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Oral Cavity Squamous Cell Carcinoma and the Clinically N0 Neck: The Past, Present, and Future of Sentinel Lymph Node Biopsy

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Abstract

Oral cavity squamous cell carcinoma (OCSCC) has a yearly incidence of 274,000 patients. Twenty percent to 30% of patients will harbor occult regional metastases, an important feature that correlates with worse outcomes. Supraomohyoid neck dissection (SND) is the gold standard treatment, but because of recent successes of sentinel lymph node (SLN) biopsy in the management of breast cancer and melanoma, many have begun evaluating its use in head and neck mucosal cancers. SLN biopsy offers patients decreased morbidity compared with SND, and has shown reproducibly low false-negative rates, high-negative predictive values, and high sensitivities. Limitations with floor-of-mouth primaries and delayed secondary SNDs have been described, but a new agent designed to address these shortcomings, Lymphoseek (Neoprobe Corp.; Dublin, OH), is currently under investigation. This article reviews the current literature on SLN biopsy and introduces a phase 3 study evaluating the efficacy of Lymphoseek in SLN biopsy of OCSCCs.

Keywords

Sentinel lymph node mapping; Oral cavity cancer; Staging; Lymphoscintigraphy; Occult lymph node metastases

Introduction

Oral cavity squamous cell carcinoma (OCSCC) is a devastating disease, with approximately 274,000 new cases and 5,000 deaths each year [1,2]. Besides mortality, OCSCC is accompanied by significant morbidity, including swallowing and speech dysfunction. Tumor, node, metastasis (TNM) staging is important for predicting prognosis and defining treatment in OCSCC. A single tumor-containing node will upstage tumors to at least stage 3, irrespective of primary tumor size. With this comes intensified multimodality therapy to the primary tumor site, including the regional lymphatic basin and a predictably worsened prognosis. Thus, nodal staging has been and remains an important component of disease management.

Patients with high-volume disease (T3 or T4) at their primary sites are known to have a high rate of regional metastases. Whether they have clinically apparent regional disease or not, patients receive treatment aimed at the regional lymphatic basin. Patients with low-volume disease (T1 or T2) at the primary site, however, will only receive regional therapy if regional

disease is present. Despite 20% to 30% of patients having occult nodal metastases, we currently have no accepted noninvasive diagnostic modality for identification of occult regional disease in patients with a clinically and radiographically negative neck (cN0) [3]. Undetectable nodal disease increases the risk of recurrence and decreases 5-year survival from 82% to 53% [4]. Additionally, a randomized study by Kligerman et al. [5] showed that a prophylactic neck dissection in patients with low volume OCSCC and a cN0 neck, reduced their recurrence rate from 33% to 12% compared with those in whom the neck is treated with watchful waiting.

In light of these findings, a staging supraomohyoid neck dissection (SND) has been recommended for all patients with T2 disease at the primary site, and possibly in T1 disease with greater than 4 mm depth of invasion [5]. Seventy percent to 80% of neck dissection specimens, however, will be negative for regional metastatic disease. Given the potential morbidity and aesthetic changes associated with neck dissection, a noninvasive approach for diagnostically assessing the cN0 neck is of great interest.

Sentinel lymph node (SLN) biopsy has been shown to be an excellent predictor of metastatic disease for both melanoma and breast cancers and is now the standard of care for both diseases [6,7]. Given this success, SLN biopsy has become of interest in OCSCC. This article discusses different options for staging the neck, reviews the history of SLN biopsy, evaluates previous studies addressing SLN biopsy in OCSCC, and introduces a multicenter SLN mapping trial using the new agent Lymphoseek (Neoprobe Corp., Dublin, OH).

Staging the Neck

Historically, clinical staging of the neck has involved thorough digital palpation, with resultant sensitivity and specificity of 64% to 72% and 85%, respectively, compared with pathologic specimens [8–10]. The recent advent of imaging technology has made additional techniques available such as ultrasound, CT, MRI, and positron emission tomography (PET) imaging. Studies have shown that more accurate staging of the neck is obtained when imaging and digital palpation are combined [8]. CT and MRI scanning are relatively equal in their ability to stage the neck with sensitivities from 38% to 92% and specificities of 41% to 100% [8,10–16]. CT is more commonly used because of the speed and ease of the examination, lower cost, and improved identification of necrotic nodes [17•]. Ultrasound has sensitivities of 50% to 82% whereas specificity increases to 100% from 66% to 96% with the addition of fine needle aspiration [10,12,13,18]. All the structural radiographic techniques define a suspicious node as larger than 1 cm.

Most recently, functional imaging with 18F-fluoro-2-deoxy-glucose PET scanning has been used to identify primary tumors and help stage the neck, but the cost of the procedure has limited its widespread use [19]. Several authors have assessed the ability of PET to replace both CT/MRI imaging and pathologic surgical staging of the neck. The sensitivity and specificity of PET scanning ranges from 71% to 96% and 86% to 94%, respectively [13–15]. In a 2005 study by Ng et al. [14], PET scanning was superior to CT/MRI for identifying pathologic nodal neck disease, showing a significantly higher sensitivity of 74.7% versus 52.6%. When combining PET and CT/MRI, they showed only a modest increase in sensitivity of 3.2%. A limiting factor of this study was a high false-negative rate of 25%.

The combined use of these modalities has proven efficacious for cases with diseased nodes larger than 1 cm. They all remain ineffective for the assessment of occult disease (tumor-containing nodes < 1 cm in size), because microscopic metastases of the lymphatics cannot be identified with imaging studies. In 2004, Habarel et al. [10] showed that palpation, ultrasound, and CT scanning were all significantly weaker at detecting occult nodal disease, compared with the gold standard, SND. Likewise, PET imaging falls into this category because of its high false-negative rate. Because SND has continually proven to be superior to imaging when

staging the cN0 neck, evaluation of SLN biopsy, a technique that combines the virtues of tissue diagnosis with a minimally invasive approach and lessened morbidity, remains of great interest.

Why SLN Biopsy Instead of SND?

SND for the management of the cN0 neck was introduced to lessen the morbidity associated with the more traditional modified radical neck dissection [20•]. The decreased morbidity relates to a more limited dissection, placing fewer structures at risk, while still providing adequate diagnostic material. SLN biopsy, a natural extension of this trend, seeks to identify relevant tissue for diagnosis while minimizing dissection, thereby sparing relevant structures. Schiefke et al. [20•] compared SLN biopsy and SND to determine differences in function, postoperative morbidity, and quality of life (QOL) measures. They retrospectively reviewed 49 patients with OCSCC and a cN0 neck. Twenty-four patients received only SLN biopsy whereas 25 patients received SND. Statistically significant findings for SLN biopsy were improved swallowing, better tactile and pain sensation, a more normal-appearing scar, an improved shoulder constant score, and less fear of disease progression. Although not statistically significant, SLN biopsy also showed a trend toward less lymphedema, less facial nerve dysfunction, and improved global shoulder active motility scores. QOL surveys showed no significant differences between the two groups postoperatively; however, authors reported subjectively observed better functional outcomes. The study was limited by a small sample size and lack of prospective data collection, both possibly accounting for conflicting results. Despite these limitations, the study showed improved clinical and functional outcomes in the SLN biopsy group and supports SLN biopsy as a less morbid procedure compared with SND. Other reports of decreased morbidity in SLN biopsy compared with SND have been published [21–24].

The ability to identify “skip” metastases and unpredictable lymphatic drainage patterns is another advantage of SLN biopsy. In 2006, Civantos et al. [25] showed that 14 of 103 (13.6%) cases revealed sentinel nodes outside expected lymph node basins. They comment that these nodes would not have been dissected with standard lymphadenectomy. Byers et al. [26] also reported that “skip” metastases occur in about 16% of oral tongue lesions. By using SLN biopsy, unpredictable metastatic patterns can be controlled more effectively than with the anatomically based SND.

A third advantage of SLN biopsy relates to the pathologic handling of the specimen. Although SND delivers more lymph nodes, examination of the lymphadenectomy specimen remains simplistic. The specimen is embedded and sectioned in total, but only single sections are stained with hematoxylin and eosin (H&E) stain. Missed micrometastases often occur with this approach. In contrast, step sectioning of the entire sentinel lymph node(s) followed by systematic staining with H&E and immunohistochemistry can be performed for the small numbers of nodes harvested with SLN biopsy, thus enhancing identification of microscopic disease [27••]. Time and expense limit the ability to perform the same analysis on full lymphadenectomy specimens, given their expansive size.

How important are micrometastases (MM)? Studies have shown that the size of the metastatic disease is prognostically useful [28,29]. Atula et al. [17•] showed that the addition of step sectioning and cytokeratin staining helped identify an additional 31.4% of patients with metastatic disease compared with standard histologic evaluation. Additionally, 6 of 15 (40%) patients with macrometastases, 6 of 13 (46%) patients with MM, and one of five (20%) patients with isolated tumor cells had further nodal disease on follow-up SND. Despite a small sample size, all groups show more than 20% risk of further metastases, thus arguing that further treatment of the neck is necessary [30]. On the basis of these findings, the Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer recommended

evaluation of all SLNs with step sectioning, H&E, and cytokeratin staining to prevent missed MM [31].

Decreased morbidity, improved identification of “skip” metastases, and improved histologic evaluation of surgical specimens are all advantages of SLN biopsy.

The History of SLN Biopsy

SLN biopsy has greatly evolved since 1955 when Seaman and Powers [32] used radioactive gold colloid to demonstrate the concept of the first echelon sentinel node. SNL biopsy, however, remained experimental until the landmark melanoma study performed by Morton et al. [33] in 1992. Using isosulfan blue dye, 82% of sentinel nodes were identified intraoperatively and a false-negative rate of only 1% was achieved. In 1996, Alex and Krag [34] expanded the success of Morton et al. [33], using lymphoscintigraphy with Tc99-labelled sulfa colloid and intraoperative γ probing to identify the sentinel node in 90% of patients with cN0 necks [34]. With the advent of lymphoscintigraphy using Tc99-labelled sulfa colloid and intraoperative γ probe, Morton et al. [33], in a multicenter trial, combined the blue dye method and lymphoscintigraphy with intraoperative γ probing, and found 99% accuracy of identifying the sentinel node compared with 95% using only blue dye. They additionally showed that SLN biopsy with selective completion lymph node dissection had similar survival rates compared with the standard elective neck dissection, thus validating SLN biopsy as the standard of care [6].

Despite success by Morton et al. [33] with SLN mapping, the number of primary head and neck melanoma cases evaluated were low compared with primary tumors of the trunk and extremities. The broadly held belief was that evaluation of the head and neck region by SLN biopsy was risky, given the concentration of critical structures, and may not be any better than cervical lymphadenectomy [35–37]. O’Brien et al. studied lymphatic drainage patterns in 97 patients using lymphoscintigraphy [35]. Based on primary tumor sites and predicted drainage patterns, 34% of preoperative nuclear studies were discordant and 22% of sentinel nodes were found outside of the expected nodal basins [35]. They concluded that complex lymphatic drainage in the head and neck region made accurate identification of sentinel nodes uncertain. Other authors reported similar discordance rates [36]. Pitfalls of SLN biopsy for melanoma in the head and neck included recurrences in previously dissected and pathologically negative nodal basins and technical difficulties in parotid dissections with compromise to the facial nerve [35–37]. Despite these concerns, success rates for sentinel lymph node mapping remained similar to those obtained with SND in cases with melanoma of the head and neck [38], thus validating the minimally invasive approach. Therefore, SLN biopsy is currently the standard of care for staging the neck in cutaneous head and neck melanoma at many institutions [27••].

High success rates of SLN biopsy in melanoma and breast cancers have clearly driven interest for SLN biopsy in staging cN0 necks for patients with mucosal head and neck squamous cell carcinomas. Concern remains regarding the reliability of lymphatic drainage patterns in OCSCC in which, unlike cutaneous melanomas that often spread to superficial nodes first, tumors drain directly into the deep cervical nodes in a more predictable fashion [27••]. Initial success rates were poor. In 1998, Pitman et al. [39] performed blue-dye SLN mapping, identifying 0 of 16 sentinel nodes in patients studied [39]. In 1999, Shoaib et al. [40] compared 26 patients by randomizing them to undergo blue dye or radiocolloid plus blue dye. The blue dye arm resulted in the detection of only 5 (39%) sentinel nodes with 3 of 5 (60%) being false negatives compared with the rest of the neck specimen. Contrary to the blue dye-only arm, the blue dye plus radioisotope method yielded 12 of 13 (94%) sentinel nodes and showed 100% sensitivity for identifying nodal neck disease based on sentinel node findings.

After the success of Shoaib et al. [40], many others began to evaluate SLN biopsy using the combined blue dye plus radioisotope method, and found reproducibly strong sensitivities ranging from 66% to 100% [41]. Small sample sizes limited these studies, thus precluding recognition and implementation by others.

In light of growing interest and improving results from independent investigators, the First International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer was held in 2001 [19]. Twenty-two centers contributed SLN biopsy data on 316 patients with cN0 neck disease treated with combined SLN biopsy and SND to compare the diagnostic accuracy of the procedure. The SLN identification rate was 95%, 76 (25%) patients were upstaged based on SLN biopsy, and the overall sensitivity was 90%. Eight patients (4%) were found to have false-negative SLN biopsy. Lower sensitivities were observed at institutions performing ≤ 10 cases (sensitivity, 57%) compared with those doing more than 10 cases (94% sensitivity). This confirmed the findings of previous studies in melanoma that showed a learning curve associated with SLN biopsy, and that strong intra-observer reliability is vital to obtaining accurate data [6]. Although this study included head and neck cancers from multiple subsites and showed poor reliability between institutions based on numbers alone, the results were sufficient to suggest that SLN biopsy should be further studied as a potential modality for staging patients with head and neck mucosal SCC.

As a consequence of this conference, several single institution studies were carried out comparing SLN biopsy to the gold standard SND to determine the validity of SLN biopsy. Most studies were small and were limited in obtaining statistical power. In 2005, Paleri et al. [42] performed a meta-analysis on 19 of these studies in order to increase the power of the studies combined. They reviewed 367 patients, and 301 patients with oral cavity lesions. They found a 97.7% sentinel node identification rate. The combined sensitivity of SLN biopsy was 92.6% with a false-negative rate of 3%. The pooled data allowed decision tree analysis to determine the overall payoff differences between SND and SLN biopsy in terms of recurrence, disease-free survival, and mortality. This showed no statistical difference between the two modalities, but did not consider morbidity data. Although no significant differences between SND and SLN biopsy were observed, a formal standardized prospective study was needed before definitive treatment guideline changes could be supported.

In 2004, Ross et al. [43] performed a prospective randomized study of 134 patients with T1/T2 oral cavity and oropharyngeal SCC. They randomized 79 patients to receive SLN biopsy alone and 55 patients to receive SLN biopsy plus elective neck dissection. Sentinel node detection rates were 93%, and 42 (34%) patients were upstaged as a result of SLN biopsy. Overall sensitivity was 93% with an average follow-up of 2 years. Importantly, sensitivity for floor-of-mouth lesions (FOM) proved to be only 80%, significantly decreased compared with other subsites in which sensitivity was 100%. Of those treated with SLN biopsy only and negative pathologic results, 3.8% had subsequent disease within 24 months. Those treated with SLN biopsy plus elective neck dissection had a 4% false-negative rate. Follow-up results of this study at 5 years revealed a small drop in sensitivity to 91% but a strong negative predictive value of 95% [44]. This study clearly showed that SLN biopsy was as good as elective neck dissection with regard to identifying metastatic disease. Importantly, it also identified the FOM as a site prone to failure with SLN biopsy.

Stoeckli et al. [45••] performed an observational study of 51 patients looking at the effects of SNB with observation, and SND reserved only for patients with positive pathologic sentinel lymph nodes. Of the 51 patients, 40% of patients were upstaged and the negative predictive value was 94% with two false-negative results. Recurrence rates were 6% in patients with SLN biopsy and observation. This parallels recurrence rates of 3% to 7% seen in patients treated with SND [46]. Importantly, 13% of sentinel nodes were identified in regions not normally dissected with

SND. With a reported regional recurrence of 3% to 7%, SLN biopsy performed as effectively as SND, and may have outperformed SND by identifying disease outside the expected nodal basin.

In 2006, Civantos et al. [25] reported their experience with SLN biopsy. Specifically, they examined 106 patients at risk for regional metastases who were cN0. Pathologic staging was performed with SLN biopsy followed by SND. Of the 106 patients, 43 had oral cavity lesions, whereas others had cutaneous melanomas. Upstaging of the neck occurred in 46.5%, and 65% of patients with a positive SLN biopsy had additional positive nonsentinel nodes. SLN biopsy was 100% accurate for T1 lesions, had a false-negative rate of 10% and a negative predictive value of 92% [25]. Fourteen percent of cases had sentinel nodes outside expected nodal basins, confirming the results of Ambrosch et al. [46].

These results formed the basis for the American College of Surgeons Oncology Group Z0360 Validation Trial [27••]. This was a well-developed multi-institutional study with strict patient selection and protocol guidelines for assessment of SLN biopsy in patients with OCSCC. Patients deemed to be cN0 by CT or MRI were eligible. PET imaging was not accepted. A total of 137 patients were enrolled. Preliminary reports revealed a sentinel node identification rate of 99.3%, an average of 3.14 sentinel nodes harvested per patient, and an upstaging or occult metastases rate of 26%. Despite surgical specimens only being evaluated with H&E staining, the negative predictive value was 94%. Again, FOM lesions were associated with a lower negative predictive value compared with other oral cavity sites, 88.5% versus 95.4%, respectively. A false-negative metastatic rate of 5% again fell within the 3% to 7% recurrence rate seen with SND. The addition of step sectioning and immunohistochemistry, currently underway, will likely improve false-negative rates at the conclusion of the study.

Limitations in SLN Biopsy

The data in aggregate, including a prospective multi-institution trial, strongly suggests SLN assessment of the cN0 neck is sensitive, has a low false-negative rate, identifies nodes outside expected basins, and produces similar long-term results as SND in patients with low volume primary tumors of the oral cavity. Four main reasons account for its lack of broad use: 1) a lack of confirming multi-institution trials; 2) recognized weakness in assessing FOM tumors; 3) surgeon proficiency and comfort; and 4) OR logistics for performing the procedure, as well as performing the completion neck dissection in cases in which the SLN biopsy is positive. The lack of confirmatory studies, as well as surgeon proficiency and comfort with the technique, has intuitive solutions and will not be further discussed.

The obvious pitfall of SLN biopsy is its poor performance identifying true sentinel nodes in patients with FOM tumors. Most authors believe the close proximity of level I and IIa nodes to the primary tumor leads to shine through radioactivity, thus masking signal from the relevant sentinel node(s) [27••,43]. This is a problem inherent not only with the anatomy but also the properties of the radiolabeled agent.

Tc99-labelled sulfa colloid is the most common agent used for lymphoscintigraphy and SLN mapping. The sulfa colloid is an insoluble mixture that, once injected into interstitial sites, drains selectively via lymphatics. Because of its insolubility, drainage is inefficient, forcing investigators to inject excess agent into the primary site, to obtain useful amounts in the draining lymph node(s). Importantly, injection needs to be done within minutes of imaging and hours of surgery, as the agent nonspecifically targets lymph nodes. Delayed imaging or biopsy after injection can result in an increased number of nodes with signal, including both true sentinel nodes as well as nonsentinel nodes, making the procedure more technically difficult. Different sizes of colloid are available, all of which deliver an imperfect balance between primary site drainage and selectivity for the SLN(s). Larger particles progress more slowly into the

lymphatics and lag in the site of injection. Small particles enter lymphatics quickly, but are then too small to be trapped only in the first echelon nodes [19].

To manage shine-through issues, some have suggested resection of the primary tumor before SLN biopsy [47]. This approach has been effective in cutaneous melanomas of the head and neck in which resection margins tend to be larger, but has diminished success in the oral cavity in which margins are generally on the order of 1 cm. A different agent with selectivity for sentinel node(s) and more efficient drainage from the primary site of injection would enhance the effectiveness of SLN mapping in patients with FOM tumors.

OR logistics management represents another major obstacle for successful SLN biopsy. The properties of sulfa colloid demand that agent injection into the primary tumor site and lymphoscintigraphic imaging of the neck be performed within minutes to several hours. Additionally, SLN biopsy ideally is performed within 3 to 6 h from the time of injection. This imposes challenges related to OR management, coordination with the nuclear imaging service, and process coordination that may not be easy to accommodate in many settings, given common constraints and cost associated with OR utilization. A standard SND is predictable and requires much less coordination. An agent allowing injection and imaging the afternoon before surgery, while still providing a strong and specific signal the next day, would ease the OR logistics of SLN biopsy.

Future Refinements in SLN Biopsy

The perfect agent for SLN mapping would allow for high sensitivity of localization, rapid washout from the primary tumor site, and selective targeting of sentinel nodes. Additionally, stable selective targeting of sentinel nodes would be advantageous, allowing for injection and imaging to be performed the day before surgical biopsy. Lymphoseek, a new agent currently in advanced stages of testing, delivers these properties.

Lymphoseek is a dextran-based product modified to allow labeling with technetium-99 (Tc99). The particles are an average size of 5 nm, designed to enhance primary site efflux. Its sugar base makes the molecule soluble in water, thus promoting highly efficient drainage from the primary site of injection. The product also exhibits long-lasting selectivity for sentinel nodes as it targets the mannose receptor expressed on macrophages and dendritic cells enriched within lymph nodes. Phase 1 and 2 clinical trials comparing Tc99-labeled Lymphoseek to filtered [⁹⁹Tc] sulfur colloid for SLN biopsy in patients with breast cancer [48•] and melanoma [49] have substantiated the agents efficient drainage from the site of injection and its selective targeting of first echelon nodes. SLN labeling has also shown stability within sentinel nodes to support surgical biopsy up to 30 h after injection, with a strong safety profile.

A US Food and Drug Administration monitored, open-label, prospective multi-institution phase 3 trial of Lymphoseek for SLN biopsy in patients with OCSCC who have cN0 necks is currently accruing patients. The trial specifically examines the effectiveness of Lymphoseek in identifying sentinel lymph nodes and seeks to establish a false-negative rate, and negative predictive value for SLN biopsy using this agent.

Conclusions

Although SND is currently the standard of care for staging cN0 necks in patients with low volume (T1 and T2) OCSCC, SLN biopsy is showing significant promise as a minimally invasive surgical technique to help stratify patients with and without occult metastases. Current data strongly suggest that SLN biopsy delivers sensitivity and false-negative rates comparable to that achieved with SND, excluding patients with primary tumors of the FOM. New agents

currently under evaluation, such as Lymphoseek, promise improvement in procedure logistics, as well as improved diagnostic efficacy, in all subsites of the oral cavity.

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