SENTINEL NODE BIOPSY IN LIEU OF NECK DISSECTION FOR STAGING ORAL CANCER

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IMPORTANCE Neck dissection is the standard staging procedure to ascertain the pathologic status of cervical lymph nodes in patients with oral cavity squamous cell carcinoma (OSCC), but it results in multiple morbidities.

OBJECTIVE To examine outcomes of patients with OSCC who underwent sentinel node biopsy (SNB) as the sole neck staging procedure.

DESIGN Retrospective review of patients who underwent SNB during the period 2005 through 2011.

SETTING National Cancer Institute–designated comprehensive cancer center.

PARTICIPANTS Thirty-eight patients with clinically T1 or T2NO OSCC.

INTERVENTIONS Preoperative lymphoscintigraphy with intraoperative gamma probe localization was used. Sentinel lymph nodes were serially sectioned, formalin fixed, and examined at 3 levels. All patients with positive SNB results underwent neck dissection, and the patients with negative SNB results were observed clinically.

MAIN OUTCOMES AND MEASURES Sensitivity and predictive value of SNB, recurrence rates, and disease-specific survival rates.

RESULTS There were 18 T1 and 20 T2 tumors. Five patients had positive SNB results, of whom 3 had additional positive nodes on subsequent neck dissection. Two of 33 patients with negative SNB results developed a regional recurrence. The sensitivity and negative predictive value for staging the neck with SNB alone were 71% (5 of 7) and 94% (31 of 33), respectively. Mean follow-up was 31 months. The mean disease-free survival duration for patients with positive and negative SNB results was 30 and 65 months, respectively (P = .08). The disease-specific survival rate for patients with positive and negative SNB results was 80% and 91%, respectively. There was no significant difference in disease-specific survival between patients with true-negative and false-negative SNB results (34 vs 44 months; P = .38).

CONCLUSIONS AND RELEVANCE The majority of patients with positive results on SNB had additional positive nodes on neck dissection. A low rate of isolated neck recurrence was found in patients with negative results on SNB. Individuals with negative results on SNB exhibited better overall and disease-specific survival than those with positive results.
he pathologic status of cervical lymph nodes in patients with oral cavity squamous cell carcinoma (OSCC) is an important prognosticator for local recurrence and overall patient survival. Management of the clinically negative (cN0) neck in OSCC continues to be a source of controversy. Elective neck dissection remains the gold standard as the key staging procedure for the cN0 neck. The downside is that it results in unnecessary morbidity in individuals without occult nodal disease. More than 70% to 80% of patients with early-stage OSCC do not present with occult metastases to the cervical lymph nodes, leading to the possibility of overtreatment in a substantial number of individuals. Therefore, clinical observation of the cN0 neck has been advocated by some. However, given the substantial prevalence of occult nodal disease and the negative impact on prognosis, this strategy is not optimal or widely accepted.

Although commonly used in the staging of melanoma and breast cancer, sentinel node biopsy (SNB) has only recently emerged as a staging procedure for OSCC in several centers throughout the world. The use of preoperative peritumoral injection of a radionuclide and intraoperative gamma probe guidance allows the selection of a limited number of sentinel lymph nodes (SLNs) that are most likely to receive the initial primary tumor lymphatic drainage. The accuracy of SNB relies on the anatomic and biologic notion that the status of SLNs will accurately reflect that of the remaining nonsentinel nodes. In addition, a limited number of SLNs can be carefully scrutinized using various histopathologic techniques to detect micrometastases, something that is impractical for an entire neck dissection specimen. Overall, the inherent value of SNB is to accurately detect subclinical nodal metastases while eliminating the multiple morbidities related to elective staging neck dissection.

The primary objective of this study was to examine the clinical outcomes of patients with early-stage OSCC who underwent SNB as the sole pathologic neck staging procedure at our institution. A secondary objective was to determine the sensitivity and negative predictive value of the SNB in this cohort.

Methods

We conducted a retrospective review of patients with OSCC who underwent SNB during the period 2005 through 2011. Patients were included if they had a previously untreated T1 or T2 primary OSCC and underwent a staging SNB at the time of primary tumor resection. Only patients with a cN0 neck, as determined by means of physical examination and computed tomography, were selected for review. A minimum follow-up of 3 months was required for inclusion in the study. A total of 38 patients met the inclusion criteria for this analysis. All patients underwent staging SNB alone. Subsequent neck dissection was performed on all patients with positive results on SNB, whereas those with negative results were observed clinically.

All SNB procedures were carried out by means of previously described techniques that used preoperative peritumoral injection of a sulfur-technetium radiocolloid and lymphoscintigraphy, followed by intraoperative gamma probe SLN localization. All primary tumors were surgically resected prior to SNB procedures to eliminate background radioactivity shadowing effect (“shine through”).

All harvested SLNs were serially sectioned in 2-mm to 3-mm intervals, fixed in 10% neutral buffered formalin, and sectioned at 3 levels for histopathological examination. No immunohistochemical studies or analysis of frozen sections were performed. All patients were observed longitudinally by means of physical examinations, as well as imaging. During the first year after treatment, patients underwent a complete head and neck examination by the attending surgeon every 4 to 6 weeks. After the first year onward, the examination interval was every 8 to 12 weeks, and neck computed tomographic scans were performed annually.

Patient demographic characteristics, dates of surgery, primary tumor site, tumor pathologic characteristics, SLN status, neck dissection pathologic characteristics, date and site of recurrence, and follow-up status at regular intervals were recorded. Outcomes analysis was performed using SPSS, version 16.0 for Windows (SPSS). Kaplan-Meier survival curves were generated with log-rank and Breslow tests for survival comparisons between patient groups. A P < .05 was considered statistically significant. Descriptive statistics were reported as percentages. Disease-specific survival rate, overall local recurrence rate, locoregional recurrence rate, and isolated neck recurrence rate were evaluated. Mean time to recurrence was calculated from the date of the initial SNB procedure.

Results

The patient group included 23 men and 15 women with a median (range) age of 62 (19-84) years. There were 18 T1 (47%) and 20 T2 (53%) cancers. The most common tumor subsite within the oral cavity was the anterior tongue (Table 1).

The mean number of SLNs harvested per patient was 2. In our cohort of 38 patients, 5 (13%) had disease that was staged SLN positive and 33 (87%) had disease that was staged SLN negative. The patients with negative results on SNB were observed clinically. None of the patients with No neck received radiation therapy. All 5 patients with positive results on SNB underwent a subsequent neck dissection, and 3 demonstrated additional positive nodes (pN+) in the neck dissection. These 3 patients received adjuvant concurrent chemoradiation therapy. The total number of additional positive nodes, the corresponding neck levels for the patients with positive SNB results, and adjuvant chemoradiation therapy are presented in Table 2. Among the group with negative SNB results, 2 patients (6%) developed regional recurrence, which was noted on clinical follow-up. The first was treated for a floor of mouth carcinoma and had an isolated nodal recurrence in level 1. The second patient, with an oral tongue cancer, had a nodal recurrence at 3 months following the false-negative SNB result and subsequently developed recurrence at the site of the primary cancer. Both patients were offered radiation therapy; 1 underwent adjuvant radiotherapy and 1 refused additional
treatment. The time to recurrence, number and level of positive nodes, presence of extracapsular invasion, and adjuvant chemoradiation therapy in the false-negative cases are given in Table 3.

The mean (range) follow-up for the entire cohort was 31 (3-71) months. The disease-free survival rate for the entire cohort was 89% (34 of 38). The mean disease-free survival duration for patients with negative and positive results on SNB was 65 and 30 months, respectively ($P = .08$). The disease-specific survival rate for patients with negative and positive results on SNB was 91% and 80%, respectively. The overall local recurrence rate was 18%. The combined local and regional recurrence rate was 21%. The rate of isolated neck recurrence for the entire cohort was 5% (2 of 38). These 2 patients had a false-negative SNB result. Taking them into account, a total of 7 of 38 patients (18%) exhibited occult nodal disease. This resulted in a sensitivity of 71% (5 of 7) and a negative predictive value of 94% (31 of 33) for staging the neck with SNB alone. The 2 patients with false-negative SNB results were subsequently treated and remained disease free at 40-month and 48-month follow-up, respectively. There was no significant difference in disease-specific survival between the patients with true-negative and false-negative SNB results (34 vs 44 months; $P = .38$). The mean time to recurrence in patients with positive and negative results on SNB was 36.4 and 56.3 months, respectively.

Discussion

Management of the cN0 neck in early OSCC remains controversial. Although elective neck dissection is the standard surgical procedure for pathologic staging of the neck in these patients, substantial morbidities associated with it—including chronic pain, limited mobility of the neck, decreased shoulder strength, and poor cosmetic outcomes—must be considered in the overall management strategy for patients with early-stage OSCC.8

Sentinel node biopsy has emerged as a viable minimally invasive technique for pathologic staging of the neck.4-6,10 Furthermore, SNB provides the possibility for accurately staging the cervical nodes via more intensive pathologic evaluation of the harvested lymph nodes. In addition, the use of preop-
operative lymphoscintigraphy combined with intraoperative gamma probe SLN localization may identify atypical nodal drainage patterns, which, in turn, may allow early detection and treatment of occult nodal disease.

A multi-institutional study sponsored by the American College of Surgeons demonstrated the utility and accuracy of SLN biopsy in patients with OSCC who also underwent a synchronous neck dissection, whereas a recent European multi-institutional trial concluded that SNB alone is a safe approach to staging the cN0 neck for early OSCC and oropharyngeal cancers. In our study, SNB was also the sole procedure used for staging the cN0 neck in patients with T1 and T2 OSCC.

As expected, in our cohort, the majority of patients with positive SNB result had additional positive nodes found on subsequent neck dissection, confirming the need for additional treatment of the neck. Also, consistent with prior studies, individuals in our cohort with SLN-negative biopsy results exhibited better overall and disease-specific survival than those with SLN-positive results. One of 38 patients in our cohort developed an isolated neck recurrence. This patient had a negative staging SNB result and represents a false-negative result. This individual was 1 of 3 patients with cancer of the floor of the mouth, a subsite known to be associated with lower SNB accuracy due to shine through effect. The other patient with a false-negative SNB result had an oral tongue cancer and developed a positive level II node, suggesting that the sentinel node was probably missed. Of note, both of these patients remained disease free 3 to 4 years following subsequent treatment. Given the short interval to recurrence (3 months) of the 2 patients with false-negative SNB results, we believe that our follow-up schedule, of clinical examination and imaging, was adequate and does not need modification. Because of the small sample size of floor of mouth cancers, we are unable to determine whether these patients should be excluded from staging SNB, although we can confirm that this subsite represents a technical challenge.

In spite of the limited sample size, these results are consistent with those of previous multicenter studies, which demonstrate that SNB is a useful procedure for pathologic staging of the cN0 neck in previously untreated patients with oral cavity cancer with the exception perhaps of floor of the mouth squamous cell carcinomas. These results may be useful in the development of additional multi-institutional randomized clinical trials, which are necessary to further validate SNB as the singular procedure for pathologic staging of the cN0 neck of patients with squamous cell carcinoma of the oral cavity.

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REFERENCES