Original Article

Predictive Factors for Failure to Identify Sentinel Nodes in Head and Neck Squamous Cell Carcinoma

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Abstract: Background. The aim of this study was to ascertain which factors determine success of sentinel node biopsy (SNB).

Methods. We conducted a retrospective review of 121 patients with head and neck squamous cell carcinoma undergoing SNB to stage the neck. All patients underwent the triple-diagnostic procedure of preoperative lymphoscintigraphy, intraoperative blue dye, and a gamma probe. Factors contributing to failure of SNB were identified.

Results. SNB was unsuccessful in 12 of 121 patients (10%). Seven of the 12 patients had cT1/cT2 tumors, and 6 of these were located in the floor of mouth. SN identification was more likely to be successful in patients with cN0 necks, but this did not reach statistical significance (92% vs 84%, p = .268). Factors associated with failure included T classification (p = .01), tumor site (p = .05), and negative preoperative lymphoscintigraphy (p = .0174).


Keywords: sentinel lymph node biopsy; carcinoma; squamous cell; head and neck neoplasms; radionuclide imaging; mouth neoplasms

In patients with head and neck squamous cell carcinoma (HNSCC), the presence of cervical lymph node metastases is an important prognostic factor.1–3 Noninvasive staging by clinical examination and imaging techniques (eg, MRI, CT, ultrasound) have proven not to be sufficiently sensitive in detecting occult neck metastases.1,3,4 Therefore, neck dissection and subsequent pathologic examination of the excised nodes is generally accepted to be the gold standard for staging early head and neck carcinoma.4,5 Traditional management of the clinically N0 neck involves the use of elective neck dissection for patients with a greater than 20% chance of subclinical nodal involvement. However, three fourths of patients with clinically negative necks do not have positive cervical nodes, and neck dissection, with its associated morbidity, is unnecessary in these patients.6–8

More recently, sentinel node biopsy (SNB) has emerged as an alternative staging procedure. The concept of the sentinel lymph node states that the lymphatic flow from a tumor travels sequentially to the first echelon lymph node, or sentinel node,
and then on to the rest of the nodal basin. Identification, harvesting, and subsequent pathologic examination of the sentinel node has been shown to provide an accurate reflection of the tumor status of the rest of the nodal basin.6,9

SNB uses a triple diagnostic approach. Within 24 hours prior to operation, radiocolloid is injected around the primary tumor site. Static lymphoscintigraphy is used to identify the location of the sentinel node(s) preoperatively, before intraoperative identification using both blue dye (visual identification) and a hand-held gamma probe.4,6,9

SNB and lymphatic mapping have been proposed as the standard of care in melanoma and breast cancer.10–12 In early HNSCC, there have been promising results using SNB, with a sentinel node detection rate of 97% and a 96% negative predictive value for a negative sentinel node.8,13,14 However, in some patients, identification and subsequent harvest of the sentinel node is unsuccessful. The aim of this study was to identify which factors are associated with failure of SNB in HNSCC.

PATIENTS AND METHODS

Patients. This is a retrospective review of all patients with biopsy proven HNSCC in whom SNB was used to stage the neck between January 1998 and May 2002. Local research ethics committee’s approval was obtained prior to commencing the study.

Definitions. In this study, a SNB failure was defined as the failure to identify and harvest a blue or radioactive lymph node from the neck in a patient with HNSCC.

Methods. The triple diagnostic procedure of preoperative lymphoscintigraphy and intraoperative use of blue dye and a handheld gamma probe has been previously described4,6,7,9,15 and is outlined here. Within 24 hours of operation, Tc99m-labeled colloidal human serum albumin (Nanocoll or Albures) was injected around the tumor site. Consecutive static lymphoscintigraphy was then performed at 15, 30, and 60 minutes, and the sites of any sentinel lymph node noted and marked. Intraoperatively, Patent Blue V dye was injected around the tumor site. The sentinel lymph nodes could then be identified using a combination of handheld gamma probe and visual identification of the blue dye. Radioactivity of the sentinel nodes was confirmed ex vivo; if this was negative, the node was designated a “nonsentinel node.” If no sentinel nodes were identified, enlarged, suspicious, or nonsentinel nodes were sent for full pathologic evaluation, and neck dissection was then performed. Treatment of the primary tumor can then proceed.

Sentinel nodes are examined with hematoxylin-eosin (H&E) staining on approximately 2 mm thick blocks. If a neck dissection is performed, all nodes greater than approximately 2.5 mm diameter are processed for histological examination.

Statistics. Descriptive statistics used in this study included mean, median, range, and standard deviation. Comparisons were made using Student’s t, Fisher’s exact, and Pearson’s chi-square tests where appropriate. A p value of <.05 was considered statistically significant.

RESULTS

Between January 1998 and May 2002, a total of 121 SNB procedures were performed at our center. Ninety-four of the 121 patients (78%) had cT1 or cT2 disease, while the remaining 22% had cT3/cT4 tumors. Ninety-six patients (79%) had cN0 disease, while 25 (21%) had clinically positive neck disease (Table 1).

Sentinel nodes were successfully located and excised in 109 of the 121 cases. In the remaining 12 patients (10%), SNB failed to localize the sentinel node(s). In these 12 patients, 14 necks were explored and SNB failed in 13 of them. Two patients had a bilateral procedure, and in 1 of them a sentinel node was successfully harvested from the ipsilateral side. From the contralateral side, however, no sentinel nodes were identified. The minimum follow-up was 5 years (range, 5–7 years).

Of the 12 patients in whom SNB failed, there were 10 men and 2 women. The mean age was 55 years (range, 29–74). There were no significant differences observed in the sex distribution (p = .6) or mean age (p = .21) between the successful and unsuccessful SNB groups (Table 1). Four of the 12 patients in the unsuccessful group had T1 disease, 3 had T2, 1 had T3, and, 4 had T4 disease. Eight of the 12 patients were clinically N0, while the remaining 4 patients were cN+. Patients with clinical N+ necks were observed to be twice as likely to have an unsuccessful SNB procedure (n = 4/25, 16%; compared with 8/96, 8% for cN0 patients), although this did not reach significance (p = .268; Table 1).
Patients who were clinically N0 demonstrated a significantly greater risk of failure when the primary tumor was located in the anterior tongue or floor of mouth (FOM) \((n = 8/66, 12\%)\) compared with tumors in other sites \((n = 0/30, 0\%; p = .05, \text{Table 2})\).

Table 1 demonstrates that patients with cT3 or cT4 tumors appear to have a higher risk of SNB failure compared with cT1/cT2 patients. However,

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Successful group</th>
<th>Unsuccessful group</th>
<th>Unsuccessful, %</th>
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<tbody>
<tr>
<td>FOM/anterior tongue</td>
<td>58 (66%)</td>
<td>8 (100%)</td>
<td>12</td>
</tr>
<tr>
<td>Other sites</td>
<td>30 (34%)</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>8</td>
<td>8</td>
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Abbreviation: FOM, floor of mouth.
Note: cN0 patients with FOM or anterior tongue tumors were most likely to have a failed SNB compared with other primary tumor sites. The remaining 4 cN+ patients who had unsuccessful SNB had primary tumors located in the floor of mouth, posterior tongue, buccal mucosa, and lower alveolus, respectively.

Fisher’s exact test fails to reach statistical significance \((p = .134)\). Repeating this comparison for only those patients with non-FOM tumors demonstrates that cT3/cT4 patients are more likely to have an unsuccessful procedure \((Table 3; p = .01)\).

Preoperative lymphoscintigraphy demonstrated nodes in 88 patients and no nodes in 33. Eighty-three of the 88 patients with positive lymphoscintigraphy nodes had a successful sentinel node harvest \((94\%)\). This was significantly greater compared with the proportion of patients who had negative lymphoscintigraphy and a successful SNB \((26/33, 79\%; p = .0174)\) \((Table 4)\).

Following failure of the SNB, all primary tumors were treated with surgical resection \((n = 9)\) or brachytherapy \((n = 3)\). Management of the neck following SNB failure was according to protocol. In 5 patients with T1cN0 disease, a wait and see policy was adopted. Five patients with locally advanced and/or cN+ disease underwent neck dissection immediately following SNB and primary resection. One patient with a midline tumor and bilateral cN+ disease underwent bilateral neck dissection. One patient with a midline tumor and unilateral cN+ disease underwent ipsilateral neck dissection and contralateral wait and see approach following failed SNB.

All patients have been followed up for 5 years. Of the 5 patients in whom a wait and see policy was adapted, 1 patient developed local recurrence and 1 patient developed locoregional recurrence. All 7 patients who underwent neck dissection following SNB failure were found to be N+. Of these, 2 patients developed local recurrence and

<table>
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<tr>
<th>Tumor classification (cT)</th>
<th>Unsuccessful SNB (%)</th>
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<tr>
<td>cT1/cT2</td>
<td>25/58 (3.4)</td>
</tr>
<tr>
<td>cT3/cT4</td>
<td>5/20 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>7/78 (9)</td>
</tr>
</tbody>
</table>

Abbreviations: SNB, sentinel node biopsy; FOM, floor of mouth.
Note: Fisher’s exact test: \(p = .21\).

| Abbreviation: SNB, sentinel node biopsy; LSG, lymphoscintigraphy.
Note: Fisher’s exact test: \(p = .21\).
Failure to Identify Sentinel Nodes in HNSCC

2 patients developed locoregional recurrence. Mean time to first local recurrence was 13 months (range, 5–29), while the mean time to first nodal recurrence was 11 months (range, 5–20).

DISCUSSION

The results of this study have identified a number of factors associated with an increased likelihood of failure to identify and harvest sentinel nodes. Patients with a negative preoperative lymphoscintigraphy were found more likely to have an unsuccessful SNB procedure, as were patients with clinically advanced primary tumors or cN+ disease. Tumors located in the anterior tongue or FOM were also found to have a higher likelihood of SNB failure.

This study demonstrates a significant correlation between tumor classification and the likelihood of unsuccessful sentinel node harvest. There are several factors that may contribute to this finding. First, a larger primary tumor site may be more difficult to completely surround with injected radiocolloid or dye, leading to inconsistencies in sentinel node drainage and identification. Furthermore, the likelihood of local lymph node involvement increases with tumor classification. Previous studies evaluating the use of SNB in HNSCC and breast cancer have demonstrated that the presence of nodal disease is an independent predictor of failure for sentinel node harvest. The presence of nodal involvement may lead to distortion of the normal lymphatic architecture by tumor, eventually blocking drainage to the sentinel node and forcing an alternative drainage pathway. This may lead to incorrect identification of the sentinel node or to complete failure of identification.

In breast cancer, several studies have shown that an increasing number of positive axillary nodes is associated with a decrease in the sentinel node identification rate. Similarly, in a study of 26 patients undergoing SNB assisted therapeutic neck dissection for HNSCC, no sentinel nodes were found containing metastases in clinically N+ patients. This led to the recommendation that SNB should only be used in clinically N0 patients. The results of the current study demonstrate a trend towards clinically N+ patients having more unsuccessful SNB harvests compared with cN0 patients, supporting this recommendation.

Previous reports have suggested that primary tumor site may be an important determinant of SNB success and our results are in keeping with this. Primary tumors in the anterior tongue and FOM were found to have a greater risk of failure compared with tumors in other sites (Table 2). Of all oral tumors, FOM tumors have proven to be the hardest site in which to perform a SNB with accurate results. The lymph drainage from the anterior oral cavity drains via lymph nodes located in superficial tissue of the floor of the mouth, above the lingual nerve, to the cervical lymph nodes in level I. These nodes are referred to as the lingual lymph nodes. Sentinel nodes in level I and the lingual lymph nodes are easily missed on lymphoscintigraphy due to close proximity of the sentinel node to the injection site. This is especially true for low anterior tumors in the anterior tongue of FOM, and is referred to as the “shine through” phenomenon. Techniques such as software masking and lead shields can be helpful, but identification and harvest of sentinel nodes from these patients remains problematic. From the authors’ experience, excision of the primary tumor after injection of blue dye has not proven useful in reducing the problem of shine-through and may be detrimental to the visual identification of lymphatic channels and nodes.

This study has shown a significantly higher success rate for sentinel node harvest in patients with a positive preoperative lymphoscintigraphy (94%) compared with patients with a negative preoperative lymphoscintigraphy (79%) (p = .01). This is in keeping with previous studies, which have demonstrated that preoperative lymphoscintigraphy visualization of sentinel nodes is a significant predictor of whether SNB will be successful. In early-stage breast cancer, intraoperative sentinel node identification success rates following negative lymphoscintigraphy vary from 66% to 84.6%, compared with 93.2% to 97% success rates following positive lymphoscintigraphy. Although there is limited data on the predictive value of lymphoscintigraphy in HNSCC, previous studies from this unit have shown that the presence of sentinel nodes on lymphoscintigraphy is a significant predictor of successful SNB.

CONCLUSION

This study evaluated the factors associated with an increased risk for failure of sentinel node harvest in patients with HNSCC. The results have demonstrated that increasing T classification and negative preoperative lymphoscintigraphy have significantly greater likelihood of
failure. Clinical N+ disease and tumors located in the anterior tongue or FOM may also create difficulties in the identification and harvest of sentinel lymph nodes. SNB has previously demonstrated a high sensitivity and specificity for the detection of occult cervical node metastases in early HNSCC. However, this technique is not suitable for all patients, and judicious patient selection is required to minimize the risk of SNB failure.

REFERENCES