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ORIGINAL REPORT

Sentinel Lymph Node Biopsy Accurately Stages the Regional Lymph Nodes for T1-T2 Oral Squamous Cell Carcinomas: Results of a Prospective Multi-Institutional Trial

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ABSTRACT

Purpose
The validity of sentinel lymph node biopsy (SLNB) for T1 or T2, clinically N0, oral cancer was tested by correlation of sentinel node pathologic status with that of nodes within the completion neck dissection.

Methods
This prospective, cooperative group trial involved 25 institutions over a 3-year period. One hundred forty patients with invasive oral cancers, stage T1 and T2, N0 including 95 cancers of the tongue, 26 of the floor of mouth, and 19 other oral cancers were studied. The study excluded lesions with diameter smaller than 6 mm or minimal invasion. Imaging was used to exclude nonpalpable gross nodal disease. Patients underwent injection of the lesion with ^{99m}Tc-sulfur colloid, nuclear imaging, narrow-exposure SLNB, and completion selective neck dissection. The major end point was the negative-predictive value (NPV) of SLNB.

Results
In the 106 SLNBs, which were found to be pathologically and clinically node-negative by routine hematoxylin and eosin stain, 100 patients were found to have no other pathologically positive nodes, corresponding to a NPV of 94%. With additional sectioning and immunohistochemistry, NPV was improved to 96%. In the forty patients with proven cervical metastases, the true-positive rate was 90.2% and was superior for tongue tumors relative to floor of mouth. For T1 lesions, metastases were correctly identified in 100%.

Conclusion
For T1 or T2 N0 oral squamous cell carcinoma, SLNB with step sectioning and immunohistochemistry, performed by surgeons of mixed experience levels, correctly predicted a pathologically negative neck in 96% of patients (NPV, 96%).

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INTRODUCTION

Lymphatic metastases will develop in 20% to 30% of patients with early oral cancers and imply decreased survival.[1-6] Physical examination, imaging, and histopathologic characteristics are not accurate enough to reliably guide treatment.[6-10] Although close observation (ie, watchful waiting) and elective neck irradiation remain options, most specialists favor resection of regional lymphatics, based on retrospective data.[11-13] However, 70% to 80% of patients ultimately are pN0 pathologically and are theoretically overtreated.

Although selective neck dissection (ND) is less morbid than modified radical dissection, measurable morbidity exists, including shoulder dysfunction, pain, contour changes, and lower lip paresis. This has been demonstrated in quality of life studies and objective functional assessments.[14-16] This morbidity has led many to selectively apply watchful waiting. Sentinel lymph node biopsy (SLNB) represents an intermediate response to this controversy.

The sensitivity for detecting lymphatic metastasis in patients with melanoma and breast carcinoma has significantly increased by the use of SLNB.[17-22] Identification of positive sentinel nodes can direct intensification of therapy. In these tumor types, absence of metastases in the SLN correlates with nonexistence of metastases in the draining

nodal basin, and morbidity can be reduced by leaving the remainder of the regional lymphatics undissected.

Multiple single-center pathologic validation studies involving radioguided SLNB followed by ND indicate the SLNB can accurately stage the clinically negative neck in oral squamous cell carcinoma (OSCC), with negative predictive values between 90% and 98%.[23-37] A prospective trial in six European centers studied SNLB in T1-T2 N0 tumors of the oral cavity and oropharynx. Two hundred twenty-seven patients underwent SLNB either alone or followed by ND. Upstaging occurred in 43 (34%) of 125 of patients. The false-negative rate was 7.1%. Overall, three patients (two patients SLNB-only group, one patient in SLNB-to-ND group) either developed recurrence in the cervical lymph node basin or a nonsentinel node in the ND group had metastasis.[38]

False negatives can occur through multiple mechanisms, including uneven radionuclide injection, obscuring of SLN by the radioactive signal of the primary tumor, and lymphatic obstruction by gross tumor, resulting in redirection of lymphatic flow.[30,32] The latter risk should be reduced by imaging and careful intraoperative palpation.[7,8,30,33,34] The literature also emphasizes the importance of surgical and pathologic training and experience.[26,28,35,36]

METHODS

We sought to validate SLNB pathologically when compared with completion selective ND for patients with early, invasive oral cancers. The study schema is provided in Figure 1. The protocol was funded by the National Cancer Institute through the Head and Neck Working Group of the American College of Surgeons Oncology Group, with formal oversight by the Cancer Therapy Evaluation Program of the National Cancer Institute.

Our primary objective was to ascertain whether a negative hematoxylin and eosin (H&E) finding from the SLNB procedure accurately predicted the negativity of the other cervical lymph nodes (LNs). Equally important were the results of step sectioning and immunohistochemistry (IHC) to assess LNs in the central laboratory.

Twenty-five institutions and 34 surgeons registered 161 adult patients with newly diagnosed T1 or T2, clinically N0, OSCC over a 3-year period. One hundred forty patients qualified and received the study intervention. Patients signed informed consent, approved by central and institutional review boards. Eastern Cooperative Oncology Group/Zubrod performance status ≤ 2 was required. Since all patients ultimately received completion selective ND, we sought to define a group at low, but significant, risk of developing lymphatic metastases. Therefore, minimally invasive lesions and lesions smaller than 6 mm in diameter were excluded. Prior neck surgery, lip involvement, trauma, radiation, or other recent cancer history led to exclusion.

Emphasis was placed on surgical training and standardization of technique. Fourteen surgeons with experience in SLNB for oral cancer submitted operative reports and pathology reports for five oral cancers receiving SLNB. Twenty less experienced surgeons participated in five cases of SLNB for melanoma or breast cancer, watched an instructional video, and took a written test.

All patients received either contrasted computed tomography or gadollinium-enhanced magnetic resonance of the neck. Imaging was deemed negative by a head and neck radiologist, using standardized criteria.

One hundred forty patients were eligible and evaluable. These patients received primary site injection with unfiltered ^{99}Tc-sulfur colloid within 18 hours of the surgical procedure. Injection was performed late the day before, or on the morning of the procedure. Dosage was 400 to 500 microcuries in 5 aliquots of 0.1 mL in patients injected less than 8 hours before the procedure. Dosage was 1 mCi for patients injected the afternoon before. Standardized injection technique sought to narrowly and evenly encompass the borders of the lesion. Serial nuclear imaging was then acquired. Unexpected patterns of drainage were discussed with the patient and addressed during subsequent surgery.

Transoral resection of the primary tumor was followed by SLNB, through as small an incision as possible within the planned incision for selective ND. Subsequent extension of the incision and flap elevation was followed by completion ND with removal of levels I, II (including IIB), III, and IV. Bilateral ND was required when primary lesions involved the midline or when contralateral drainage occurred on lymphoscintigraphy.

All SLNs identified using the gamma probe were removed, including any LN exhibiting 10% or more of the radioactivity of the most radioactive node. If more than four SLNs met this criterion, at least four SLNs with the highest radioactivity were excised. Tumor-suspicious lymph nodes were identified separately at that time and tagged. The SLNB portion of the procedure was distinct from the completion ND. However, since the surgeon had knowledge, both through imaging and previous gamma probe use, of the true lymphatic drainage pattern of the tumor, this information was naturally addressed during the neck dissection. The term gamma probe guided neck dissection aptly describes this procedure.

ND specimens were divided into LN groups 1 through 4. The most prominent nonsentinel node at each level was identified. Routine H&E histopathology was used at the clinical sites to evaluate the SLN(s) and non-SLN(s). SLNs were sectioned from hilum to periphery, longitudinally, at 2- to 3-mm intervals of thickness and placed into cassettes at the individual sites. A diligent search for lymph nodes by the pathologist was performed, commonly rendering more than 30 nodes in a ND specimen. Additional sectioning and staining at the site was permitted based on institutional standards.

The blocks of the primary tumor or 20 unstained slides of the SLN(s) and the largest non-SLNs at each level of the neck dissection were subsequently sent to the central specimen bank. If the H&E analysis of the SLN was not grossly positive, the central laboratory evaluated the SLN(s) and the largest identifiable non-SLN at each level of the ND by staining representative slides from each block by IHC for cytokeratin. These were previously sectioned and placed in separate blocks at 2- to 3-mm intervals at the local sites.

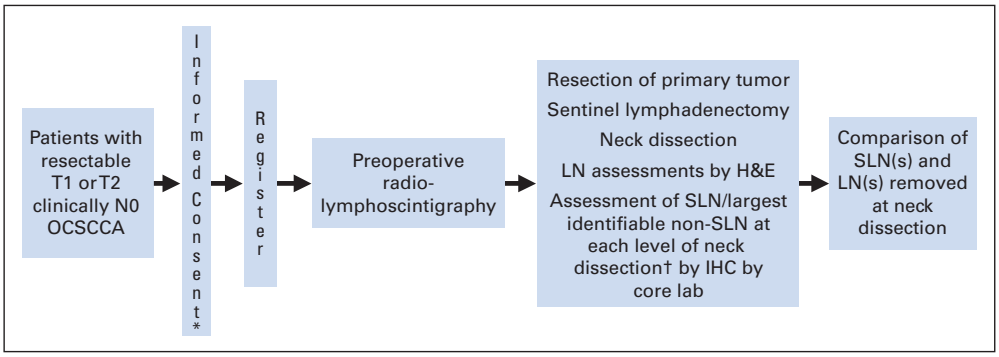

Fig 1. Study schema. OCSCCA, oral cavity squamous cell carcinoma; LN, lymph nodes; H&E, hematoxylin and eosin; SLN, sentinel lymph nodes; IHC, immunohistochemistry.

At the central laboratory, four slides for each H&E negative SLN/largest identifiable non-SLN, already prepared at the sites in 2- to 3-mm slices per block, were stained for keratin by standard immunoperoxidase technique with a commonly used panel of antibodies for cytokeratin (anticytokeratins AE1/AE3, Cam5.2, clone MNF-116, and 8/18).[39] All cytokeratin-positive cell clusters were reviewed for morphology consistent with OSCC. Deeper sections were taken as needed to clarify the pathologic status. Pathologists were blinded as to institutional results.

The primary objective was to evaluate whether a negative SLN(s) would accurately predict negativity of the other cervical LNs (ON). The relative performance of the test was evaluated using a negative-predictive value (NPV) defined as the proportion of patients who were negative with respect to ON among the patients who were classified as SLN negative. Since the sentinel node procedure is designed for application in a group at relatively low, though significant, risk, and since watchful waiting is a traditional alternative in this group, the negative predictive value was felt to be the most appropriate means of evaluating SLNB. Negative predictive value most closely parallels the important clinical question regarding the likelihood of not having cancer recurrence in the lymphatic basin of a patient with a negative SLNB.

It was hypothesized prospectively that the NPV would exceed 0.8 in a group of surgeons of mixed experience levels. The study was designed to evaluate 107 evaluable and eligible SLN-negative patients so as to have a power of 0.89, at the one-sided level of .043, if the true proportion were 0.9.

The binomial proportions were estimated using sample proportions. Binomial proportions were estimated using the observed proportions and exact Clopper-Pearson[40] interval estimators at the 0.95 level of confidence. Inference for contingency tables was carried out using Fisher's test.[41] The agreement between binary ratings was quantified using Cohen's kappa.[42] The difference between two distributions was assessed using the Wilcoxon rank sum test.[43]

Per protocol, the primary hypothesis was tested at a one-sided level. All other hypotheses and interval estimators are two sided.

RESULTS

The median patient age was 58 (range, 24 to 90), with 85 males (60.7%) and 55 females (39.3%). There were 52 T1 lesions (37.1%) and 88 stage T2 (62.9%). The mean depth of invasion of the primary oral cancer was 0.85 cm for patients with positive lymph nodes and 0.72 cm with negative lymph nodes, which was not a significant correlation in the selected population. There were two cases with positive cervical nodes despite depth of invasion less than 2 mm. Tumors were found to arise from several oral cavity subsites including the tongue in 95 patients (67.9%), floor of mouth in 26 (18.6%), and 19 from other sites (Table 1). The median number of sentinel nodes removed per patient was three. Pathologic status of the sentinel node and number of nodes removed did not correlate significantly with interval of time between injection and SLNB (Table 2). There was a trend suggesting that the number of excised SLN was correlated with greater T stage ($P < .096$).

Forty patients (28.0%) had cancer in the cervical nodes based on initial pathology. Forty-one positives were present after central step sectioning/IHC (29.0%). There were two cases of purported single positive micrometastases that were changed to negative on central laboratory analysis, and three cases of false negatives that became true positives after the identification of unrecognized micrometastases in a sentinel node. In 21 of 41 positives, the sentinel node was the only positive node. Extracapsular extension of cancer was noted in one case, and grossly palpable cancer was present in four cases despite negative imaging.

Pathologic analysis of the SLNs by routine H&E at the various sites resulted in 106 negative SLNB. Among these 106 patients, 100 were classified as truly negative by virtue of H&E of the ND specimen (one-sided $P < .0001$). This corresponds to a NPV of 0.94 (95% CI, 0.88 to 0.98; Table 3). Step sectioning and immunohistochemistry increased the NPV to 0.96 (95% CI, 0.90 to 0.98; one-sided $P < .00001$; based on baseline probability of 0.8). NPV was similar across the different anatomic subsites (Tables 4 and 5). Sentinel node status was more predictive of the status of the neck for T1 lesions (NPV = 1.0) relative to T2 lesions (NPV = 0.94), as shown in Table 6.

Table 1. Tumor Characteristics

Characteristic	No.	%
Clinical T stage		
T1	52	37.1
T2	88	62.9
Pathologic T stage		
T1	77	56.2
T2	58	42.3
T3	1	0.7
T4	1	0.7
Tumor location		
Tongue	95	67.9
Floor of mouth	26	18.6
Alveolar ridge	4	2.9
Retromolar trigone	8	5.7
Hard palate	0	0.0
Buccal mucosa	7	5.0
Oral vestibule	0	0.0

Table 2. False-Negative Rate by Time of Injection

	Timing				
	12 Hours or Fewer		Longer Than 12 Hours		
Clinical Status	No.	%	No.	%	Total
False negatives	3	10.3	1	11.1	4
Other positives	26	89.7	8	88.9	34
Total	29		9		38

Table 3. Negative Predictive Value Based on Pathologic Analysis at Local Investigative Site

H&E status (NPV = 0.94)	No.	%
True negative	100	71.4
False negative	7	5.0
True positive	33	23.6
True positive breakdown		
SN only positive	20	60.6
SN and ON positive	13	39.4
False negatives		
False negatives	7	17.5
All other positives	33	82.5

Abbreviations: H&E, hematoxylin and eosin; NPV, negative predictive value; SN, sentinel node; ON, other cervical lymph node.

Table 4. Results Based on Central Pathology/IHC

Central Pathologic Status (NPV = 0.96)	No.	%
True negative	99	70.7
False negative	4	2.9
True positive	37	26.4
Positive breakdown		
SN only positive	21	56.8
SN and ON positive	16	43.2
False negatives		
False negatives	4	9.8
All other positives	37	90.2

Abbreviations: IHC, immunohistochemistry; NPV, negative predictive value; SN, sentinel node; ON, other cervical lymph node.

Table 6. Results Based on Central Pathology/IHC by Stage

Clinical Status	Clinical Stage T1 (NPV = 1.0) No.	%	T2 (NPV = 0.94) No.	%	Total
TN	39	75.0	60	68.2	99
FN	0	0.0	4	4.5	4
True positive	13	25.0	24	27.3	37
Total	52		88		140

Abbreviations: IHC, immunohistochemistry; NPV, negative predictive value; TN, true negative; FN, false negative.

The NPV of procedures performed by surgeons who entered the trial with more experience in the use of SLNB for oral cancer was 100%, versus 95% for less experienced surgeons. This corresponds to an agreement as quantified by Cohen's kappa of 0.90 (95% CI, 0.81 to 1.0).

The false-negative rate (Table 7) was 9.8% overall (four false negatives of 41 known positives). It was 10% for tongue cancers, 25% for floor of mouth (one of four), and 0% for the other oral cavity sites.

DISCUSSION

Minimal access approaches are becoming commonplace to reduce surgical morbidity. ND for early oral lesions contradicts this trend. Accurate staging of the lymphatics at the time of transoral resection by SLNB is more consistent with a minimally invasive transoral approach. Thus, if SLNB provided timely information regarding the status of the neck, it would likely be attractive to patients and physicians alike.

The validation format used here is an excellent means of evaluating the oncologic safety of SLNB, as each patient serves as his own control. However, a limitation of this study design is that the sentinel lymph node procedure may have changed the way the ND is performed, and vice versa. We believe our study design may actually lead to underestimation of the accuracy of this technique relative to selective ND, given that NDs were guided by the information gained with nuclear imaging and the use of the gamma probe in the preceding SLNB.[26-31] If standard selective ND were compared to gamma probe guided ND, one might find that there is also a small false-negative rate for standard selective ND, and that cancer can be left behind after this procedure.

Table 5. Results Based on Central Pathology/IHC by Anatomic Subsite

Clinical Status	Tumor Location Floor of Mouth (NPV = 0.96) No.	%	Tongue (NPV = 0.96) No.	%	Other (NPV = 1.0) No.	%	Total No.
TN	22	84.6	64	67.4	13	68.4	99
FN	1	3.8	3	3.2	0	0.0	4
Positive	3	11.5	28	29.5	6	31.6	37
Total	26		95		19		140

Abbreviations: IHC, immunohistochemistry; NPV, negative predictive value; TN, true negative; FN, false negative.

Other limitations include the fact that none of the surgeons were experienced at levels currently considered appropriate for surgeons caring for breast cancer or melanoma. Pathologic evaluation occurred at multiple locations, and doses of radiocolloid and nuclear imaging techniques were extrapolated from those used for cutaneous lesions. Central step sectioning at 2 to 3 mm is much thicker than the 150-μ sectioning advocated in some studies.[26,37] Blue dye was not used as a second tracer. Nonetheless, our NPV was higher than anticipated for a multi-institutional setting with relatively inexperienced surgeons. Only a trial where negative SLNBs are observed, without complete ND, with several years of follow-up, would provide the true NPV of SLNB.

Ongoing developments could enhance the clinical application of SLNB. These might include the preoperative use of positron emission tomography,[44] biologic staging of primary site biopsies,[45] more lymph node–avid radionuclides,[46] ultrasound-detectable injectable contrast agents (a potential second tracer),[47] intraoperative reverse transcriptase polymerase chain reaction for analysis of the sentinel node,[48] endoscopic SLNB,[49] and other innovations.

Our study was designed with NPV as the primary clinical end point. For T1 lesions, the negative predictive value was 100%. The procedure is particularly suited for smaller lesions, given that there were significantly more radioactive lymph nodes with larger lesions. When excessive lymph nodes are mapped this precludes a minimally invasive procedure. For the more experienced surgeons the NPV was 100%.

Extrapolating from our data, with an overall NPV of 0.96, in a population with a 30% chance of having metastatic disease, a negative SLNB would likely result in recurrence in the neck in 4%. If applied to a higher-risk population the failure rate would be higher. Close observation could allow salvage of the 4% of patients at risk, and the rare risk of failing would need to be balanced against the potential for reduced morbidity in the other 96%, morbidity that is significant and permanent for a large population without metastatic disease. Among our 140 patients, 100 could theoretically have been spared formal neck dissection if SLNB had been used to guide treatment.

The false-negative rate of 9.8% indicates the risk in a group of patients in which we expect 100% to harbor cancer, a group to which this procedure would never logically be applied. While the 9.8% value would seem high for experienced surgeons, it was lower than anticipated for our mixed group of surgeons and likely reflects the learning curve. Furthermore, the total number of false negatives is small[4] of a

Table 7. Central Path False Negative Rate by Tumor Location, Clinical Stage, and Surgeon Experience

	Tumor Location					Tumor Location					Clinical Stage					Surgeon Experience				
	Floor of Mouth		Other		Total	Tongue		Other		Total	T1		T2		Total	Experienced		Inexperienced		Total
Clinical Status	No.	%	No.	%	No.	No.	%	No.	%	No.	No.	%	No.	%	No.	No.	%	No.	%	No.
False negatives	1	25.0	3	8.1	4	3	9.7	1	10.0	4	0	0.0	4	14.3	4	0	0.0	4	13.3	4
Other positives	3	75.0	34	91.9	37	28	90.3	9	90.0	37	13	100.0	24	85.7	37	11	100.0	26	86.7	37
Total	4		37		41	31		10		41	13		28		41	11		30		41

small total of 41 positive patients, and changes in a few values would significantly affect the false negative rate. To produce an accurate false-negative rate would require a much larger group of patients in order to generate enough positives to produce a statistically significant value.

For surgeons designated prospectively as experienced the false-negative rate was 0%. It is unclear how many cases are needed to achieve acceptable proficiency. However, we would argue that our results suggest that if applied initially in an appropriately low-risk group, the procedure provides reasonable results even in relatively inexperienced hands after appropriate training.

The most common anatomic subsite for primary tumors in this series was the oral tongue, where the NPV was 96% and false-negative rate was 10%. Sites other than oral tongue and floor of mouth had a NPV of 100% and false-negative rate of 0%. The number of positive patients was small for the floor of mouth cancers (four positives of 26 total), so conclusions are difficult; and the false-negative rate of 25% (one of four positives) was high. The proximity of the level 1 lymphatics to the radioactive primary site has represented a technical challenge in this site,[37,38] and it is unclear, with this small number of positives, whether our study confirms this observation. The small numbers in each group make it difficult to validly interpret differences by anatomic site.

The effect of the procedure on the smaller group of true positives is also an issue because the pathologic status of the sentinel node is sometimes not known until days after surgery. Thus, some patients would require two surgeries instead of one to accomplish completion therapeutic ND. Ultimately the answer to this dilemma may lie in the development of rapid analysis of the sentinel lymph node using molecular techniques, and such technologies are already in development.[48]

Given that the watchful waiting approach persists for selected lesions, and that some patients have circumstances that make the moderate morbidities of ND unacceptable, it is likely that there may be a role for sentinel node biopsy as an intermediate option.

In conclusion, we compared two surgical techniques for evaluating the cervical lymphatics. The negative predictive value of SLNB, defined as the proportion of patients with negative sentinel nodes who were negative with respect to other nodes in the neck, was 96% for a population of T1 and T2 oral cancers. For T1 lesions, and for more experienced surgeons, the negative predictive value was 100%.

We conclude that it is reasonable to initiate clinical trials involving SLNB, with completion ND only for patients with positive sentinel nodes, as a lower morbidity approach for selected patients with T1 and T2 oral cancers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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