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IMPORTANCE OF SENTINEL LYMPH NODE BIOPSY IN ORAL CANCER - A REVIEW

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ABSTRACT
The status of the regional lymphatics is one of the most important prognostic parameters in patients with head and neck cancer for treatment and survival. Currently popular approach to the problem of node dissection associated morbidity is to restrict node biopsy to one or a very small number of nodes—a technique known as sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) is defined as the lymph node on the direct drainage pathway from the primary tumor. In the past decade, the technique of SLNB has been applied to a vast array of primary neoplasm, ranging from head and neck melanoma to vulvar carcinoma. Multiple validation studies in the context of elective neck dissections revealed sentinel node detection rates above 95% and negative predictive values for negative sentinel nodes of 95%. Lymphoscintigraphy (LSG) and gamma probe-guided localization have emerged as useful techniques for identification of the SLN later confirmed with histologic and immunohistochemical analysis. SLNB is a cost-effective technique but its use in clinical practice is still limited. SLNB in head and neck squamous cell carcinoma (HNSCC) is probably considered a best investigational technique and its role continues to generate considerable debate at this time.

KEYWORDS: Cancer, Lymphoscintigraphy, Melanoma, Neck dissection, Sentinel Lymph node.

INTRODUCTION
Oral cancer is considered an important part of the global burden of cancer.[1] Its occurrence happens to be particularly high in India, credited to the addictive habits of the people along with the ethnic and cultural aspects. Causative factors include tobacco and tobacco related products, alcohol, genetic predisposition and hormonal factors.[2,3] As one of the most important prognostic factors, lymph node status has to be determined in patients with newly diagnosed OSCC. Routine staging includes physical examination, ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI), whereas fluorodeoxyglucose (FDG) positron emission tomography (PET) is not standard of care in many institutes. US-guided fine-needle aspiration cytology (USgFNAC) appears to have a higher sensitivity for the detection of occult lymph node metastases, but reported sensitivities vary largely around 50%. In any event, these staging procedures are not accurate enough for the final determination of the nodal status, mainly due to their reduced sensitivity for small (occult) metastases.[4,5] If the status of the neck is assessed by palpation alone, most sites and stages of HNSCC qualify for elective treatment on this basis. For most patients, however, this policy results in overtreatment of the neck. Much effort has been directed to increase the accuracy of the assessment of the N0 neck. Despite of other methods, sentinel lymph node (SN) biopsy has been proposed as a potential alternative for staging of the N0 neck.[6,7] The SN concept is based on the theory of orderly progression of tumor cells within the lymphatic system. This so called sentinel node will be the first lymph node to receive metastatic tumor cells. The SN concept assumes that lymphatic metastases, if present, will always be found at least in the SN. A tumor-negative SN would preclude the presence of other regional metastases.[8,9] In large clinical studies of patients with breast cancer and malignant melanoma, preoperative SN identification by LSG and subsequent SN biopsy has been shown to be an accurate staging technique.[10,11] This article brief's about importance of SLNB and its effectiveness in treating oral malignancies in the day today practice.

HISTORY
LSG and SLNB were first reported by Cabanas in 1977 for use in penile cancer. Since then, the concept of sentinel lymph node biopsy has been extensively studied

and validated for patients with cutaneous melanoma and breast cancer.[3] In 1992, Morton et al refined the technique and used it for the staging of disease in patients with intermediate-thickness malignant melanomas. In 1996, Alex and Krag were the first to report the use of SLNB for HNSCC.[12]

PROCEDURE

Radiolocalization of the SN consists of a preoperative LSG and the intraoperative use of a hand-held gamma probe. Radiolabeled colloid solution is injected around the primary tumor and drains along the afferent lymphatics to the first-echelon lymph nodes, where it accumulates and may be visualized using a gamma camera. Such a camera provides real-time imaging of the SN and can detect and localize those nodes, even if located near the injection area. A gamma camera increases certainty about the accuracy and completeness of the excision of the radioactive nodes, since it facilitates postexcision monitoring.[11,14,26] A variety of 99Tcm-labeled colloids are commercially available; however, availability varies between countries and licensing issues may dictate the colloid used.[15] LSG imaging can be either static or dynamic, and there is no evidence to favor either technique. Outside of the primary injection site, all other visualized areas of focal increased uptake should be considered SN regardless of the sequence they arise. Anterior and lateral plane views should be obtained, and oblique planes may be helpful in difficult cases.[12] This allows for safe and reliable SLN detection with a previously published SLN detection rate of 96%. Indelible marker should be used to mark the skin overlying any visualized SLNs. The emergent technology of single photon emission computed tomography with CT (SPECT/CT) has recently become available in some centers. A benefit of SPECT/CT over dynamic planar LSG alone has been described in preliminary reports, particularly for carcinomas in close proximity to the lymph node basin, such as the floor of mouth. While SPECT/CT undoubtedly affords the surgeon better topographical orientation and delineation of SLNs against the surrounding anatomy, it has not been consistently shown to influence the outcome of the procedure. This was demonstrated in a recent comparison of SPECT/ CT with planar LSG, with no differences observed in the SN identification rate between the groups. While planar LSG appears sufficient for successful lymphatic mapping, the additional data provided by SPECT/CT may aid the surgeon with three dimensional orientation.[11,13] In order to ensure detectable radioactivity levels, SLNB should be performed within 24h of radiocolloid injection. The initial incision should be placed according to the preoperative LSG, skin markings and relaxed skin tension lines and should be positioned to allow easy excision of the scar in the event of a subsequent neck dissection.[12] The preoperative LSG images should be available in the operating theatre and the initial dissection should be directed by these. A hand-held gamma probe fitted with a 14 mm diameter collimated probe is also used, with excision of all "hot" (radioactive) nodes. The surgical bed should be free of radiation at the end of the procedure, as detected by the hand-held gamma camera.[14,24] When no radioactivity is present, the neck can be closed. In SNB, the number of lymph nodes to be examined is considerably reduced relative to elective neck dissection, leading to a reduction in workload for the pathologist and potentially allowing more in-depth evaluation.[13]

HISTOPATHOLOGICAL ASSESMENT

The optimum level of sectioning has not yet been elucidated, and it has previously been shown that more extensive sectioning of neck dissection specimens also increases the detection of occult disease[7]. The current recommendation, formulated at the Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer in 2003, is step-serial sectioning of the entire SLNs at intervals of 150 micrometer.[13] Hematoxylin and Eosin staining is standard, and immunohistochemistry with cytokeratin staining must also be available for further processing of SLNs that appear negative on H&E.[23] The term "occult metastasis" refers to any histologically detected lymph node metastasis in a patient with a clinically node-negative neck. These include metastases, micrometastases, and isolated tumor cells (small clusters of tumor cells within the lymph node sinuses; referred to as ITC), which are distinguished according to well-defined histologic criteria as described by Hermanek et al[16] The sixth edition of the TNM classification of malignant tumors defines ITC as "single tumor cells or small clusters of cells not more than 0.2 mm in greatest dimension that are usually detected by immunohistochemistry or molecular methods, but which may be verified with H&E stains. ITC do not typically show evidence of metastatic activity (e.g., proliferation or stromal reaction) or penetration of vascular or lymphatic sinus walls".[13] Micrometastases are tumor deposits <2 mm, while metastases are >2 mm, and both represent infiltrations of the lymph node parenchyma. While the prognostic and therapeutic implications of these distinctions remain largely unclear, the classification has been proposed and accepted for use in the context of SNB for oral and oropharyngeal SCC.[7,17] One might speculate, if neck dissection could be omitted in patients with ITC only in the sentinel nodes.

GENERAL INDICATIONS FOR SPECT/CT IN SENTINEL LYMPH NODE BIOPSY

As sentinel node mapping in the head and neck region is used for lymph node staging, only patients with clinically and radiologically negative lymph node assessment (stage N0) are considered for this procedure. The exact role of lymph node staging with SLNB in oral cancer has not been clearly defined yet, though several authors use the procedure to stage T1 or T1 and T2 lesions.[18] The indications for SNB in OSCC are threefold: First and most commonly, SNB is undertaken in order to stage the ipsilateral cN0 neck in the setting of a unilateral primary

tumor. Second, SNB may be used to assess bilateral cN0 necks in the setting of a primary tumor close to or crossing the midline. The Final indication is for evaluation of the contralateral cN0 neck in a patient with a primary tumor close to or crossing the midline, and an ipsilateral cN+ neck. In such patients, SNB may be used to aid the choice between a unilateral or bilateral neck dissection.[13] A diagnostic meta-analysis by Paleri et al. showed a good sensitivity (92.6%) of the sentinel node procedure in squamous cell cancer of the oral cavity an oral pharynx, while Civantos et al. found a negative predictive value of 96% for this procedure. If enlarged lymph nodes are found by physical examination or ultrasound aspiration cytology, the presence of nodal metastases can be confirmed and patients can proceed to selective or (modified) radical neck dissection. Controversy exists regarding the appropriate indication for sentinel node biopsy in melanoma and squamous cell carcinoma. The indication for sentinel node mapping in melanoma generally depends on the Breslow thickness of the tumor, although ulceration and other prognostic factors might also be taken into account. In thin lesions, the low risk of finding nodal metastases can be a reason to omit sentinel node staging and many authors do not use sentinel node biopsy in such lesions (e.g., less than 0.75mm or less than 1.0mm). In thick lesions, the high risk of synchronous distant metastases may outweigh the possible therapeutic and prognostic benefits of lymphadenectomy or sentinel node mapping.[4,18] Two large prospective clinical observational trials of SNB in OSCC have been published to date. The first, a European multicenter trial based at the Cannies burn plastic surgery department in Scotland, described the outcomes of SNB in 134 cT1/2 cN0 patients from six institutions. The authors reported a 93% SN identification rate and 93% sensitivity for the SNB procedure at 2 years of follow-up in 2004 and 91% sensitivity and negative predictive value of 95% after 5 years of follow-up. Both the SN identification rate and sensitivity were found to be significantly poorer for patients with tumors in the floor of the mouth, where access to the primary tumor may prove difficult and the first-echelon lymph nodes lie in close proximity, potentially masking their position. The second study represents the largest single-institution experience published to date, describing a series of 51 consecutive patients with cT1/2 cN0 OSCC. The sentinel node detection rate was 98%, and 40% of patients were upstaged by SNB. There were two patients with false-negative SNBs and the negative predictive value was therefore 94%. All patients with positive SNB were treated with a therapeutic selective neck dissection of levels I–III for oral cavity primaries, and levels II–IV for oropharyngeal SCC. Based on these results, the authors advocate that SNB may be reliably used as the sole staging procedure in this patient group, and SNB-positive patients may be safely treated surgically without postoperative radiotherapy.[13]

ADVANTAGES

The main advantage of the technique is, it prevents the unnecessary removal of the functional lymph nodes and thus provides valuable treatment insights for the patients without the side effects of neck dissection surgery. Another advantage is its ability to identify skip metastases and unpredictable lymphatic drainage pattern.[3] 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.[19] Skip metastases was also reported by Byers et al 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.[20] 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 provides 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. This also saves the time and expense required to perform such an analysis on full lymphadenectomy specimen. Decreased morbidity, improved identification of skip metastases, and improved histologic evaluation of surgical specimens are all advantages of SLNB.[3,7,21]

LIMITATIONS

However, the technique is not without drawbacks. 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 tumor which may lead to shine through radioactivity, thus masking signal from the relevant sentinel node(s). Another drawback is that SNB with respect to the primary tumor size. Large tumors are difficult to completely surround with the tracer injection, and show a tendency to drain to multiple lymphatic basins.[4,22] This technique only has therapeutic value in patients with positive nodes. Failure to detect cancer cells in the sentinel node can lead to a false negative result — there may still be cancerous cells in the lymph node basin.[6,7,24] The delay between SNB and traditional pathological processing necessitates a second surgical procedure for SNB-positive patients—a significant disadvantage to the SNB technique. To circumvent this, several groups have investigated the accuracy of frozen section analysis of SLNs and, despite concerns regarding freezing artifacts, loss of tissue and high expenditures of labor and time, results have proven encouraging.[7, 13]

RADIOPHARMACEUTICALS

There is variety of colloidal and soluble tracers available which have been introduced for lymph studies. The main radiopharmaceutical used in European studies of SN localization in oral cancers is Tc-99m labelled human

serum albumin colloid (Nanocoll) (GE Healthcare) which is having a particle size range of 5– 80 nm, with a reported mean size of 8–30 nm. Although in theory a larger particle such as Albures (GE Healthcare) or Sentiscint (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 tumor types studied.[15,25] 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- 99 m rhenium sulfide colloid (Nanocis, IBA), which has been shown to have a mean particle size of 23–25 nm. Tc-99 m sulfide colloid has also been used[3]. In Europe, most frequently ^{99m}Tc-nanocolloids are used, whereas in the USA filtered ^{99m}Tc-sulphur colloids are common. The injected activity recommended by the practice guidelines ranges from 15 to 120 MBq in 0.4–1.0 ml depending on the intended time interval between injection and surgery. ^{99m}Tc-tilmanocept (^{99m}Tc-diethylenetriaminepentaacetic acid-mannosyl-dextran), a dedicated tracer for SLNB, binds specifically to mannose receptors (CD206) expressed within lymph nodes. Promising results, including fast drainage from the injection site, no drainage to second echelons and specific binding over 30 h, were shown in phase III trials in patients with melanoma and breast cancer. Due to the complex drainage and close proximity of the injection site and SLNs, these characteristics of ^{99m}Tc-tilmanocept are of great interest in OSCC patients. ^{99m}Tc-tilmanocept has been examined in 20 patients with oral cancer using elective neck dissection as reference standard. The NPV in this cohort including five patients with tumors of the floor of the mouth was 100 %. Using histopathological examination of the neck specimen as reference standard, a recent study of 85 head and neck cancers (93 % OSCC) showed a detection rate of 97.6 %, a sensitivity of 97.4 % and an NPV of 97.8 %. This tracer has recently been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in OSCC.[4]

COMPLICATIONS

The overall risk of complications from SLN biopsy is low with adverse events rarely reported. Risks include allergic reaction and anaphylaxis to the blue dye used intraoperatively. Others like lymphedema, wound dehiscence, hematoma, seroma, cutaneous lymphatic fistula, wound infection and dehiscence have also been reported.[11]

CONCLUSION

Sentinel node biopsy is increasingly being used to provide accurate staging in early stage head and neck malignancies. Lymphatic mapping in the head and neck area can be complicated because of the complex anatomy and variable drainage patterns in this area and easy obscuration of sentinel node by the primary injection site. Despite of false-negative results, SLNB has proven as safe & accurate method which prevents unnecessary removal of uninvolved lymph nodes. Since, majority of validation studies have compared SNB to the gold standard, its application may define patient populations a new standard of care and aid in better prognosis.

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