Is there a role for lymphoscintigraphy and sentinel node biopsy in the management of the regional lymphatics in mucosal squamous cell carcinoma of the head and neck?

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Introduction

Few data currently exist regarding the utility of the techniques of lymphoscintigraphy and sentinel node biopsy in mucosal squamous cell carcinoma of the head and neck. The available data are further reduced when considering certain anatomical sub-sites within this region, particularly the hypopharynx, larynx and upper oesophagus. Indeed, the largest body of evidence relates to the oral cavity and oropharynx, which in itself is not surprising as these are the most accessible. Specifically a Medline search revealed only 11 reports [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] in the literature in relation to lymphoscintigraphy of the regional lymphatics and only a further 13 articles exploring the sentinel node concept in this disease [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. Of the latter, one describes use of sentinel node identification to improve the accuracy of ultrasound-guided fine-needle aspiration cytology [USFNAC] [12] and a further two merely detail possible methods for sentinel node biopsy [13, 14]. The rest almost exclusively report small series; however all but one [17] allude to encouraging results.

Background

The dilemma in management of the regional lymphatics in patients with mucosal squamous cell carcinoma of the head and neck is confined to those who present with early primary site disease and an absence of clinical or radiological evidence of metastatic disease in the neck (the N0 neck). For patients who present with advanced primary site disease, or with evidence of established metastatic neck disease, treatment planning is straightforward, with some form of therapeutic intervention warranted for the regional lymphatics. This takes the form of a neck dissection or irradiation or (as is often the case) a combination of the two.

It is only in the relatively recent past that there has been an appreciation of the significant rate of occult nodal metastases that elude detection by conventional imaging in this patient group. Previously a "watch and wait" policy had been adopted in relation to the neck, with treatment only being instituted when metastatic disease became clinically overt. However, there is now a sound body of evidence to show that a number of mucosal sites within the head and neck, even in early disease, are at significant risk (≥20%), of occult cervical nodal metastases [25]. Thus a watch and wait policy often results in patients presenting with advanced disease, despite close clinical follow-up in dedicated head and neck oncology units [26]. Finally, evidence is starting to emerge that a survival benefit may be gained by elective treatment to the neck [27] in selected patient groups.

One of the main reasons why conventional imaging modalities [computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), USFNAC] fail in this situation is the criteria used by radiologists to designate an imaged lymph node as suspicious (Table 1). Data from several authors suggest these criteria to be unhelpful or misleading. Woolgar [25], Van den Brekel et al. [28] and Don et al. [29] have all reported histological series in which more than 50% of occult nodal metastases were found in lymph nodes less than 10 mm in axial diameter. In addition, Woolgar [25] found only a 9% incidence of cystic change/central necrosis in occult lymph node metastases.

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Table 1. Radiological criteria determining likely nodal metastatic disease

Nodes >10 mm in axial diameter
Nodes which are spherical rather than flat or bean shaped
Nodes containing areas of central necrosis/cystic degeneration
Abnormally grouped lymph nodes
Pericapsular extension

Table 2. Meta-analysis of sensitivities and specificities of the various imaging modalities used to assess the clinically node-negative neck for occult cervical metastases (from Van den Breckel et al. [31])

Method of pre-operative assessment	Sensitivity Mean (range)	Specificity Mean (range)
Palpation	35% (30%–40%)	35% (27%–42%)
CT	45% (17%–86%)	11% (3%–21%)
US	46% (42%–50%)	21% (11%–33%)
MRI	42% (20%–71%)	14% (5%–26%)
USFNAC	42% (27%–50%)	0%

Woolgar [30] also investigated the incidence of micrometastases, defining these as single or multiple deposits of tumour found within lymph nodes with minimal disturbance of nodal architecture and being less than 3 mm in axial diameter. There was an 8% incidence of such disease overall in a series of 178 patients. However, 20% of all the false negative necks in this series were upstaged by micrometastatic disease alone. The same author has previously reported histologically false negative neck rates secondary to micrometastases of between 27% and 38%.

To quantify the inaccuracy inherent in utilising these modalities to stage the neck, Van den Breckel et al. [31] conducted a meta-analysis of the currently available data in this area, the results of which are illustrated in Table 2. Even if one accepts that such wide ranges may skew the data, false negative rates of 25%–30% are the norm in the majority of series. This is a direct result of the utilisation of the above criteria and the significant incidence of positive nodes containing only micrometastases, which clearly fall below the current resolution of CT, MRI, or US.

Current practice, therefore, is to offer this patient group elective treatment to the neck when managing the primary site disease. This is in the knowledge that in ~70% of such patients this treatment will be unnecessary, but it is justified by the adverse effects on morbidity and mortality inherent in adopting a watch and wait policy for the ~30% who harbour occult disease at initial presentation. There are therefore clear concerns with regard to the induction of significant morbidity for the majority of patients in whom occult disease is not present. Equally, there are significant implications for precious health service resources. Against this background, there is a need for a different approach to pre-treatment staging of the clinically N0 neck.

The sentinel node in head and neck mucosal squamous cell carcinoma

As previously stated, there are limited reports detailing the use of lymphoscintigraphy and sentinel node biopsy in mucosal squamous cell carcinoma of the head and neck. The first report to appear was by Schwab et al. in 1964 [1] investigating the utility of lymphoscintigraphy for delineation of the cervical lymphatics in relation to the upper aerodigestive tract. This was followed by the publication of further data in which he and his co-workers reported their in vivo findings on cervical lymphatic drainage, whilst investigating the effect that surgery and radiotherapy produced on lymphatic function [2, 3, 4, 5]. However, they were not using the technique to identify nodal metastases.

More recently, other authors have used lymphoscintigraphy specifically to identify cervical nodal metastases to aid treatment planning [6, 7, 8, 9]. These reports have concerned a variety of sites of primary tumour in the head and neck, but have been limited by small numbers. In a much larger study by Klutmann et al. [11], a dual-tracer technique was used in an attempt to localise more accurately the draining lymphatics in relation to the local anatomy. They successfully demonstrated the drainage pattern in 53/75 patients and concluded that their technique could provide valuable pre-operative information that might influence the pattern of lymphadenectomy chosen by the surgeon. The explanation given for the lack of flow of the tracer in 22 of the patients (the congenital absence of local lymphatics) is less robust. There are in excess of 350 lymph nodes within the head and neck, and the associated mucosa has a rich lymphatic plexus. It is much more likely that this failure was due to the injection technique rather than aberrant anatomy. It is important that the radiopharmaceutical is injected into the submucosal layer and it is our experience that this is best performed by the surgeon managing the patient (Fig. 1).

In an innovative approach to pre-treatment staging of the clinically N0 neck, Nieuwenhuis et al. [12] reported the use of lymphoscintigraphic identification of the sentinel node in an attempt to improve the utility of US-FNAC. Only 11 patients were studied; however, the sentinel node was successfully aspirated in all patients, as demonstrated by gamma activity within the obtained samples.

The choice between static and dynamic imaging is also a matter of contention, with opinion split. However, we would suggest that, given the complexity of the anatomy, the frequently short distance from the primary site to the sentinel node, and the variable pattern of lymphat-

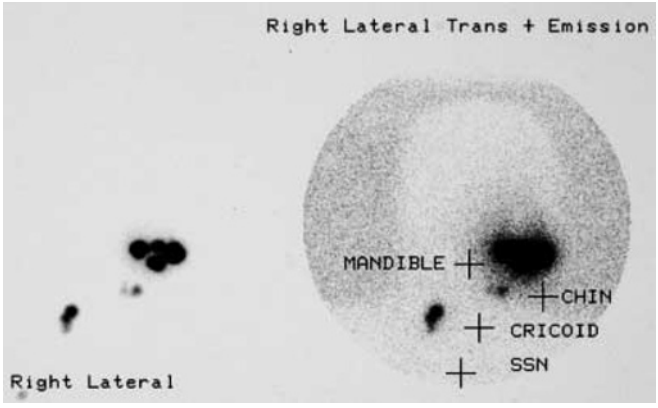

Fig. 1. Lymphoscintigram in a patient with oral squamous cell carcinoma

ic drainage, dynamic imaging offers the optimum pre-operative information.

With regard to the latter there has been a relatively recent, and increasing recognition of non-sequential involvement of the various nodal levels in the neck [32, 33]. This is at odds with traditional concepts of lymphatic drainage within the head and neck [34] and is most commonly seen with tongue and floor of mouth carcinomas, particularly those sited more posteriorly. We believe that dynamic imaging offers a unique insight into this phenomenon, which will enhance our understanding and permit a more informed approach to treatment planning in terms of either extent of lymphadenectomy or selection of radiotherapy fields (Fig. 2).

Alex and Krag [15] in 1996 reported the first successful sentinel node biopsy of a patient with a squamous cell carcinoma of the supraglottic region using intra-operative gamma probe-assisted biopsy. In 1997, Pitman et al. [10] reported a series of 16 patients with mucosal squamous cell carcinoma of the head and neck in whom they attempted to intra-operatively map the lymphatics and identify the sentinel node. The dye used was isosulphan blue, but they aborted their study when they failed to demonstrate any staining of the neck lymphatics. This failure to identify blue-stained lymphatics is at odds with other reports, and our own experience.

We use 2.5% Patent Blue dye (Laboratoire Guerbet, Alnay Sans-Bois, France), injecting 0.25 ml submucosally at four sites around the periphery of the tumour. As with the radiopharmaceutical, it is crucial that the dye is injected into the submucosal space to maximise the delineation of the locoregional lymphatics. Timing is also a significant factor. With rapid transit of the dye, a significant delay between injection and surgical access to the neck may result in the majority of the dye being washed through the lymphatics, making interpretation difficult. It is our policy only to inject the dye once we are ready to access the neck. The time interval is then limited to no more than 20 min and utilising this regimen we have never failed to demonstrate the lymphatics adequately.

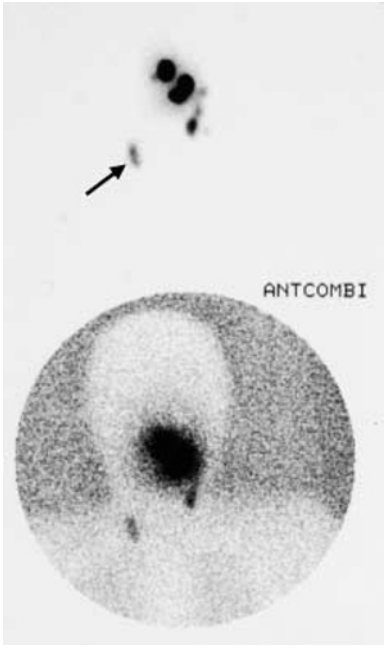

Fig. 2. Lymphoscintigram demonstrating non-sequential involvement of a level 4 lymph node in carcinoma of the tongue (Arrow)

This further supports the premise that the surgeon managing the case should be responsible for performing the injections in order to ensure reproducibility (Fig. 3).

It is clear that in order to maximise success in sentinel node biopsy in this anatomically complex area, a combination of pre-operative lymphoscintigraphy, intra-operative lymphatic mapping with blue dye and gamma probe-assisted localisation is required. This is certainly our own experience, and is now supported by others working in this area, in relation to both mucosal squamous cell carcinoma [13, 14, 19, 20, 21, 22, 23, 24] and melanoma of the head and neck [35, 36]. The latter clearly has the potential to metastasise to the same lymphatic basins and is therefore directly comparable with mucosal squamous cell carcinoma; in addition, the role of the aforementioned combination in melanoma in general is supported by figures published recently by several authors [37, 38, 39].

Is the technique of lymphoscintigraphy and sentinel node biopsy feasible in mucosal squamous cell carcinoma of the head and neck? Our experience would suggest that it is, but as in other areas where it has been used, there is a learning curve and close co-operation is required between surgeons and nuclear medicine physicians/departments. We are not alone in our enthusiasm for the technique, as demonstrated by five recent papers [19, 20, 21, 22, 23, 24]. The largest and most recent of these studies is that reported by Shoaib et al. [24]. In their series, 40 N0 necks in 37 patients were investigated. They successfully biopsied the sentinel node in 36 necks (90%), and 50% of the neck dissection specimens contained tumour. In these 20 specimens, sentinel node

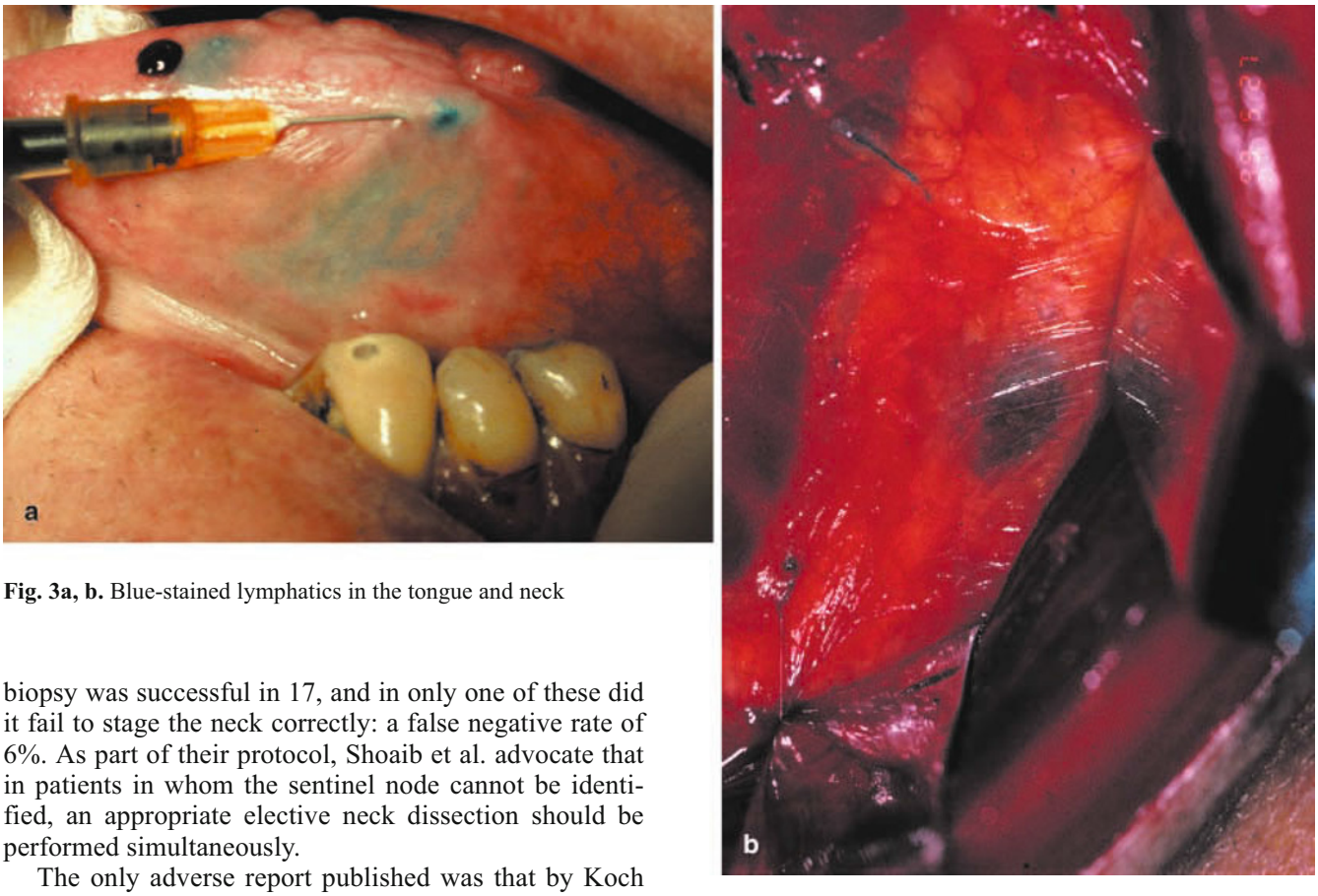

Fig. 3a, b. Blue-stained lymphatics in the tongue and neck

biopsy was successful in 17, and in only one of these did it fail to stage the neck correctly: a false negative rate of 6%. As part of their protocol, Shoaib et al. advocate that in patients in whom the sentinel node cannot be identified, an appropriate elective neck dissection should be performed simultaneously.

The only adverse report published was that by Koch et al. [17], which documented a small pilot study of only five patients. However, as the authors pointed out, one patient had had previous radiotherapy, which under our protocols would exclude them from lymphoscintigraphy owing to the undoubted alteration in patterns of lymphatic drainage that previous surgery or radiotherapy confers. In two cases, hot nodes containing metastatic carcinoma were found, although one of these was not seen on pre-operative lymphoscintigraphy. In the other two cases there were no positive nodes on histological examination of the neck dissection specimen, essentially invalidating any comment on the accuracy of the technique. It is noteworthy that these authors did not use intra-operative mapping with blue dye, and based on the above we feel it was premature to denounce the utility of the technique.

Interest and expertise continue to develop, and this year saw the first international conference (held in Glasgow) on lymphoscintigraphy and sentinel node biopsy in mucosal squamous cell carcinoma of the head and neck. One area of interest was the management of the contralateral neck when tumours approach the midline or are sited in areas renowned for bilateral lymphatic drainage (i.e. posterior one-third or base of tongue). In this regard it would seem logical to extend the technique to patients who present with more advanced locoegional disease which is predominantly unilateral, but in whom the contralateral neck is at risk. Lymphoscintigraphy and sentinel node biopsy would seem the ideal pre-operative staging technique for the contralateral neck; if the results prove negative, additional significant surgical morbidity will be avoided. Currently in this circumstance the patient would be subjected to a bilateral neck dissection.

The future

We have already touched on the difficulties posed by the close proximity of the primary tumour and its draining lymphatics, superimposed upon anatomical complexity. Such constraints make pre-operative lymphoscintigraphy more difficult to interpret, and also make sentinel node biopsy more problematic. Two new developments may enhance the utility of sentinel node theory in this region. Firstly, advanced cameras have been developed which incorporate other imaging modalities such as CT. These permit co-localisation of gamma activity on defined anatomical structures, thereby permitting a more accurate assessment of the site of the sentinel node (Fig. 4). Secondly, hand-held gamma cameras are now being developed that allow for intra-operative visualisation of the sentinel node and may be particularly useful for sentinel node biopsy when the primary site activity and that from the sentinel node are close on pre-operative lymphoscintigraphy (Fig. 5).

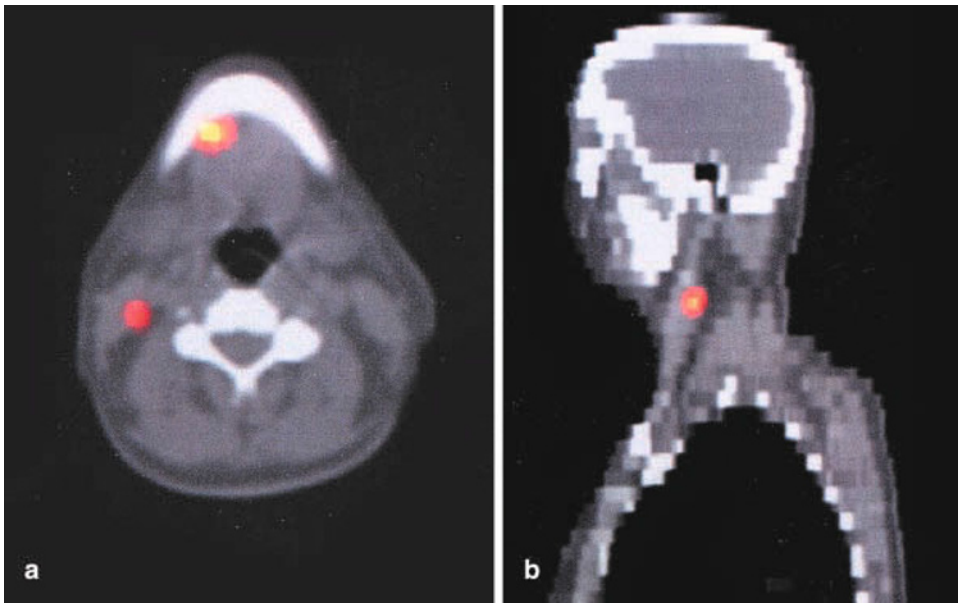

Fig. 4a, b. Emission/CT transmission fusion image of a sentinel node study for a patient with a squamous cell carcinoma of the left lateral border of the tongue. (Hawkeye Millennium VG – International General Electric, Milwaukee, USA)

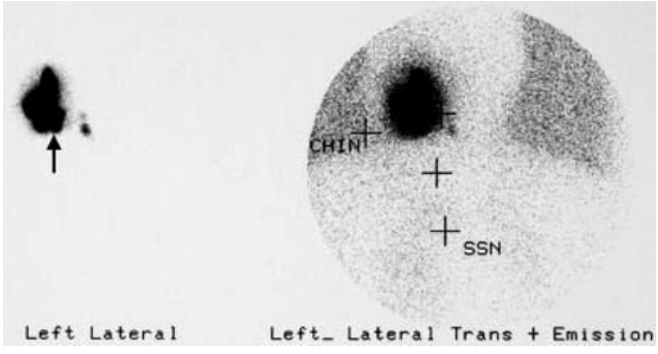

Fig. 5. Lymphoscintigram with sentinel node (Arrow) close to primary injection site

Conclusion

Whilst there are undoubted similarities between melanoma, carcinoma of the breast and mucosal squamous cell carcinoma of the head and neck, there are also significant differences in their biology and natural history. In melanoma and breast carcinoma the presence of regional lymph node metastases is often the marker of systemic involvement, which is not generally the case in mucosal squamous cell carcinoma. Whilst the correct staging of the regional lymphatics is fundamental to the management of all three diseases, it may have a more profound effect in mucosal squamous cell carcinoma of the head and neck than it has hitherto had in breast carcinoma and melanoma. If we are to improve our mortality figures and prevent unnecessary morbidity in this disease, improved pre-operative staging of the neck, allowing better neck management, is crucial.

It is our opinion that lymphoscintigraphy and sentinel node biopsy are feasible and reproducible in mucosal head and neck malignancy. It would seem wise for those interested in pursuing this technology to employ all three available interventions (i.e. pre-operative lymphoscintigraphy with both dynamic and static imaging, intra-operative lymphatic mapping and sentinel node biopsy using a combination of vital blue dye and radiolocalisation) to maximise success. Liaison with other interested surgeons already performing the techniques, perhaps in breast carcinoma or melanoma, is recommended as there is much common ground and there is a significant learning curve: this technique is not for the occasional operator. Any such work should be conducted within the confines of a prospective clinical trial so as to improve our evidence base, with surgeons, nuclear medicine physicians and pathologists all working in close co-operation.

Currently we overtreat the majority of patients with early mucosal squamous cell carcinoma of the head and neck owing to the absence of accurate pre-operative staging techniques for the N0 neck. It would appear that sentinel node theory might provide the opportunity to redress this imbalance.

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