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Role of sentinel lymph node biopsy for oral squamous cell carcinoma: current evidence and future challenges

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Abstract

Sentinel lymph node biopsy (SLNB) has been used across oncological specialties for prognostication, staging, and identification of occult nodal metastasis. Recent studies demonstrated the potential clinical utility of SLNB in oral cavity squamous cell carcinoma (OCSCC). Elective neck dissection is the current standard of care in early management of OCSCC with depth of invasion greater than 2–4mm, however, majority of patients ultimately do not have nodal disease on final pathology. SLNB is an alternative procedure widely adopted in early cancer management in many oncological subspecialities. Several considerations such as depth of invasion, nodal mapping, histopathology methods, operator variability, post-operative complications, and advancement in preoperative and intraoperative imaging technology can guide the appropriate application to SLNB in OCSCC. The aim of this review is to discuss the current evidence for SLNB in the treatment of early stage OCSCC, current imaging technologies that support SLNB procedures, and studies that are currently underway.

Keywords

Sentinel lymph node biopsy; oral squamous cell carcinoma

Introduction

Sentinel lymph node biopsy (SLNB) is a surgical procedure to remove and examine the first echelon nodal basin, or sentinel lymph node(s), to which a primary tumor drains. Interrogation of SLNs allows for targeted identification of occult metastatic disease in which nodal involvement plays a key role in determining cancer staging and prognosis.

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Disclosures

SY Lai is a medical affairs consultant for Cardinal Health.

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This procedure was first described in 1977 by Cabanas for penile carcinoma with 100 patients undergoing lymphangiogram with subsequent primary lymph node drainage pattern examined.[1] The accuracy of sentinel lymph node for predicting nodal metastasis was then validated in breast cancer using lymphazurin blue dye; in 60 patients with negative sentinel lymph nodes, only one non-sentinel node was identified to harbor metastasis.[2] Since then, there has been cross-specialty adoption of SLNB for surgical treatment of multiple cancers. The effectiveness and sensitivity of SLNB is well described in literature for breast cancer and melanoma starting in the late 1990s.[3–8] These studies included a randomized control trial with n=516 in 2003[9] which established SLNB as standard of care for breast cancer. Similarly, SLNB is the standard of care for melanoma[10–13] and endometrial cancer.[14,15]

In this article, we will review the current data for SLNB for oral cavity squamous cell carcinoma (OCSCC), technical considerations for SLNB, and the advancement in novel imaging modalities to increase visualization of the lymphatic system. Our aim is to make this information available to not only guide surgeons in making informed decisions regarding the suitability of SLNB for their patients, but also optimize modifiable factors to maximize favorable clinical outcomes.

Role of sentinel lymph node biopsy in oral cavity SCC

The surgical treatment of the neck in early-stage node-negative (N0) OCSCC has been evolving. Of patients presenting with stage I or II disease, up to 30% will have occult cervical metastatic disease[16,17], despite negative clinical and radiographic evaluation. As a result, management of clinically node negative oral cavity tumors has traditionally involved either therapeutic neck dissection (ND), with surgical salvage at the time of neck recurrence, or elective ND (END) at the time of primary treatment. Previously, no superiority was established between therapeutic ND[18,19] and END[20–23] approaches. A landmark, prospective, randomized controlled trial (RCT) in 2015 by D'Cruz et al demonstrated that elective ND resulted in significant improvement of both disease-free (DFS) and overall survival (OS) compared to therapeutic ND in 596 patients.[24] The patients in the END arm received higher rates of adjuvant radiation therapy and potentially insufficient surveillance imaging diagnostic modalities in the therapeutic ND arm, which may have contributed to improved outcomes for END. To address some of these possible biases, JCOG1601 is an ongoing in Japan (for oral cavity cancer with DOI 3–10mm) which includes scheduled follow up with both physical exam and imaging.[25] Nevertheless, this study established active management of the neck as standard of care for the treatment of node-negative OCSCC.

Following the rise of END in this patient population, there has been growing interest in the role of SLNB in early-stage N0 OCSCC. The current NCCN guidelines[26] for oral cavity tumors states tumors with DOI less than 2mm can be observed and DOI greater than 3mm is strongly recommended for elective neck dissection. However, DOI of greater than 2–4 mm is the generally accepted cut off for elective treatment of the neck over observation, based on clinician discretion. As SLNB becomes a more accepted practice, more practitioners in the US may use SLNB as an adjunct to the evaluation of nodal disease in early-stage tumors. Up to 70–80% of patients who undergo elective neck dissection do not ultimately have nodal

disease on final pathology.[27] SLNB presents an opportunity to decrease surgical intervention and potentially associated morbidity for patients who are ultimately N0.

A National Cancer Data Base retrospective study compared outcomes in early-stage OCSCC patients treated with SLNB compared to END between 2012–2015.[28] The study showed that there was an equivalent overall survival in the two study group (SLNB 82% vs END 78%, p=0.40) and the SLNB group had a reduced median length of hospital stay (SLNB 1 day vs END 3 days, p<0.001). Further, multiple prospective studies (Table 1) have shown that SLNB is a safe and effective diagnostic tool for staging the neck in early oral cavity carcinomas with high negative predictive value, excellent overall survival, and disease specific survival in negative SLNB patients.[29] The European SENT trial also demonstrated the feasibility of SLNB for oral cavity cancers, with sentinel nodes identified in 99.5% of cases and 86% sensitivity of negative sentinel nodes.[30] Similarly, a multi-institutional US phase II trial (ACOSOF Z0360) demonstrated high negative predictive value of SLNB of 96% for oral cavity lesions.[31] Several meta-analyses also support the high specificity and sensitivity of SLNB in T1 and T2 N0 OCSCC.[32–34]

Other studies highlight the potential advantages of SLNB. For example, one study showed that up to 40% of patients had aberrant sentinel nodes identified outside of the planned neck dissection field, and several studies report varying rates of contralateral sentinel lymph node drainage (Table 2).[29,30,35–37] Another observational study confirmed that SLNB confers similar disease free and overall survival as END, but with 23% reduced total cost.[38]

Recently, two randomized controlled trials (RCT) have reported outcomes comparing END and SLNB in the management head and neck squamous cell carcinoma (HNSCC), demonstrating non-inferiority of SLNB compared to END with regard to overall survival and recurrence free survival. In 2020, Garrel et al reported results of a multi-center RCT trial, Senti-MERORL, with 307 patients (28 excluded, 139 in END arm, 140 in SLNB arm) with oral cavity and oropharyngeal cancer demonstrating similar recurrence free survival and overall survival at 2 years.[39] This study also potentially demonstrated lower morbidity in the SLNB arm up to 6 months after surgery. Hasegawa et al performed another randomized control trial in 275 patients (4 excluded, 137 in END arm, 134 in SLNB arm) with a 3-year follow-up showing non-inferiority in survival and reduced postoperative complications in the SLNB cohort.[40] The non-inferiority margins for the two studies were 10% and 12%, respectively. While the outcomes of these studies are promising, neither is definitive. NRG-HN006 is a currently ongoing, multicenter randomized controlled trial in the US led by NRG Oncology comparing SLNB and END in early-stage oral cavity cancer with non-inferiority margins aimed at 5% for oncologic outcomes (NCT043333537).[41] In addition, the NRG HN006 has a primary objective to determine superiority of functional outcome as the main focus of its phase II trial. If the superiority of function is established, the study will continue to determine non-inferiority of oncologic outcomes in the phase III setting.

Considerations in SLNB

As with any procedure, there are several factors to consider when performing and evaluating SLNB. The following will discuss topics ranging from pre-operative, intra-operative and post-operative factors that affect clinical outcomes of surgery.

Depth of invasion as a predictor of occult nodal metastasis

The current, 8th edition of the American Joint Committee on Cancer (AJCC) guidelines utilizes depth of invasion (DOI) as a key parameter in tumor classification (T) with oral cavity T1 and T2 being ≤5 mm or ≤10 mm, respectively.[42,43] Previously, tumor thickness and DOI were used interchangeably, but a series of studies have shown evidence that the two values differ in relation to risk of nodal metastasis.[44–46] Leading up to the change in the AJCC guidelines, there have been several studies that established DOI as a superior predictor for occult lymph node metastasis in OCSCC compared to other measures. One study investigated the histopathologic parameters and found that invasive, large, cohesive aggregates had a better prognosis than a neoplasm invading as a thin, irregular, individual cells which supports the usage of DOI.[47]Another study also concluded that in early OCSCC, DOI is the most significant histopathological predictor of subclinical neck disease, and that tumors with DOI of greater than or equal to 5 mm were at high risk for nodal metastasis[48].

Currently, 2–4 mm DOI is commonly used as a cutoff for proceeding with an END. With regards to SLNB, guidelines from Schilling et al[30] in 2015 suggest utility of SLNB up to 10 mm DOI. In the RCT by Hasegawa et al, T1-T2 lesions with DOI of at least 4 mm were studied.[40] Other biomarkers such as CD44 have been associated with DOI in predicting occult nodal metastasis, but DOI remains the best clinical predictor with one study showing a 31% increased risk of nodal metastasis with each mm increase in DOI.[49] The discussion of the optimal cut off DOI indicated for SLNB is ongoing due to variability in study outcomes and warrants a future study.

Sentinel lymph node identification and nodal distribution

One of the key factors required for the widespread use of SLNB is reliable identification of lymphatic drainage from the primary tumor. Depending on the primary site of the oral cancer, the common drainage pattern differs as the sentinel node does not always have to be the closest node to the primary. One study had 16 head and neck surgeons or nuclear medicine physicians independently read lymphoscintigram and SPECT/CT of 53 patients who underwent SLNB with ^{99m}Tc-nanocolloid.[50] There was 88% identification of the SLN(s) with moderate agreement among observers, sensitivity of 75%, and negative predictive value of 98%. This study also showed 30% of drainage patterns deviated from the expected drainage patterns with higher distortion in patients with a history of prior neck radiation therapy. Overall, prospective studies (Table 1) have demonstrated high sensitivity (75%−100%) of SLNB for the oral cavity and oropharynx, and high negative predictive value for negative SLN(s) (91%−100%). False negatives contribute to less than 100% sensitivity, where the SNLB missed the true nodal metastasis. Variation in the surgeon experience with SLNB, presences of skip lesions, histopathologic methods such as sectioning thickness, and anatomic differences in individual lymphatic drainage pattern may

contribute to low sensitivity in some series. Also, Garrel et al[39] reported SLN localization failure in 5.7% of patients which can contribute to decreased sensitivity, and these patients proceeded with an elective neck dissection.

However, lower sensitivity has been demonstrated in floor of mouth tumors,[51] likely due to the “shine through” phenomenon.[52] In the floor of mouth, first echelon nodes are often in close proximity (e.g. level IA & IB) to the primary tumor where the radiotracer may remain post-injection in a relatively high concentration, and signal can “shine through” to obscure SLN detection in the adjacent nodal basin. This results in difficulty localizing a sentinel node and potentially mistakenly confusing non-sentinel tissue for a sentinel node. Methods for mitigating this effect include resection of the primary lesion prior to SLN localization, cross-reference to multiple imaging studies modalities or use of injected dye adjuncts to help reduce this error.[53,54]

Along with knowledge of the lymphatic drainage pattern, ability to identify and remove all identified sentinel nodes increases diagnostic accuracy.[55] In breast cancer, one study demonstrated a mean of 2.9 sentinel nodes were found in 501 patients using ^{99m}Tc-nanocolloid (brand name Nanocoll, Bucks, UK) and blue dye (brand name Patent Blue V, Roissy, France). Lower false negative rates were achieved when multiple sentinel nodes were removed, however, removing more than four axillary nodes in breast cancer was unnecessary.[56] Specific to OCSCC, a range of 2 to 3.2 sentinel nodes were harvested across several studies including Garrel,[39] Hasegawa,[40] and SENT study[30] (Table 2). Level 2 was the most common drainage site ranging from 20–57% amongst the studies.[57,58] Contralateral sentinel lymph node drainage can occur in the oral cavity with some Studies showing 2–17% incidence and bilateral drainage in 5–10%,[35,59] with floor of mouth tumors demonstrating the highest rates. (Table 2) This emphasizes the need to have clear visualization of the sentinel nodes and accurate identification of the lymphatic drainage pattern to achieve a successful clinical outcome.

Another potential mechanism for false-negative sentinel nodes is the presence of skip metastasis which have been reported in OCSCC.[57,60] In such cases, nodal metastasis may travel beyond the likely first nodal basin, and be identified in the lower neck levels III & IV. In particular for patients with prior neck treatment, one study showed a higher rate of unusual lymphatic drainage.[61] Therefore, proponents of END support the complete removal of all nodes at risk to address these potential skip metastases. In a retrospective study, Minamikawa et al found that 10 out of 296 oral cavity cancer patients harbored skip metastases, all of whom presented with primary oral tongue tumors.[62] These patients primarily had level III involvement (8 of the 10) without level I/II nodal metastases, with the additional two patients demonstrating level IV/V involvement. The limited literature on skip metastases suggests that recurrence in lower levels of the neck without level I-II involvement is associated with oral tongue primaries.[60,63,64] This skip metastasis phenomenon may be mitigated by careful step-sectioning of sentinel nodes that may reveal micrometastases in higher neck level nodes, reducing the rate of true skip metastases.

Histopathology methods

Careful pathological evaluation of SLNs is critical to avoid false-negative sentinel node results that put patients at risk for untreated disease and eventual recurrence. Traditionally, permanent sections have been used on SLNs to provide high-quality slides utilizing immunohistochemistry and additional stains of the nodal samples. The result is not immediately available and therefore requires a two-stage surgery for a completion neck dissection if a positive sentinel node is identified. Furthermore, for improved accuracy for identification of subclinical micrometastasis, step-sectioning is recommended at 150 μm for sentinel lymph node evaluation, as performed in a multicenter study in 2015.[53] King et al evaluated 90 patients where initial SLN biopsy was negative for carcinoma; these SLNs were submitted for step-sectioning at 150 μm and 19.5% of patients were upstaged, highlighting the importance of serial section for detection of occult nodal micrometastases.[65] Another study of 51 oral cavity patients undergoing SLNB using ^{99m}Tc-nanocolloid demonstrated that only 2 of 11 positive sentinel nodes were identified with standard H&E, highlighting the limitations of frozen section evaluation.[57] However, in optimizing the histopathology methods, considerations of the increased work burden and time of the surgical pathologists must be made. Utilization of thin step sectioning at 150 μm significantly increases the pathologic sections, more than 10-fold compared to standard 2mm sections or bisection of nodes.

Both the Hasewaga and Garrel trials utilized frozen section pathology; the Hasegawa trial utilized 2mm sections for frozen evaluation and in the Garrel trial frozen evaluation method was per pathologist choice. These frozen sections were able to identify 64–68% of positive sentinel nodes for which patients were able to receive a single stage complete neck dissection at the time of SLNB. However, the remaining patients with positive SLN after permanent pathology evaluation still required a second stage neck dissection.[39,40] Of note, method of frozen section histopathology is destructive to a portion of the node that would be used for formal serial sectioning and is not supported by SLN assessment in breast cancer due to non-optimal sensitivity. Most centers do not have the pathologic resources to perform thin step sectioning for frozen evaluation of sentinel nodes on frozen section, but about 64–68% of positive sentinel nodes were able to be identified on frozen section and spared patients a second procedure.[39,40] Therefore, frozen section of sentinel nodes may be considered, but current practices in the US generally favor a second stage completion neck dissection. Currently literature on the optimal increment for sectioning and utility of frozen section is limited and further research is warranted as under sampling may lead to false-negatives and over sampling increases the time and resource burden on the surgical pathologist.

Operator variability and clinical outcome

Surgical outcomes for accurate identification of sentinel lymph nodes can vary by both individual operator surgical experience as well as institutional coordination of nuclear imaging resources. The learning curve for this procedure is well described in the literature in breast cancer[66], endometrial cancer[67], and melanoma[68] which describe various aspects such as performing a full lymph node dissection alongside SLNB until the operator has competency in identifying common lymphatic drainage for the respective anatomical

regions. The melanoma study compared the first set of 30 SLNB with the second set of 30 SLNB performed and found an increase of sentinel node identification from 90% to 97% using a combination of radioactive probe and blue dye. A study in breast cancer demonstrated that surgeon inexperience was associated with greater inability to identify SLN and understaging. This understaging can negatively impact survival and increase costs associated with operative time, radiocolloid use and more frozen sections sent to pathology.[66] In regards to the learning curve of SLNB in OCSCC, Civantos et al demonstrated improved negative predictive value in more experienced surgeons.[31] However, studies on this topic are limited and future studies are warranted to elucidate differences based on surgeon experience to reduce variation among operators.

Post-operative complications

One of the main factors driving consideration of SLNB for early-stage OCSCC is the potential to reduce overall morbidity for patients with truly node-negative disease. Potential complications from neck dissection, particularly to shoulder function, are well established. Shoulder dysfunction was first described by Alan et al in 1961 as the “shoulder syndrome” where patients had trapezius palsy, shoulder pain, and limited abduction caused by damage to the spinal accessory nerve.[69] Other structures such as the internal jugular vein, hypoglossal nerve, vagus nerve and thoracic duct are also potential risk for injury and resultant morbidity. Postoperative sequelae can be exacerbated if adjuvant radiotherapy is recommended which can cause further scarring, lymphedema, and sensory dysfunction.[70] Due to the smaller incision needed for SLNB and minimal lymph node removal, a reduction in risk for these complications in node-negative patients undergoing SLNB may be expected. Garrel et al found that the END group had a significantly worse self-reported neck-shoulder impairment scores during the first 12 months, but no difference by 24 months.[39] This study also reported significant impairment of arm abduction at 2, 4, and 6 months but not in the later time points. Similarly, Hasegawa et al reported significantly worse functional scores in neck stiffness, and numbness up to 12 months. Shoulder drop, neck appearance and arm abduction test were worse up to 6 months after surgery in the END group.[40]

Neck lymphedema is another common late complication after lymph node dissection also seen in breast cancer[71] and melanoma[72] related treatments. In the head and neck, lymphedema can contribute to difficulty swallowing, chewing, voice changes, and physical appearance among others which all affects quality of life.[73] Measurement tools for lymphedema are not widely validated in head and neck, and understanding the differences in lymphedema between the two surgical approaches remains an open area of study.

In regards to hospital stay, a retrospective review of the National Cancer Database in the US (n=8,328) showed there was a decrease in median length of hospital stay from 3 days in the END group to 1 day in the SLNB group with similar adjusted overall survival on the 3-year follow up.[28] Garrel et al showed similar trend of decreased hospitalization in SLNB compared to END (8.09 vs 10.4 days) in a European population.[39] Future studies may help to more clearly elucidate magnitude of differences in post-operative complications between SLNB and END, and more clearly define potential benefits of SLNB.

There are several OCSCC studies which demonstrate decreased cost of SLNB in Europe[38,74] by 15%−42% and Asia[75] by 41% depending whether the identified SLN was a true positive. Since each country have its own standard of management and health care system (i.e. length of hospital stay post-operation, management of comorbidity while hospitalized, cost of medical staff, etc), the extent of the cost difference may vary. However, there are currently no studies in the US that directly evaluate the cost of SLNB and END[38] for OCSCC patients and additional work in this area of study is warranted.

Preoperative and intraoperative tools

Accurate preoperative imaging and intraoperative tools can significantly aid in accurate sentinel lymph node identification, particularly in the head and neck region.

Preoperative imaging modality

For SLNB, lymphoscintigraphy is a valuable diagnostic nuclear imaging tool that utilizes radiopharmaceutical agents in mapping the lymphatic system and was first introduced in the late 1900s (Figure 1a).[7,76] This modality is coupled with a radiotracer injection at the primary site and imaging timed shortly thereafter. Although lymphoscintigraphy can visualize entire lymphatic drainage patterns, anatomical relationships can be difficult to distinguish with planar imaging. Therefore, dual SPECT imaging modality of lymphoscintigraphy superimposed on CT is becoming more frequently utilized preoperatively, particularly in the head and neck for visualization of sentinel nodes in relationship to known anatomical landmarks (Figure 1b).[77,78] For head and neck melanoma with periparotid sentinel nodes, the additional information gained from use of SPECT/CT altered surgical planning in 57% of cases.[79] These specialized imaging techniques are not universally available, and alternative imaging methods may be needed in such cases. Usage of radiotracer with intraoperative gamma probe alone, without preoperative imaging, is also a viable method of SLN detection. If nuclear medicine resources are not available, performing an elective neck dissection may be an alternative route of management rather than doing an SLNB with low accuracy.

Intraoperative tracers

In adjunct with the preoperative imaging, intraoperative dyes and radiotracers are often used to localize sentinel lymph nodes intraoperatively. Previously, a blue dye (brand name Lymphazurin, CT, USA) was commonly used to visually identify sentinel nodes. While sensitivity was good, a major limitation is the transient pass through of dye that limits the time interval that the sentinel node can be visualized, leading to potential for false-negative results.[80,81] In lower resourced regions, blue dye may be used as an adjunct to improve SLN identification.

In the modern era, dye has been predominately replaced by radiotracers. Radiotracers are not only visible on preoperative nuclear imaging, but can also facilitate intraoperative sentinel node localization and confirmation using a gamma probe. ^{99m}Tc-serum albumin nanocolloid (HAS)[82] is the most commonly used radiotracer in Europe and filtered or unfiltered ^{99m}Tc-sulfur colloid[31] in the United States (Tc: technetium). ^{99m}Tc has a half-life

of 6 hours allowing for sustained signal after injection. Differences in formulation give rise to variability in particle size and stability. Nanocolloid exhibits a size range of 4–100nm in diameter and filtered sulfur colloid can range in size between 50–200nm, which can increase during storage.[83] Particle size stability after filtration was the primary reason why the FDA only approved unfiltered Tc-sulfur colloid for SLN. Along with particle size and stability, the specificity and retention of the particle in the lymph node are important factors.[84] More recently, ^{99m}Tc-tilmanocept (brand name Lymphoseek, OH, USA) has been widely used for SLNB since receiving FDA approval in 2013 (pediatric SLN approval in 2021). This first-class targeted agent has a low false-negative rate due to its specific targeting of the mannose receptors (CD206) expressed on the surface of macrophages and dendritic cells, and was specifically designed for lymphoscintigraphy.[85–88]

Use of intraoperative radiotracers has been widely adopted in sentinel lymph node biopsies. During the procedure, these tracers provide added spatial awareness which is supplemented by preoperative imaging. This technology does have some limitations. The gamma probe identifies the general location of the sentinel lymph node, but probe detection windows are generally larger than a single lymph node which can limit specific node identification. The probe also does not convey the depth of signal, and the surgeon must estimate the depth based on anatomy and previous experience. Further, if there are multiple lymph nodes in the region or nodal basin, distinguishing between the sentinel and non-sentinel node may require additional time or experience. Specific to oral cavity cancer, primary sites involving the floor of the mouth have shown decreased success with SLNB.[31,89] This is likely due to its close proximity of the primary tumor site to the sentinel node, resulting in a “shine through” effect where the sentinel node signal can be overshadowed by scatter from the primary site. With the first echelon nodal basin being in close proximity to the primary site, this phenomenon may make reliance on the gamma probe for accurate sentinel node isolation difficult.

A new intraoperative technology that is rising in popularity to counter the “shine through” phenomena is the free hand SPECT (FhSPECT).[90] A dynamic, three-dimensional image is extrapolated based on the anatomical landmarks calibrated to the patient at the start of the procedure. This allows the surgeon to visualize the depth of the sentinel node, which the gamma probe was not able to provide.

Furthermore, there are several near-infrared (NIR) fluorescence imaging modalities paired with indocyanine green (ICG) and other NIR dyes, such as IRDye800CW, that have been piloted in the clinical setting. ICG is a non-radioactive mapping agent with an excitation wavelength of 740–800nm which has been granted FDA approval in 1959[91] and has been readily used in many surgical subspecialties for intraoperative anatomical visualization. ICG is detected with an NIR imaging system at 2 hours after injection, and when used in conjunction with technetium, detected by the gamma probe, has shown to increase sensitivity for SLNB.[92,93] Feasibility of utilizing this real time, visual feedback of ICG has been shown in minimally invasive SLNB and END in head and neck surgery via the retroauricular approach using Da Vinci Xi robotic surgical system paired with Firefly, an FDA approved (2014) NIR fluorescent imaging system specific to this surgical system.[94,95] Another NIR dye that is being tested in early phase clinical trials in head and neck surgery is IRDye800CW labeled monoclonal antibodies for improved localization of tumor tissue

intravenously rather than SLN such as Cetuximab-IRDye800CW[96–98] and Panitumumab-IRDye800CW.[99–101] More specific to SLNs, fluorescent-labelled tilmanocept has shown feasibility for SLNB for prostate and bladder cancer in animal models.[102,103] Despite the relatively confined area of head and neck cancers, this visual technology may help to overcome challenges of "shine through" and identification of SLNs in dense nodal regions. These fluorescent tracers may also represent an alternative option that can be used in patients with contraindication to radioscopic agents or if nuclear medicine facilitates are not available.[104,105] Successful SLNB has been demonstrated in the head and neck using a combination of ICG with methylene blue.[106]

Conclusion

The standard of care for treatment of early-stage OCSCC has evolved over the decades and new high-quality studies are beginning to support the role of SNLB to reduce post-operative complications while achieving similar oncologic outcomes. In the past year, two randomized control trials were conducted to support non-inferior outcomes of SLNB compared to END. With current ongoing clinical trials and SLNB studies[107], more evidence-based data will be available to make an informative decision regarding the standard of care. Several important considerations should be addressed with the implementation of SLNB in treatment of oral cavity cancer, including surgeon experience, standards for pathologic evaluation of sentinel nodes, availability of optimal imaging techniques, improvements in radiotracers, and methods to mitigate shine through to achieve accurate sentinel node identification and ultimately improve patient outcomes.

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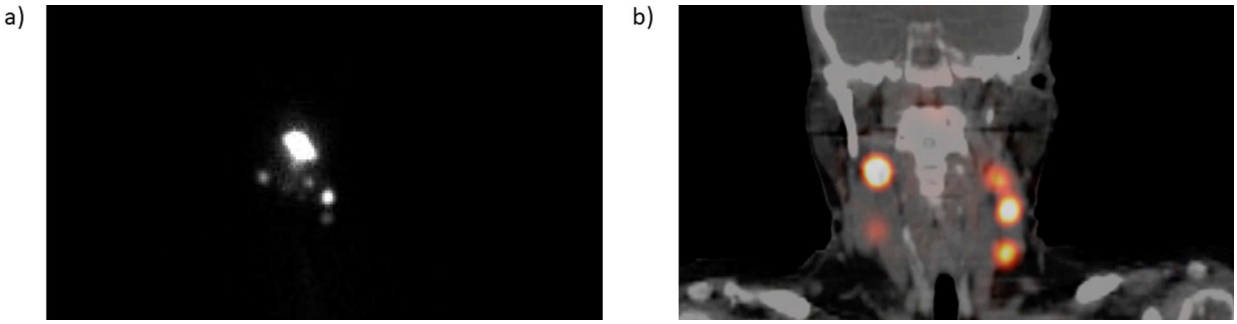

Figure 1.

a) Lymphoscintigraphy of left tongue squamous cell carcinoma showing multiple sentinel lymph nodes b) SPECT/CT imaging of same patient demonstrating additional anatomical correlation for bilateral sentinel lymph nodes.

Table 1.

Prospective studies with SLNB in early oral cavity cancers

Study	No. of participants	Study design/Inclusion	% Positive SLNB	SLN identification rate	Sensitivity	Survival data	Conclusion
Abdul-Razak (2016)[35]	30	Single institution, prospective, cT1–2N0 oral cavity SCC, majority (87%) included oral tongue. All patients underwent SLNB followed by immediate END.	50%	100%	Sensitivity: 100% NPV: 100%	NR	Sentinel node positivity correlated with increasing tumor depth.
Alkureishi (2010)[82]	134	Multi-institutional, cT1-T2N0 oral cavity and oropharynx SCC (subsite anterior tongue (50), FOM (42), other (41). Either SLNB followed by END or SLNB alone.	NR	93%	SLNB alone Sensitivity: 87% NPV: 94% SLNB assisted END Sensitivity: 96% NPV: 97%	SLNB+ DFS: 79% SLNB- DFS: 80% SLNB alone OS: 70% SLNB assisted END OS: 60%	No significant difference in locoregional DFS in SLNB+ compared to SLNB- patients. No significant overall survival difference in patients who underwent SLNB alone compared to SLNB assisted END.
Civantos (2010)[31]	140	Multi-institutional, cT1-T2N0 oral cavity SCC (subsite tongue (95), FOM (26), other (19). All underwent SLNB followed by completion SND (levels I-IV).	29% (41/140 patients)	NR	Sensitivity: 90% Specificity: 100% NPV: 96%	NR	SLNB can accurately predict the pathologically negative neck in majority of cases (NPV=96%). The negative predictive value increases for T1 lesion and for procedures performed by surgeons with more experience in the use of SLNB.
Hernando (2016)[38]	73	Single institution, prospective, cT1–2N0 oral cavity SCC Patients made informed decision to either undergo SLNB or END.	9.4%	NR	FNR:10.3%	SLNB DFS: 80% OS: 80% END DFS: 84% OS: 83%	No significant difference in DFS or OS in patients who underwent SLNB compared to END.
Hingsammer (2019)[108]	41	Single institution, cT1-T2N0 SCC tongue. SLNB + patients underwent END and SLNB- patients underwent observation.	17% (7/41 patients)	100%	NPV: 97% FNR: 3%	Recurrence rate SLNB +: 0% SLNB-: 3% Overall: OS: 80% DSS: 95% DFS: 95% SLNB+: OS: 71% DSS: 86% DFS: 86% SLNB-: OS: 82% DSS: 96% DFS: 97% *No statistical difference between	No significant survival difference between SLNB+ and SLNB- patients. Isolated tumor cells may be a risk factor for development of late cervical metastasis.

Study	No. of participants	Study design/Inclusion	% Positive SLNB	SLN identification rate	Sensitivity	Survival data	Conclusion
						SLNB+ and SLNB- Mean follow up 92 months.	
Loree (2019)[36]	108	Single institution, retrospective, T1-T4N0 SCC oral cavity (2 patients T3, 1 patient T4) (subsite tongue (65), FOM (7), buccal (13), RMT (1), lip (15), gingiva (7). SLNB + patients underwent SND/ND +/− chemoradiotherpy. SLN- patients underwent observation.	18.5%	95.4%	Sensitivity: 75% NPV:91%	DSS: 93% (SLNB- patients (SLN+ patients)	No significant survival differences between patients with positive SLN compared to patients with true negative SLN.
Miura (2017)[37]	57	Multi-institutional, phase II clinical trial, cT2-T3N0 oral cavity SCC. All underwent SLNB followed by therapeutic level 1–4 ND for SN positive patients or ipsilateral level 1–3 END for SN negative patients	17.8%	100%	Sensitivity: 95.5% NPV: 97.1% FNR: 4.5%	OS: 89.5% DFS: 82.5%	Overall, 3 year OS= 89.5%. This was significantly lower in patients with positive SNs. Overall 3 year DFS= 82.5% with no significant difference between SN positive and SN negative patients. SLNB alone is an appropriate staging tool and reliable method to determine appropriate levels for neck dissection.
Moya-Plana (2018)[109]	229	Single institution, prospective, cT1–2N0 oral cavity SCC. 50 patients underwent SLNB and systematic ND (levels 1–4) and 179 patients underwent SLNB followed by END if SLNB was positive.	21.4%	93.9%	NPV: 92.7%	OS:77.3% SLNB group OS: 76.4% RFT 80.7% Systematic ND group OS: 78.7% RFT: 77.7% *No significant difference	Tumor location on oral tongue, higher T stage, PNI, LVI, and depth of invasion ≥ 5mm all significant predictors of SN positivity. SLNB resulted in 8% complications compared to 28% for END.
Pedersen (2016)[59]	253	Single institution, retrospective, cT1-T2N0 oral cavity SCC. All underwent SLNB. SLNB+ patients were offered elective neck dissection +/− radiotherapy	27%	NR	Sensitivity: 88% NPV: 95% FNR: 5%	Recurrence rate +SLNB: 15% nodal recurrence -SLNB: 5% nodal recurrence	SLNB is safe and able to accurately stage patients with early OCSCC. Advantage of detecting unexpected locations of metastasis. Location, specifically FOM tumors, associated with SLNB failure. PNI, poor differentiation, and maximum tumor thickness associated with increased risk of occult lymph node metastases.
Pezier (2012)[29]	59	Single institution, cT1-T2N0 SCC oral cavity, no previous neck pathology or treatment to the neck. All underwent SLNB except 2 patients in which SLNB was not identified who underwent END.	30% (17/57 patients)	96% (2 patients SLN not identified)	Sensitivity: 94% Specificity:100% PPV: 100% NPV: 97.5%	NR	SLNB is safe and accurate diagnostic technique for staging of the neck.

Study	No. of participants	Study design/Inclusion	% Positive SLNB	SLN identification rate	Sensitivity	Survival data	Conclusion
Ross (2004)[51]	134	Multi-institutional, cT1-T2N0 oral cavity and oropharynx SCC (subsite anterior tongue (50), FOM (42), other (41). Either SLNB followed by END or SLNB alone.	31% (42/134 patients)	93% (9 patients SLN not identified) 88% for FOM tumors alone.	SLNB alone Sensitivity: 91% SLNB assisted END Sensitivity: 96% Combined techniques Sensitivity: 93% FOM tumors alone Sensitivity: 80%	NR	SLNB alone as a staging tool is minimally invasive with minimal morbidity and is cost effective for most oral cavity/oropharynx tumors; however, may be more difficult for FOM tumors. Identification rate of SLN and sensitivity for FOM tumors less compared to other subsites.
Schilling (2015)[30]	415	Multi-institutional, cT1-T2N0 SCC oral cavity or oropharynx	23% (94/415 patients)	99.5%	Sensitivity: 86% NPV: 95%	Recurrence rate +SLNB: 23% DSS: 94%	SLNB is a reliable and safe oncological technique for the cN0 neck with low complication rate (3%).

Note: DFS- disease free survival, DSS- disease specific survival, END- elective neck dissection, FNR- false negative rate, FOM- floor of mouth, LVI- lymphovascular invasion, NPV- negative predictive value, NR- not reported, OCSCC- oral cavity squamous cell carcinoma, OS- overall survival, PNI- perineural invasion, PPV- positive predictive value, RFT- recurrence free time, RMT- retromolar trigone, SLNB- sentinel lymph node biopsy,

Table 2.

Summary of SLN identified and drainage patterns

Study	T Classification	Top 2 Primary Sites (%)	Drainage Pattern	Level of Neck	% Identified at Level		Mean # of SLN Harvested
Abdul-Razak (2016)[35]	T1 (53%) T2 (40%) T3 (7%)	Tongue, lateral (80%) Floor of mouth (10%)	17% contralateral (level I-III) 0% contralateral (level IV-V)	I-III IV, V	60% 12%		3 (median)
Bilde (2008)[57]	T1 (45%) T2 (55%)	Tongue, anterior 2/3rd (51%) Floor of mouth (41%)	NR	 I II III IV	**AT** 25% 33% 15% NR	**FOM** 12% 38% 25% 13%	3 (median)
Garrel (2020)[39]	T1 (63%) T2 (37%)	Oral cavity (85.6) Oropharynx (14.4)	NR	NR	NR		2.93
Hasegawa (2021)[40]	T1 (19%) T2 (81%)	Tongue (83.2) Floor of mouth (10.2)	NR	NR	NR		3.2
Hernando (2016)[38]	T1 (53%) T2 (47%)	Tongue (44%) Floor of mouth (28%)	NR	Ia Ib IIa IIb III IV	25% 50% 20% 0% 0% 5%		2
Hingsammer (2019)[108]	T1 (71%) T2 (29%)	Tongue, right border (49%) Tongue, left border (49%)	NR	I II III IV	11% 57% 28% 4%		NR
Loree (2019)[36]	T1 (56%) T2 (38%) T3 (1%) T4 (6%)	Tongue (60%) Floor of mouth (6%)	98% ipsilateral 2% contralateral	I II III IV, V	31% 43% 18% 6%		2
Miura (2017)[37]	T1 (35%) T2 (56%) T3 (5%) T4 (5%)	Tongue (86%) Floor of mouth (7%)	7.4% contralateral	Ia Ib II III IV V	6% 20% 34% 34% 0% 0%		3 (median)
Pezier (2012)[29]	T1 (71%) T2 (29%)	Tongue, anterior 2/3rd (64%) Floor of mouth (15%)	89% ipsilateral 5% contralateral 5% bilateral	I IIa IIb III IV V	Not reported Not reported 0% 21% (skip lesion) 0% 0%		2.6
Schilling (2015)[30]	T1 (71%) T2 (29%)	Tongue, anterior 2/3rd (51%) Floor of mouth (25%)	87% ipsilateral 2.5% contralateral 10% bilateral	NR	NR		3.2

Note: AT- anterior tongue, FOM- floor of mouth, NR- not reporte