients had only 1 hot spot identified during lymphoscintigraphy.

All SLNs detected by lymphoscintigraphy before 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 30 SLNs were removed from the 20 patients and sent for histologic analysis. The SLN(s) was measured, bisected, or serially sectioned at 2- to 3-mm intervals along its long axis (depending on size) and submitted in toto in 1 or more cassettes. Each layer was stained with hematoxylin-eosin and cytokeratin and then evaluated by the same pathologist 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 reference pathologist then reported on the lymphadenectomy specimen in a standard fashion. 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 findings of pathologic analysis of the SLN were then compared with those of the rest of the lymphadenectomy specimen.

**RESULTS**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumor Site</th>
<th>Tumor Stage</th>
<th>Location of SLN</th>
<th>Histopathologic Status</th>
<th>Histopathologic Status of Neck Dissection*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Buccal mucosa</td>
<td>T2</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/16)</td>
</tr>
<tr>
<td>2</td>
<td>Buccal mucosa</td>
<td>T4</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/5)</td>
</tr>
<tr>
<td>3</td>
<td>Retromolar trigone</td>
<td>T2</td>
<td>Level II</td>
<td>Positive</td>
<td>Negative (0/25)</td>
</tr>
<tr>
<td>4</td>
<td>Buccal mucosa</td>
<td>T2</td>
<td>Level II</td>
<td>Negative</td>
<td>Negative (0/24)</td>
</tr>
<tr>
<td>5</td>
<td>Tonsillar fossa</td>
<td>T1</td>
<td>Level II</td>
<td>Negative</td>
<td>Negative (0/15)</td>
</tr>
<tr>
<td>6</td>
<td>Floor of mouth</td>
<td>T3</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/31)</td>
</tr>
<tr>
<td>7</td>
<td>Buccal mucosa</td>
<td>T1</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/40)</td>
</tr>
<tr>
<td>8</td>
<td>Lateral tongue</td>
<td>T3</td>
<td>Level I</td>
<td>Positive</td>
<td>Negative (0/18)</td>
</tr>
<tr>
<td>9</td>
<td>Floor of mouth</td>
<td>T2</td>
<td>Level I</td>
<td>Positive</td>
<td>Positive (7/28)</td>
</tr>
<tr>
<td>10</td>
<td>Floor of mouth</td>
<td>T3</td>
<td>Level II</td>
<td>Negative</td>
<td>Negative (0/13)</td>
</tr>
<tr>
<td>11</td>
<td>Lateral tongue</td>
<td>T2</td>
<td>Level III</td>
<td>Negative</td>
<td>Negative (0/18)</td>
</tr>
<tr>
<td>12</td>
<td>Floor of mouth</td>
<td>T2</td>
<td>Level III</td>
<td>Negative</td>
<td>Negative (0/22)</td>
</tr>
<tr>
<td>13</td>
<td>Alveolar ridge</td>
<td>T3</td>
<td>Level II</td>
<td>Negative</td>
<td>Negative (0/23)</td>
</tr>
<tr>
<td>14</td>
<td>Buccal mucosa</td>
<td>T2</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/45)</td>
</tr>
<tr>
<td>15</td>
<td>Buccal mucosa</td>
<td>T2</td>
<td>Level II</td>
<td>Negative</td>
<td>Negative (0/23)</td>
</tr>
<tr>
<td>16</td>
<td>Oral vestibule</td>
<td>T1</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/5)</td>
</tr>
<tr>
<td>17</td>
<td>Buccal mucosa</td>
<td>T2</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/35)</td>
</tr>
<tr>
<td>18</td>
<td>Lateral tongue base</td>
<td>T2</td>
<td>Level I</td>
<td>Negative</td>
<td>Negative (0/20)</td>
</tr>
<tr>
<td>19</td>
<td>Lateral tongue</td>
<td>T2</td>
<td>Level II</td>
<td>Negative</td>
<td>Negative (0/21)</td>
</tr>
<tr>
<td>20</td>
<td>Lateral tongue</td>
<td>T4</td>
<td>Level II</td>
<td>Positive</td>
<td>Negative (0/13)</td>
</tr>
</tbody>
</table>

*Excluding the SLN(s).
patient had the only positive SLN with extracapsular extension. Importantly, there were no false-negative SLNs in our study; ie, there were no instances of a negative SLN in the presence of positive neck dissection results.

**COMMENT**

Cabanas first described the theory of the SLN in 1977. He stated that a limited number of first echelon nodes are the first recipients of micrometastasis. These nodes are considered to be SLNs. If lymphatic spread occurs, the SLN should be the first involved. All other nodes are reached subsequently. According to this theory of stepwise progression of lymphatic metastases, the histologic status of the SLN should then predict the presence or absence of micrometastatic disease in the remainder of the lymphatic basin. In treating regional lymphatics in cutaneous melanoma, several researchers have demonstrated that in cases in which the first draining node (SLN) had no evidence of metastatic disease on histologic examination, fewer than 5% of the patients had micrometastasis in the remaining lymphatic basin.

Although several authors have reported using SLN biopsy in oral and oropharyngeal SCC, the feasibility of using this procedure in head and neck SCC remains debatable. The results of our study indicate that SLN radio-localization is technically feasible for oral cavity and oropharyngeal SCC. They indicate a strong predictive ability of neck status based on SLN biopsy. The results of the histologic examination of the SLNs compared with those of the neck dissection specimens demonstrated an excellent negative predictive value (100%). There was no instance in which the SLN was negative for micrometastatic disease when the remaining lymphadenectomy specimen was positive. There were 4 true positives identified in the 20 patients (20%), which is consistent with the reported rates of micrometastatic disease in NO SCC of the oral cavity and oropharynx. Interestingly, in 3 of the 4 patients with metastatic disease, the only positive nodes were the SLNs. This supports the theory of the SLN as the first encountered in the sequential drainage of the primary tumor site.

In the present study, lymphoscintigraphy after peritumoral submucosal injection of the radioactive tracer yielded excellent results. All 20 patients had 1 or more hot spots identified and marked on the skin. With the use of static images from the lymphoscintigraphy and the skin marking, all SLNs identified preoperatively were successfully located intraoperatively. No SLNs were identified intraoperatively that had not been detected by preoperative lymphoscintigraphy. The skin marking was thought by the surgical team to significantly increase the speed of acquisition of the SLNs.

It has been demonstrated that up to 46% of positive lymph nodes measure less than 10 mm in diameter. Paradoxically, nodes in excess of 20 mm may be histologically benign and enlarged as a result of reactive hyperplasia. In keeping with these findings, 8 of the 20 patients in this study had negative SLNs that were equal to or greater than 15 mm in diameter on gross examination by the pathologist. The positive nodes were larger than 15 mm in diameter in only 2 of the 4 patients with metastatic disease. The positive SLN was 15 mm in diameter in the third patient and 12 mm in the fourth patient.

Although the technique of SLN biopsy has a relatively steep learning curve, there are several technical features worth mentioning. The assistance of a qualified nuclear medicine physician was essential for the handling of the radioisotope and for interpretation of the lymphoscintigraphic imaging. Several other studies have used between 0.5 and 3.0 mCi of unfiltered technetium 99m. We found that 0.5 to 1.0 mCi in 0.5 to 1.0 mL effectively identified the SLN during lymphoscintigraphy and intraoperative gamma probing in all 20 patients. Our experience supports the theory of Taylor et al that the use of small volumes of radioactive tracer increases the likelihood of capturing those lymphatics that drain the primary tumor. Larger injected volumes associated with higher tissue pressures would be expected to diffuse more widely, potentially involving other lymphatic channels unrelated to the primary tumor. The use of isosulfan or similar blue dye has been attempted during SLN localization of oral cavity and oropharyngeal SCC, but either the results were poor or the dye was thought to interfere with resection of the primary tumor. We did not attempt to use blue dye and had no difficulty in localizing the SLNs intraoperatively with the handheld gamma probe. Several authors had no difficulty identifying the SLNs with the primary tumor in situ, but, as previously described, we found significant benefit in removing the primary tumor before SLN localization to reduce the “shine through” effect of residual radioactivity. Even with removal of the primary tumor, there were instances in which there was still significant shine through, particularly when the SLN was close to the primary site. Changing the angulation of the handpiece and adjusting the threshold parameters of the scintillation counter were effective techniques to use in situations in which the SLN was close to the primary resection site. Use of the gamma probe intraoperatively was not technically challenging, and all SLNs were identified accurately and removed within 15 minutes of neck flap elevation.

As discussed by Alex et al, critics of the SLN biopsy in head and neck SCC cite concern for “skip metastasis,” in which the disease will bypass levels I and/or II and go directly to level III or IV. The prevalence of skip metastasis has been reported to be as high as 16%. Skip metastasis, however, may represent nonstandard but sequential drainage of an individual neck. Five patients (25%) in our study had SLNs located at level III. In 2 (10% of total) of these 5 patients, the only SLN identified was in level III. In the 3 patients with SLNs at levels II and III, the level III node may represent sequential drainage from the level II site. No patients had an SLN located below level III.

The technique of lymphoscintigraphy and SLN biopsy offers the potential to differentiate those patients with NO necks who would benefit from cancer treatment of the neck from those who would not. This study adds to the body of evidence confirming that SLN biopsy, when evaluated by standard histopathologic methods, predicts the presence of occult nodal disease with a high level of accuracy. However, the clinical utility of SLN biopsy used alone (ie, without concurrent neck dissection) remains limited at pres-
ent. If our data are representative, head and neck oncologists would have to expect to treat 20% of their patients for micrometastatic nodal disease, in a delayed fashion, after SLN biopsy. This treatment would entail either revision neck surgery or radiation therapy. Such issues must be considered in the context of definitive treatment of the primary tumor, which typically involves surgical resection, particularly in oral cancers, and which often requires more extensive neck surgery than SLN biopsy either to complete the resection or to mobilize vessels for free tissue transfer reconstruction.

If a reliable assessment of the SLN could be made with frozen-section analysis, a decision regarding additional neck surgery (ie, comprehensive neck dissection) could be made safely at the time of SLN biopsy. Unnecessary operations could be avoided with confidence. The issue of frozen-section examination in the context of SLNs has raised concerns among some investigators. Several authors14,17 have expressed apprehension on behalf of their pathology departments with respect to nuclear contamination in the handling of frozen-section specimens. However, the amount of radiation exposure experienced by patients, surgeons, and pathologists participating in SLN biopsy in breast cancer has been established as minimal.22 The typical radiation dose produced by SLN biopsy in head and neck SCC is less than that in breast cancer. Civantos et al16 reported on a series of 18 patients who underwent SLN biopsy for oral cavity SCC with frozen-section analysis. In 4 of the 10 patients with histologically positive SLNs, frozen sectioning failed to identify micrometastatic disease. Frozen-section analysis may prove to be the rate-limiting step for SLN as the determining factor in concurrent neck dissection. If this technique is to become the final arbiter in making the decision to proceed with a formal neck dissection, the requirement for higher sensitivity is clear. Further attention needs to be given to this issue.

The findings of our study are in keeping with those of previous reports of SLN radiolocalization and SLN biopsy in oral cavity and oropharyngeal SCC.8,13-17 We believe that the data presented were promising enough to continue accrual of patients into the protocol and have recently added frozen sectioning to the ongoing study. These results lend support to the previous data published suggesting that SLN biopsy accurately predicts the presence of occult metastatic disease and, after further study, may be used to select patients who will benefit from selective neck dissection.

CONCLUSIONS

In this study, the technique of lymphoscintigraphy with SLN biopsy in N0 SCC of the oral cavity and oropharynx accurately identified the presence or absence of occult metastasis in all 20 patients. Sentinel lymph node biopsy is feasible and appears to accurately predict the presence of occult metastatic disease. If the results of further study corroborate the data presented herein, SLN biopsy could potentially guide head and neck oncologists to the patients with N0 disease who would benefit most from selective neck dissection and prevent the morbidity of unnecessary surgery in truly N0 patients.

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REFERENCES