

Review Article**Sentinel lymph node biopsy in oral squamous cell carcinoma - Ensuing from elective to selective**

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ABSTRACT

The status of lymph node involvement holds prime importance in the prognosis and therapy of oral squamous cell carcinoma (OSCC). Clinically and radiologically negative neck lymph nodes in early OSCC frequently create difficulty in predicting prognosis and defining treatment, owing to the chances of occult metastasis. In case of the lymphatic spread of the carcinoma, lymphatic drain will first pass through sentinel lymph nodes. The sentinel lymph node (SLN) is defined as the lymph node on the direct drainage pathway from the primary tumor. Sentinel lymph node biopsy (SLNB) is a minimally invasive technique and can be used for staging of cN0 neck in early OSCC. It helps to identify "skip" metastases and unpredictable lymphatic drainage patterns. Elective lymph node dissection (ELND) is frequently used as an adjunctive therapy to improve the cure rates of patients with cN0 OSCC and has been applied for staging as well, but it holds a greater risk of morbidity as compared to SLNB. Sentinel lymph node biopsy (SLNB) poses to be a feasible, safe and reliable prognostic tool for cN0 OSCC. Here's an attempt to understand the validity of SLNB over ELND.

Key words: Oral squamous cell carcinoma, sentinel lymph node biopsy, lymphoscintigraphy, elective lymph node dissection, prognosis

INTRODUCTION

Oral cancer is one of the most serious health problems that grips the world today. Its occurrence happens to be particularly high in India, credited to the addictive habits of the people along with the ethnic and cultural aspects. It stands first in position in terms of incidence among the men and third amongst the women. Causative factors include tobacco and tobacco related products, alcohol, genetic predisposition and hormonal factors [1]. One of the daunting properties of oral cancers, is the high frequency of metastases. The disease free survival rate is reduced to about 50% by the presence of a single positive lymph node. Thus lymph node metastases poses to be a crucial prognostic factor of head and neck squamous cell carcinomas [2]. Sentinel lymph node biopsy (SLNB) offers accurate detection of lymph node metastases and allows accurate staging with minimal morbidity.

Sentinel lymph node biopsy is a minimally invasive technique which has limited the neck dissection to patients with positive sentinel lymph nodes. The sentinel lymph node (SLN) is defined as the lymph node on the direct drainage pathway from the primary tumor [3]. This implies that when the tumour begins metastasising through the lymphatics, sentinel lymph nodes will be the first to get invaded, before subsequent nodes are involved. Thus, selective excision of the SLN followed by meticulous histopathological examination would adequately reflect the nodal status of the remaining neck. Up till now elective lymph node dissection (ELND) has been regarded as the gold standard procedure for the cN0 neck [4]. But the last two decades have witnessed a shift towards more conservative surgical methods, owing to the contribution of Lindberg, Byers and Shah in describing the common patterns of lymphatic drainage [5,6,7]. An understanding of these patterns has confined the extent of neck dissections to only

those nodal levels which are at high risk. Sentinel lymph node biopsy (SLNB) signifies an extension of this approach [8].

Emergence of sentinel lymph node biopsy

Lymphatic mapping and sentinel lymph node biopsy (SLNB) were first reported in 1977 by Cabanas for penile cancer [9]. Since then, the concept of sentinel lymph node biopsy has been extensively studied and validated for patients with cutaneous melanoma and breast cancer. Studies to date have also indicated a high level of accuracy in patients with OSCC [4]. The first successful SLNB in head and neck SCC was performed in 1996, by Alex and Krag, on a patient with a laryngeal supraglottic carcinoma [10].

Procedure of SLNB

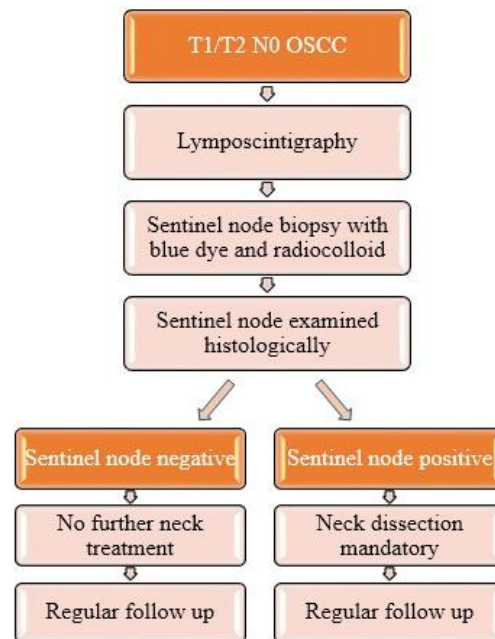
To identify a Lymphatic drainage basin, lymphoscintigraphy is used. It's an imaging technique which helps to determine the number of sentinel nodes, differentiate sentinel nodes from subsequent nodes, locate the sentinel node in an unexpected location, and mark the sentinel node over the skin for biopsy. Lymphatic mapping is done by lymphoscintigraphy preoperatively and using a portable gamma detector intraoperatively. A blue dye (isosulfan blue) and/or a radioactive tracer are injected around the tumor site. The radioactive tracer most commonly used is Tc99-labelled sulfa colloid. The lymph fluid carries the blue dye and tracer away from the tumor, to the nearest lymph nodes. The surgeon looks for the lymph nodes that have the blue dye in them, or uses a detector to find the lymph nodes that have the highest amount of tracer. These are the sentinel lymph nodes. SLNs were identified and the overlying skin is marked. These lymph nodes are removed and are checked using the gamma detector to confirm the radioactivity reading. The removal site and other neck sites are checked for absence of meaningful radioactivity. The fresh SLN or SLNs are sent pathological examination [11]. The procedure of SLNB has been summarised in fig 1.

Inclusion Criteria

The most important inclusion criterion for SLNB is a clinically negative neck. It is avoided in clinically positive neck nodes because gross lymphatic involvement can cause alteration of the normal architecture and anomalous draining patterns which may result in the biopsy of false sentinel nodes [12]. Clinically negative lymph nodes can be confirmed by

physical examination and clinical imaging [13, 14]. None of the imaging modalities, however, have the ability to detect small or micrometastatic tumour deposits, but all techniques improve on the sensitivity of palpation alone and are therefore recommended prior to SLNB [13].

Fig 1: Procedure of SLNB – demonstrating the stepwise procedure followed in an OSCC patient with clinically negative neck lymph nodes (T1/T2 N0 OSCC) going for SLNB



Exclusion Criteria

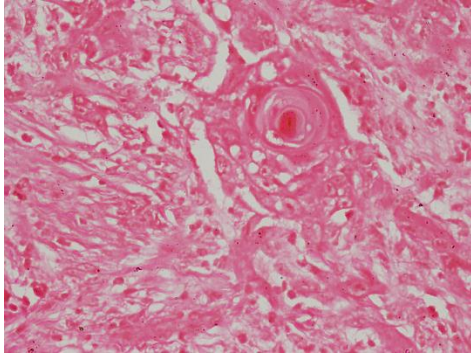
In general, sentinel node dissection is not appropriate for the candidates who are likely to have cancer in the lymph nodes, or those with any prior surgery or treatment that could have altered the normal pattern of lymph drainage. Its application in pregnant and lactation women also needs to be weighed according to the extent of its requirement [15].

Microscopy

Sections should be examined using a good quality bright field Microscope. Pathological examinations of sentinel nodes, including step sectioning and immuno-histochemistry holds considerable significance for both micrometastases (Fig 2) and Isolated Tumoral Cells (ITC) [15, 16]. In 2002, Werner reported a sensitivity of 96.7% in a series of 90 patients with head and neck

SCC, and stressed the role of serial sectioning and the need to remove all radioactive sentinel node [17]. The majority of series showed that the SLNB technique usually removes 2-3 sentinel nodes. All required detailed pathological investigation [18].

Fig 2: Micrometastasis of oral squamous cell carcinoma in a lymph node (H and E 20X)



Clinical rationale of Sentinel Lymph node biopsies

More than 50% of patients with squamous cell carcinoma of the oral cavity have lymph node metastases [19]. Bearing this in mind, it is imperative to assess the status of the lymph nodes in relation to OSCC. Sentinel lymph node status has been shown to be the most important predictor of survival [20]. There may be multiple sentinel lymph nodes involved and they need not be those closest to the tumour [21]. With the application of early dynamic lymphoscintigraphy nodes on a direct drainage pathway that are housing the tumour cells, can be distinguished with ease [4].

In 2000, Chiesa et al [22] investigated the reliability of SLNB in predicting the neck status in these patients. They concluded that the technique allows easy and safe identification of sentinel nodes and shows promise in guiding selective neck dissection. In June 2001, the 1st International Conference, held in Glasgow, stated that the overall sentinel node identification efficiency of SLNB was 98%, and sensitivity of the procedure was 90% [23]. The 2nd International Conference, held in Zurich confirmed the reliability of SLNB by stating that the identification rate of SLNB was 97% (range 90-100%), with a 96% (range 88-100%) negative predictive value of a negative sentinel node for the remainder of the neck using both pre-operative lympho-scintigraphy and intra-operative hand-held gamma probe [18].

Pitman K T. et al [24] studied the feasibility and accuracy of SLNB in head and neck squamous cell carcinoma, as a method to stage the

regional lymphatics and also to determine whether there are qualitative differences between the cutaneous and mucosal lymphatics that would affect the technique. Their results established that SLNB is a technically feasible and is a promising, minimally invasive method for staging the regional lymphatics in patients with stage N0 HNSCC. Recently a study was conducted by Murer k et al in 2011, to compare the morbidity between SLNB and ELND for treatment of the N0 neck in patients with oral squamous cell carcinoma. Sixty-two consecutive patients were included from 2000 to 2009. Two groups were analyzed consisting of 33 patients after SLNB and 29 after elective neck dissection. Subjective impairment and functional shoulder status were assessed with the Neck Dissection Impairment Index (NDII) questionnaire and the modified individual relative Constant Score. Postoperative complications were retrieved from the clinical charts. They established that SLNB is associated with significantly less postoperative morbidity and better shoulder function than elective neck dissection [25].

In 2012, a study was conducted by Gurney BA et al. to assess the implications of a positive sentinel node in oral squamous cell carcinoma. Patients with positive sentinel nodes were investigated to establish if additional metastases were present in the neck, their distribution, and their impact on outcome. In all, 109 patients (n = 109) from 15 European centers, with cT1/2, N0 tumors, and a positive sentinel lymph node were identified. The results are preliminary but suggest that both the number and the position of positive sentinel nodes may identify different prognostic groups that may allow further tailoring of management plans [26].

Civantos et al [27] found the procedure of SLNB to be extremely safe. No shoulder symptoms, lip asymmetry, contour changes, or other unexpected side effects were seen following SLNB in 106 patients in the University of Miami.

Advantages of sentinel lymph node biopsy

It is a minimally invasive technique which prevents the unnecessary removal of the functional lymph nodes and provides valuable treatment insights without the side effects of neck dissection surgery [28].

Another advantage is its ability to identify skip metastases and unpredictable lymphatic drainage pattern. Civantos et al. conducted a study in 2006

which revealed that 14 out of 103(13.6%) cases had sentinel lymph nodes outside expected lymph node basins, which would not have been dissected with standard lymphadenectomy [29]. Skip metastases was also reported by Byers et al [30] to occur in about 16% of oral tongue lesions.

SLNB is also beneficial in relation to the pathologic handling of the specimen as compared to neck dissection surgery. END delivers quite a few lymph nodes which may increase the likelihood of missing micrometastases. The small number of lymph nodes harvested with SLN biopsy provide the benefit of step sectioning of the entire SLNs followed by systematic staining with H&E and immunohistochemistry thus improving the identification of microscopic disease [27]. This also saves the time and expense required to perform such an analysis on full lymphadenectomy specimen. Thus, decreased morbidity, improved identification of skip metastases, and improved histologic evaluation of surgical specimens are all advantages of SLNB [28].

Limitation of sentinel lymph node biopsy

The main limitation is the need for additional treatment when the sentinel nodes turn out to be involved in metastases. Another pitfall is its inadequate accuracy in identifying true sentinel nodes in the patients with tumors of the floor of the mouth. According to most authors, this may be due to close proximity of level I and IIa nodes to the primary tumour which may lead to shine through radioactivity, thus masking signal from the relevant sentinel node(s) [27, 31]. The proficiency and comfort of the surgeon may pose another limitation [29]. The blue dye used in SLNB may elicit allergic response in some individuals.

SLNB vs. ELND in clinically negative and pathologically positive neck nodes patients (c N0 p N1) ELND is associated with certain amount of morbidity in terms of XI cranial nerve transection, marginal nerve injury, and chyle leak. Furthermore, no clear survival benefit has been shown with ELND [8].

L.P. Kowalski, A. Sanabria, have done a critical review on ELND in oral carcinoma in 2007 and they have stated that the number of negative elective neck dissections could be as high as 80%. The recent introduction of SLNB in oral cavity tumours, used to better select candidates for neck dissection, appears to be a good alternative [19].

To determine the differences between SLNB and ELND in terms of function, postoperative morbidity and quality of life (QOL) measures, Schiefke et al [32] did a comparative study. They retrospectively reviewed 49 patients with OCSCC and a cN0 neck. Twenty-four patients received only SLNB whereas 25 patients received SND. Statistically significant findings for SLNB 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.

Radiopharmaceuticals

With time, a variety of colloidal and soluble tracers have been introduced for lymph studies. The main radiopharmaceutical used in European studies of sentinel node localization in oral cancers is Tc-99m labelled human serum albumin colloid (Nanocoll) (GE Healthcare). Nanocoll has a particle size range of 5–80 nm, with a reported mean size of 8–30 nm [33]. Although in theory a larger particle such as Albures (GE Healthcare) or Senticint (Medi-Radiopharma) may be preferred for tumors in the floor of mouth or anterior tongue where lymphatic densities are high, Nanocoll performs satisfactorily in all tumour types studied [34]. Nanocoll migrates to the sentinel node within minutes, yet prolonged retention allows surgery to take place the following day. Other radiocolloids which have been used include Tc-99m rhenium sulfide colloid (Nanocis, IBA), which has been shown to have a mean particle size of 23–25 nm [35]. Tc-99m sulfide colloid has also been used. While there are currently no clinical studies comparing different radiopharmaceuticals, investigators have described satisfactory results with each of the available colloids [36, 37].

Recent advances in the field of sentinel lymph node biopsy

The major challenge in SLNB lies in optimizing intraoperative visualization of sentinel nodes. The development of a gamma camera with a multilane

detection system (e.g., two heads) might enable real-time three-dimensional visualization. Furthermore, the development of new tracers or a slower migrating alternative to patent blue might improve the direct intraoperative localization of sentinel nodes in the neck. Another option may be the development of a dual-tracer, which contains radioactivity as well as colour and can be used for lymphoscintigraphy and intraoperative visual and auditive (gamma probe) at the same time.

Lymphoseek (Neoprobe Corp.; Dublin, OH), is a recently introduced reagent, which addresses the limitations of SLNB in relation to floor of the mouth primaries and delayed detection of secondary sentinel lymph nodes. Lymphoseek is a dextran-based product modified to allow labelling 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. Over the next years, the use of SPECT/CT might become routine procedure for patients with planar images which are difficult to interpret [28].

CONCLUSION

SLNB is a minimally invasive technique used for c N0 p N1 patients, that reduces the morbidity associated with ELND. Instead of removing several lymph nodes and examining all of them for cancer, it is more conservative to remove the ones that are most likely to harbour metastases. If the sentinel node does contain cancer, another treatment step may be needed. The use of preoperative planar lymphoscintigraphy and an intraoperative hand-held gamma probe results in excellent sentinel node-detection rates. Thus it can be concluded that SLNB offers a reliable, safe, and individual treatment plan for each patient's unique lymphatic drainage pattern.

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