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REVIEW ARTICLE

Application of Sentinel Node Biopsy to Non-oral Head and Neck Cancer

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ABSTRACT

Cervical lymph node status is a significant prognostic factor for all patients with head and neck cancer. There is still ongoing deliberation on the extent of surgical therapy to offer patients, particularly those who have a clinically negative (cN0) neck. Currently, preoperative examination and investigation [routinely ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)] are utilized for treatment planning and the extent of surgery based on evidence of metastatic spread or perceived risk of occult metastasis.

It has been shown that that sentinel node biopsy (SNB) is a reliable staging test to detect occult metastases in early oral carcinoma, and its routine use has been advocated in the UK by the National Institute of Health and Clinical Excellence (NICE). Sentinel node biopsy can be used in most solid tumors that spread via lymphatics but its application to extraoral head and neck malignancies (other than primary skin tumors) has not been widely reported. In this article, we review the potential application of SNB in new areas of the head and neck.

Keywords: Laryngeal cancer, Metastasis, Neck dissection, Salivary cancer, Sentinel node, Thyroid cancer.

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INTRODUCTION

Almost one-third of the body's lymph nodes are found in the head and neck region.[1] Locoregional metastases to these lymph nodes reduce survival by up to 50%[2] not only for patients affected by oral cancer but also thyroid, laryngeal, and salivary malignancies.

The SNB, initially a novel concept, was accepted into routine clinical practice following the work of Morton et al.[3] in relation to malignant melanoma. The SNB was subsequently evaluated and applied to staging of breast, colonic, urogenital, lung, and head and neck cancers.

Sentinel node biopsy works on the principle that primary tumor sites are lymphatically drained in a sequential manner, the first node or group of nodes to drain a site are known as the sentinel node(s) (SN). Identification, harvesting, and detailed pathological examination of the SN allow accurate detection of micrometastatic deposits (negative predictive value 94%[4]) and the decision for further lymph node dissection is based upon SN status. The standard applied is that if the SN are free from disease, then more distal disease is unlikely, thus in head and neck cancer, completion neck dissection is judged unnecessary following a negative SNB.

TECHNIQUE AND DEVELOPMENT IN ORAL CANCER

The standard technique of SNB involves a preoperative peritumoral injection of ^{99m}Tc-labeled colloid tracer often together with an intraoperative tumoral injection of blue dye or fluorescent tracer (indocyanine green) to enhance visual detection of SNs.[5-8] Preoperative lymphoscintigraphy is performed within 24 hours prior to surgery and the position of identified SNs marked externally. During surgery, SN are identified by gamma probe detection of radioactivity and these "hot" or blue/fluorescent nodes are harvested for intensive pathological examination. Each SN undergoes serial step sectioning at 150 µm intervals followed by immunohistochemical staining, allowing identification of micrometastatic deposits and viable isolated tumor cells.

A multicenter European trial (The Sentinel European Node Trial—SENT) was conducted (2005–2010) in which 415 patients with cT1/2N0 oral squamous cell carcinoma underwent SNB as staging followed by neck dissection only if positive. The 3-year results showed overall survival of 88 with 23% of patients upstaged by the test. The SNB had a sensitivity of 86%, and a false-negative rate (FNR) of 14%.[4] The SNB was recognized as a safe and reliable procedure associated with minimal short-term morbidity (seroma, hematoma, local infection, and lymphedema).

In 2016, the UK's NICE performed cost-effectiveness analysis of SNB in oral cancer, recommending that it should be offered to all patients with a clinically

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N0 neck who do not require simultaneous microvascular reconstruction.[9]

There is potential to apply SNB to nonoral cancer patients with clinically N0 necks in an effort to ensure that they can be individually managed according to their tumor site. The evidence for this is further discussed below.

SALIVARY CARCINOMA

Salivary gland malignancy represents 0.3% of all cancer types. Because of the diversity and scarcity of salivary tumors, there is a deficit of high-level evidence regarding treatment, a fact recognized by recently published UK management guidelines.[10] The rate of occult metastases in salivary malignancy is 10–30%[11-13] and in many cases, the metastatic nodes are located outside the traditional neck dissection fields. Up to 75% of positive nodes are intra- or periparotid[11] and there is a recognized tendency to "skip-metastases" in levels III and IV without involvement of more proximal nodes.[13]

Despite Gould et al.'s[14] report of SNB in salivary gland disease, there has been little advance in the topic over the last 50 years. His series of 28 patients with parotid tumors had the "angular node" subjected to frozen section analysis in order to decide if radical neck dissection was necessary. There were major limitations to his approach: Gould did not use any tracer to map the lymphatic flow but assumed that the SN would be the same in each case, and on final histopathology, 20 of the 28 cases were benign. In total, three of the malignant cases had positive SNs. Despite these flaws, his approach served as the foundation for the development of SNB in other areas of the body, but use in salivary malignancy stalled.

In 2006, a case series of six patients with parotid carcinoma was reported.[15] The authors used ^{99m}Tc-labeled nanocolloid (50 MBq) injected at eight sites around the tumor. A SN was identified on static lymphoscintigraphy within 10 minutes of injection in all patients. The study group underwent SNB and concomitant levels II–IV or V neck dissection depending upon the location of the SN. Positive SNs were found in two patients and in one, there was a false-negative result. In this case, the false-negative result was attributed to an intraglandular metastatic node disrupting drainage. Lymphoscintigraphy images from this study show that the entire gland was hot, presumably due to the large number of peritumoral injections given. This combined with the poor anatomical detail gleaned from static lymphoscintigraphy would certainly preclude the identification of intra- and periglandular nodes, thus reducing the sensitivity of the technique significantly.

More recently, two case reports looked at modern techniques in salivary SNB. Schilling et al.[16] used navigation surgery in parotid malignancy (Fig. 1) and Moreno et al.[17] in adenocarcinoma of a minor salivary gland, where negative SNB resulted in conservative surgical management and avoided neck dissection without affecting outcome.

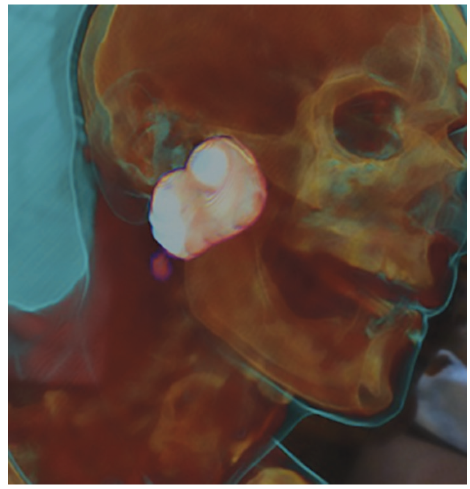

Fig. 1: Three-dimensional single photon emission CT (SPECT) projected onto patient at time of surgery demonstrating right parotid gland sentinel node identification

This limited evidence indicates that SNB can be applied to salivary neoplasms, but multicenter long-term trials are required to evaluate the true SN detection rates (which may vary depending on tumor site and epithelial origin) with identification of FNR by concurrent neck dissection or longer-term follow-up with clinical and radiological surveillance. The foreseen difficulty in evaluating this group of patients is that often postoperative radiotherapy (RT) is recommended for features of the primary tumor and the rate of nodal relapse due to false-negative SNB result may be underestimated.

THYROID CARCINOMA

Thyroid cancer is the most common type of endocrine malignancy, and constitutes 1.7% of all malignancies worldwide. The incidence of thyroid cancer has increased over the last three decades, but cure rate for differentiated thyroid cancer (DTC) remains high with an 80–90% 10-year survival rate, even in patients with regional metastatic disease.

Occult lymph node metastasis is thought to occur in 20–50% of DTC;[18] however, the significance of this spread is debatable. Most patients will receive postoperative radioiodine, which ablates both residual thyroid tissue and metastatic disease. This offers excellent tumor control, but there is a small subset of patients who relapse. Criteria for these "high-risk" patients include male gender, age over 45 years, tumor over 4 cm, and extracapsular or extrathyroid disease. Elective central neck dissection (clearance of levels VI and VII) is recommended in high-risk patients, although the procedure is associated with an increased risk of recurrent laryngeal nerve damage and hypoparathyroidism.[19,20] On the opposite end of the spectrum, there are clinical trials in progress looking at whether patients with low-risk disease can be spared iodine treatment.[21]

There is lack of consensus about the extent of lymph node sampling required to stage both high- and low-risk patients, to which SNB may offer a solution.

Two meta-analysis reviews have looked at the use of SNB in thyroid carcinoma staging. The first analyzed 14 studies with a pool of 457 patients. A key conclusion drawn was that the type of tracer used (^{99m}Tc-Colloid *vs* Blue dye) played an important role in SN detection rate and overall, the use ^{99m}Tc-Colloid yielded a 13% higher detection rate.[22] This review did not consider SN detection rates among studies, or how the presence of a positive SN could predict likely further nodal disease or represent skip metastases. It also failed to consider complications associated with the SNB procedure and was unable to comment on the longer term clinical implications of staging using SNB (such as recurrence), but described the practicality of the technique—which was demonstrated as feasible. A second meta-analysis by Balasubramanian and Harrison[23] included 24 cohort studies evaluating the efficacy of sentinel lymph node biopsy (SLNB) in papillary thyroid cancers. This analysis yielded an overall combined SN detection rate of 86%; however, of note, the majority of included studies used blue dye alone for detection which was by this time already shown to be less efficacious at detecting SLN. Analyzed data also acknowledged that with the use of SNB, central END could have been avoided in 57% of cN0 patients.[23] In addition, 23% of cN0 patients were found to have a positive SN in the lateral neck compartment and in 15% of these patients, this was the only identified SN,[23] further raising two further clinical considerations regarding whether the extent of prophylactic elective neck dissections in this group of patients is enough and the question of when lateral neck compartment dissection should be performed.

Data on FNR for detection of metastases in lymph nodes varied greatly between studies, mostly reflecting the variation in nodal examination methods (serial section, immunohistochemistry, or frozen section) with combination of serial section and immunohistochemistry showing the highest sensitivity range from 84 to 100%.[24,25]

A third review[26] concluded that SNB additionally identifies positive nodes outside of the central compartment allowing for more rigorous individual surgical and extension of lymphadenectomy if required.[26] In this scenario, SNB could help stratify patients with local metastatic disease who would benefit from Iodine ablation therapy *vs* avoidance of iodine ablation in low-risk or neck-negative patient groups. Heterogeneity between the majority of available studies unfortunately means that clear conclusion and firm treatment protocol cannot be identified as of yet.

Of notable mention, a recently published cohort study of 42 patients evaluated the use of single-photon emission computed tomography (SPECT)/CT lymphoscintigraphy and SNB in early T1/2 papillary thyroid carcinomas in cN0 patients.[27] The method which echoed methods now used in oral cancer gleaned very promising results, demonstrating that lymph node metastasis occurred in 46%, of which 18% were located in the lateral neck compartments and that central node dissection could be avoided in 44.6%. A true FNR could not be obtained, as routine central neck dissection was not performed on all patients; however, local compartments where SN were identified were cleared and based on this, an FNR of 8.1% was identified. This study revealed that 37.8% of patients would have been understaged, if conventional methods alone were used to evaluate the neck compartments.

LARYNGEAL CARCINOMA

The treatment of laryngeal cancer is dependent on tumor size, with the emphasis upon preserving function. Small tumors (T1–T2) can be treated by RT, transoral laser microsurgery, or transoral robotic surgery. Traditionally, more advanced tumors (T2b-3) are offered chemoradiotherapy; however, certain cases may be suitable for function-sparing surgery, such as vertical partial laryngectomy. In node-positive disease, it is recommended[28] that levels II to V should be treated on the involved side. Elective treatment of the N0 neck is recommend in T3 and T4 disease. Radiotherapy or surgery ± postoperative RT is provided to at least lymph node levels II, III, and IV bilaterally.

The incidence of occult cervical metastasis laryngeal cancer is proportionally related to the T staging and in T3/T4, disease is reported as 21.4–78%.[29-31] Furthermore, there is a known association of risk of occult metastasis to site of primary tumor with the highest incidence in supraglottic (40%), followed by subglottic (30%) and glottis carcinomas (10%).[32]

Although the reported range is wide, it is likely patients are undergoing unnecessary treatment with the additional burden of both sides of the neck being affected. Additionally, there is controversy over the management of paratracheal nodes which are found to harbor occult metastasis in 9–27% of cases, but do not form part of the routine neck dissection.[33]

Several studies have evaluated the use of SNB in laryngeal carcinoma.[32,34-38] These publications have typically included small study populations (10–50 participants) of previously untreated patients focusing on one subsite, or included all laryngeal subsites and some with inclusion of oral data. Further differences between these studies included the method of primary tumor control and SN detection (Table 1). As a result of these studies, it has been

Table 1: Comparison of sentinel node studies in laryngeal cancers in the clinically N0 neck

Study	*Tumor site(s)*	*Participants (laryngeal primary/ total population)*	*Method*	*SN detection rate (%)*	*Sensitivity (%)*	*FNRs (%)*	*Occult neck metastases rate (%)*
Flach et al.[32]	Supraglottic, glottic, transglottic	13/19 previously untreated necks 6/19 previously treated	• Primary or recurrent laryngeal cancer, rN0 • Patients underwent total laryngectomy ± uni- or bilateral SND • Intraoperative injection of tracer with SN detection *ex vivo* with neck specimen by gamma probe post-END (5–6 hours postinjection)	68.4 (previously untreated neck)	80 (previously untreated neck)	7.7%	18
Yoshimoto et al.[34]	Oral (157), larynx, and hypopharynx (20)	20/177	• Retrospective analysis • Preoperative SN detection with lymphoscintigraphy ± SPECT-CT, intraoperative detection with gamma probe, and frozen section analysis • Patients underwent immediate neck dissection based on frozen section results	100	100	6.9	9.3%
Cheng et al. 2010[35]	Larynx (40) and hypolarynx (10)	40/50	• Comparison study assessing SN detection rates of SPECT-CT and blue dye lymphoscintigraphy	82 (radioactive tracer) 66% (blue dye)	83.3	Not reported	24
Lawson et al.[36]	Supraglottic (29)	29/29	• Prospective analysis • Primary T1–T3 supraglottic tumors, c+rN0 neck. SN identification with gamma probe, all patients underwent synchronized bilateral MRND with primary site CO_2 laser resection	100	100	3	48 (based on MRND detection)
Li et al.[37] 2009	Laryngeal and hypolarynx	45/45	• Primary T1–T4 N0 tumors • Radiotracer injection with lymphoscintigraphy 2 hours later and intra-operative identification 10–12 hours postinjection with a gamma probe • All hot nodes harvested as SLN and analyzed • All patients underwent END and primary tumors were resected depending on location and T stage	92.7	93.7	6.3	29
Tomifuji et al.[38] 2008	Laryngeal and hypolarynx	20/20	• T2-T4 c and rN0 necks • Tracer injection and scintigraphy were performed the day before surgery, with SN marked externally on skin • Total or partial laryngopharyngectomy plus either MRND or END was performed, where primaries crossed the midline or SNs were found in the contralateral neck and contralateral ND was added	100	83	7	30
Werner et al.[39] 2004	Oral, oropharynx, larynx, and hypopharynx	44/90	• Tumors were injected intraoperatively and SN identified with a gamma probe • Uni- or bilateral ND was completed followed by resection of the primary tumor	100	96.7	3.3	22.2
Hoft et al.[40]	Oral, tonsil and laryngeal	12/50	• Initially radiocolloid injected on the day of operation with preoperative scintigraphy; after May 2002, injections all made intraoperatively. Node detection made after cutaneous flaps and muscle retracted using a gamma probe. Following SNB, END was continued	92	Not reported	Not reported	Not reported
Werner et al.[41]	Oropharynx, larynx and hypopharynx	14/50	• rN0 necks (confirmed by ultrasound scanning) • Previously untreated necks • Tracer was injected at the start of the procedure and SLN detected between 2 and 6 hours later during END	100	89	2	18

MRND: modified radical neck dissection

suggested that use of SNB may be better placed in patients undergoing transoral procedures rather than open surgery to avoid complications from a second surgery in the neck in the event of a positive SNB.[32] Most of the studies reviewed used a reference of application of the SN concept in the clinically N0 patient and the majority of studies concluded that negative SN accurately concurred with pathological neck staging. However, one limitation for use of SLNB in laryngeal carcinoma patients may be the ability to inject radiotracer accurately around the margin of the tumor. Hoft et al.[39] weakly established this in their study of 50 participants, in which four patients who underwent incomplete peritumoral tracer injection were excluded following the finding that all nodes accumulating tracer were identified as negative for disease with two patients (50%) being found to harbor occult neck disease. Thus, it can be deduced that in patients where the caudal margin cannot be accessed for tracer application, the FNR of SNs biopsied may be increased and, as such, these patients may not be eligible for the staging technique. Studies since have sought to improve access to this margin and have developed application methods of use of winged butterfly cannulas.[32] Caution is recommended in cases of difficult tumor visualization, where elective neck dissection may be indicated. In cases of more advanced laryngeal tumor staging (T3–T4), more evidence is required to show the advantage of a staged SN procedure over a one-stage primary tumor resection and elective neck dissection.

SUMMARY

The SNB has sound physiological basis that applies to solid tumors that spread via the lymphatic route. The technique has been described by many as in its infancy in tumors of the head and neck, but has shown great potential to answer some of the management-related controversies as outlined earlier. The promise of reducing treatment-related morbidity through harnessing technology to provide individualized treatment embodies the ethos of 21st-century medicine in the developed world. However, there are a number of potential areas where the SNB technique can be improved. Presently in oral cancer, the FNR of SNB is 14%. In contrast, the equivalent failure rate of elective neck dissection is reported between 6% and 18%,[40-44] with most papers reporting neck recurrence after END in the pN0 neck to be ≤12%.[45] On balance, a slightly higher failure rate may be accepted for SNB in return for the improved morbidity and treatment cost, but ideally, it should be explored if it is possible to reduce the FNR to a level that is the same or better than the alternative treatment.

In terms of application to other solid head and neck cancers, there is more varied evidence. Certainly in the case of salivary gland tumors, isolated cases and small series have demonstrated that SLNB is a feasible technique and may even allow for a more conservative surgical approach to this heterogeneous group of tumors. Currently, however, there is a vast deficit in evidence supporting its use as a diagnostic tool in staging for these tumors and further large population trials are required to evaluate its potential value.

The use of SNB in thyroid and laryngeal carcinomas has been more widely evaluated and it has been well demonstrated that the use of SNB as a diagnostic tool can lead to more accurate staging of patients. It is of note, however, that larger, multicenter studies similar to the SENT trial have yet to be published for thyroid and laryngeal cancers and moving forward, it is what is required in order to wholly evaluate the use of a standardized technique in these patient groups and how results may impact and change the current conventional methods of surgical treatment.

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