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Main Article

Sentinel lymph node biopsy in node-negative squamous cell carcinoma of the oral cavity and oropharynx

P Burns, A Foster*, P Walshe, T O'Dwyer

Abstract

Objectives: Considerable controversy exists regarding the merits of elective neck dissection in patients with early stage oral cavity and oropharyngeal squamous cell carcinoma. It is highly desirable to have a method of identifying those patients who would benefit from further treatment of the neck when they are clinically node-negative. The purpose of the present study was to examine the use of sentinel lymph node biopsy in identifying occult neck disease in a cohort of patients with node-negative oral cavity and oropharyngeal squamous cell carcinoma.

Design: We evaluated a total of 13 patients with oral cavity and oropharyngeal cancer who were clinically and radiologically node-negative.

Results: A sentinel lymph node was found in all 13 patients, revealing metastatic disease in five patients, four of whom had one or more positive sentinel lymph nodes. There was one false negative result, in which the sentinel lymph node was negative for tumour whereas histological examination of the neck dissection specimen showed occult disease.

Conclusion: In view of these findings, we would recommend the use of sentinel lymph node biopsy in cases of oral cavity and oropharyngeal squamous cell carcinoma, in order to aid the differentiation of those patients whose necks are harbouring occult disease and who require further treatment.

Key words: Head and Neck Neoplasms; Lymph Node; Neoplasm Metastasis

Introduction

Squamous cell carcinoma (SCC) is the most common malignancy of the upper aero-digestive tract. For patients with head and neck SCC, the histopathological status of the cervical lymph nodes is of critical prognostic importance, as the presence of lymph node metastasis has been shown to decrease survival by up to 50 per cent.[1]

In our institution, all patients presenting with tumour $(T)_2$ or T_3 lesions of the oral cavity or oropharynx undergo elective neck dissection, as 21–33 per cent of elective neck dissections performed on patients clinically staged as T_2 node $(N)_0$ or T_3 N_0 have been found to reveal evidence of pathological metastases.[2] Similarly, high rates of regional recurrence (20–57 per cent) have been reported among patients with N_0 disease of the oral cavity and oropharynx who undergo primary clinical observation of the neck.[2]

All patients presenting to our service with T_1 tumours of the oral cavity or oropharynx, and with evidence of an infiltrative pattern of invasion or with a depth of tumour penetration greater than 5 mm, undergo an elective neck dissection, as the senior author has previously shown an increased risk of metastatic disease and loco-regional recurrence rate in the presence of these features.[2]

However, in patients in whom the histopathological status of the neck is truly N_0, this surgery is unnecessary. Therefore, a method that accurately identifies metastatic disease in the N_0 neck is highly desirable. Such a method would minimise the number of neck dissections and courses of radiotherapy for patients whose necks are definitively N_0.

The theory behind sentinel node biopsy is that flow from a tumour travels sequentially to the first echelon node (i.e. the sentinel node) and then to the remaining lymph node basin.[3] Therefore, pathological evaluation of the harvested sentinel node should give an accurate reflection of the disease status within the rest of the draining node basin. In melanoma and breast cancer, the sentinel node identifies node-positive patients with over 95 per cent sensitivity,[4] thus, accurately predicting which patients do not require lymph node dissection.

Our aims for the present study were: (1) to assess the feasibility of sentinel lymph node localisation, using pre-operative lymphoscintigraphy

From the Departments of Otorhinolaryngology and *Radiology, Mater Hospital, Dublin, Ireland.
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and intra-operative gamma-probe radiolocalisation; and (2) to determine the accuracy of sentinel lymph node biopsy in diagnosing occult metastasis of the neck in patients with N_0 SCC of the oral cavity and oropharynx.

Methods

Patients with biopsy-proven T_1–T_3 SCC of the oral cavity and oropharynx who had no clinical or radiological evidence of cervical lymph node involvement (on computed tomography (CT) and magnetic resonance imaging (MRI)) were eligible for this prospective study. All patients presenting to the head and neck department of the Mater Hospital, Dublin, between January 2005 and January 2007 who adhered to the above criteria were enrolled in the study. Local ethics committee approval was granted, and informed consent was obtained from all patients.

Patients underwent lymphoscintigraphy on the morning of surgery in the nuclear medicine department. In this procedure, 1.1 mCi (40MBq) of technetium Tc 99 m-labelled colloidal human serum albumin, in approximately 0.5–1 ml of normal saline, was injected at as many points as necessary in an attempt to completely surround the primary tumour on its deep and lateral aspects. Static lymphoscintigraphy was performed at 15, 30 and 60 minute intervals after injection, or until the first appearance of sentinel nodes within the neck. The location of the radioactive lymph nodes was marked on the skin.

During surgery, approximately 0.5–2 ml of Patent Blue V dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was injected around the primary tumour. A neck dissection incision was made, with subsequent elevation of subplatysmal flaps. Blue-stained lymphatics, if seen, were traced to the first draining lymph node, which was harvested. All radioactive sentinel lymph nodes were identified with a Neoprobe 1500 hand-held gamma probe (Neoprobe Corporation, Dublin, Ohio, USA), including those nodes marked during lymphoscintigraphy. Radioactive sentinel lymph nodes were excised, and radioactivity within the node was confirmed *ex vivo*. Sentinel nodes were labelled according to their colour, radioactivity and anatomical level. An appropriate neck dissection completed the surgical procedure.

The sentinel lymph nodes were fixed in 10 per cent neutral buffered formalin and, after fixation, were bisected through their longest axis. If the thickness of the halves was more than 2 mm, the slices were trimmed further to provide additional 2 mm thick blocks. Each layer was stained with haematoxylin and eosin (H&E) and cytokeratin and then evaluated for the presence of metastatic disease. The remainder of the neck specimen was dissected after fixation, and all lymph nodes larger than approximately 2.5 mm in maximum dimension were identified in their anatomical groups. Each lymph node was bisected through its long axis and one-half was processed for histological examination. One H&E-stained section was prepared from each block and was examined for the presence of lymph node involvement by tumour.

Patients were followed in the out-patients department after completion of their treatment.

Results

Thirteen patients completed the study, nine men and four women. Their ages ranged from 38 to 80 years, with a mean age of 59.2 years. The location and T-staging of the primary tumours are shown in Table I. The disease in all patients was staged as N_0 by clinical examination, and CT or MRI.

Lymphoscintigraphy was performed in all cases, and revealed one or more sentinel lymph nodes in all 13 patients. Two 'hot spots' were identified in three patients. In these patients, it was likely that the radioactive tracer had spread distal to the sentinel lymph node; however, the hot spots were considered as possible sentinel lymph nodes and were removed separately. The remaining 10 patients had only one hot spot identified on lymphoscintigraphy.

All sentinel lymph nodes detected by lymphoscintigraphy before surgery were identified by the hand-held gamma probe through the intact skin, and in the

TABLE I

SUMMARY OF PATIENT RESULTS

Pt no	Tumour site	T stage	SLN (*n*)	'Blue' nodes (*n*)	SLN status	+ve nodes on ND (*n*)
1	Oral tongue	T_2	1	0	−ve	0
2	FOM	T_3	2	0	−ve	2
3	FOM	T_2	1	0	−ve	0
4	Tonsil	T_2	2	1	+ve	4
5	Oral tongue	T_2	1	0	−ve	0
6	Tonsil	T_2	1	1	−ve	0
7	FOM	T_1	1	0	−ve	0
8	Oral tongue	T_2	1	0	−ve	0
9	RMT	T_2	2	0	+ve	0
10	Tongue base	T_2	2	0	−ve	0
11	Oral tongue	T_1	1	0	+ve	0
12	FOM	T_2	1	1	−ve	0
13	Oral tongue	T_2	1	0	+ve	0

Pt no = patient number; T = tumour; SLN = sentinel lymph node; +ve = positive; −ve = negative; ND = neck dissection; FOM = floor of mouth; RMT = Retro-molar Trigone

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open lymphatic bed after elevation of appropriate flaps. A total of 17 sentinel lymph nodes were removed from the 13 patients and sent for histological analysis. The mean size was 18 mm (range, 8–29 mm). The mean number of lymph nodes removed by neck dissection, including sentinel lymph nodes, was 26 per patient (range, eight to 49). Blue lymphatic channels were identified in only two patients, and we found that the use of blue dye impeded our excision of the primary tumour, as adequate margins were difficult to assess.

Histological examination revealed metastatic disease in five patients, four of whom had one or more positive sentinel lymph nodes. Nodal metastasis was restricted to the sentinel lymph node alone in three of these four patients. The fourth patient had four positive nodes in addition to the sentinel lymph node, which was the only sentinel lymph node noted to have extracapsular spread. The fifth patient with metastatic disease in the neck dissection specimen had a negative sentinel lymph node, i.e. a false negative result. This patient had an extensive, T_3, floor of mouth SCC, and negative sentinel lymph nodes were found in levels one and two, with tumour being found within a non-sentinel level two node. There were two patients in whom we found a blue-stained sentinel lymph node. In only one of these cases was the blue node positive for occult metastatic disease.

The duration of follow up in the out-patients clinic ranged from nine months to two years. At the end of the follow-up period, 11 of the 13 patients were alive and well, while two had succumbed to illnesses not related to their primary disease (one had suffered myocardial infarction, the other pulmonary embolism). Patients in whom the sentinel lymph node was negative, with corresponding negative neck dissection specimens, showed no evidence of loco-regional recurrence. All patients with a positive sentinel lymph node and evidence of metastatic disease in their neck dissection specimen were referred on for adjuvant chemo-radiation; none of these patients showed any evidence of recurrence on follow up.

Discussion

In patients with carcinoma of the oral cavity or oropharynx, regional control of the neck is the most important determinant of treatment outcome. Although evidence from several studies suggests an increased survival following elective neck dissection in patients with early oral cavity or oropharyngeal tumours who are likely to be harbouring occult neck disease,[5–8] this must be weighed against the fact that the majority of these patients will never develop neck disease, and so stand to derive little benefit from any neck treatment. Therefore, in order to improve outcome among patients with early carcinoma of the oral cavity or oropharynx, while avoiding unnecessary morbidity, it seems clear that the identification of those patients who are at increased risk of neck disease is crucial. Sheahan *et al.*[2] showed that tumour thickness, tumour size and histological pattern of invasion were all statistically significant predictors of neck disease in patients with early stage carcinoma of the oral cavity. Rather than depending on predictors of neck disease, sentinel node biopsy offers an immediate insight into the status of the neck and hence identifies those patients in whom further treatment will be of benefit. The importance of identifying these patients was stressed by Sheahan *et al.*,[2] who showed a three-year survival rate of only 20 per cent in those patients harbouring occult neck disease who were treated with neck observation alone.

Because the prognosis for delayed cervical metastases is poor and the treatment of the clinically negative neck correlates with improved survival, elective neck dissection must be considered in the treatment of most oral cavity or oropharyngeal tumours without palpable lymph nodes. Most institutions favour elective neck dissection in cases in which the expected incidence of microscopic or sub-clinical disease exceeds 15 per cent.[9] In effect, elective neck dissection is used as a staging procedure to pathologically determine the need for adjuvant treatment. We use conventional radiotherapy post-operatively in cases in which there are: two or more nodes with tumour; extracapsular spread of disease; or lymphovascular or perivascular tumour invasion. One of the great advantages of sentinel node biopsy is that it focuses the pathological evaluation on one or a few lymph nodes, thereby being able to predict if further surgery, with or without adjuvant treatment, is required.

The type of neck dissection used to treat the neck with a positive sentinel lymph node remains debatable. In the largest study of the use of sentinel lymph nodes in the management of head and neck cancer patients, Ross *et al.*[10] showed that the majority of sentinel lymph nodes harvested from their 125 lymph node positive patients were from levels one to three. Many centres have adopted the supraomohyoid neck dissection to treat the clinically T_1/T_2 N_0 tumour of the oral cavity or oropharynx. In Ross and colleagues' study,[10] 4 per cent of patients with a positive sentinel lymph node had disease in level four, and so would have been missed had a supraomohyoid neck dissection been used. Therefore, Ross *et al.* recommended a modified radical neck dissection for sentinel lymph node positive disease, thereby clearing all levels (one to five) and reducing the risk of regional recurrence. Although none of our patients showed metastatic disease outside level three, we would routinely include level four in our neck clearance, and we feel that the morbidity associated with a modified radical neck dissection is unnecessary.

The technique of sentinel lymph node biopsy is easily learned; as greater numbers are performed, the sensitivity rates for accurate sentinel lymph node identification increase. Of our cohort of 13 patients, we accurately identified the sentinel lymph node in all 13 (100 per cent), and this figure is in keeping with other published results.[10–12] In Ross and colleagues' study,[10] of 134 patients, a sentinel node was accurately identified in 93 per cent (125/134). Of these 125 patients, 42 (34 per cent) with

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T_1/T_2 SCC of the oral cavity or oropharynx were upstaged, reflecting the importance of sentinel lymph node biopsy in the management of these patients. The results for the 22 centres involved in the First International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer[9] were analysed together, and showed an overall sensitivity of the procedure of 90 per cent. The results from the conference also showed that centres which had performed less than 10 procedures had a lower sensitivity (57 per cent), compared with those which had performed more than 10 procedures (which had a sensitivity of 94 per cent).

Ross *et al.*[10] suggested that the success of sentinel lymph node identification varied for different tumour sites. Their identification rate for floor of mouth tumours (86 per cent) was less than that for tumours at other sites (96 per cent). Their sensitivity for floor of mouth tumours was 80 per cent, compared with 100 per cent for other tumour groups. Our experience with floor of mouth tumours was similar, with a sentinel lymph node identified in all four such cases. However, in only three of these cases did the sentinel lymph node accurately reflect the status of the neck. It would seem that the close proximity of the floor of the mouth to the draining nodal basin leads to difficulty in both identifying and harvesting the sentinel lymph node, and more care must be taken to ensure that bilateral sentinel lymph nodes are not overlooked in such cases.

Localisation of the sentinel lymph node with the hand-held gamma probe should always be performed through the intact skin, in order to assess the feasibility of future selective sentinel lymph node excision via a very small incision.[11] In our experience, exact localisation of the sentinel lymph node through the intact skin was always possible, and excision of the sentinel lymph node through a minimal skin incision was feasible.

In order to exactly define the sentinel lymph node in the open neck with the help of the gamma probe, the activity of the node and the background should be compared. Statistical analysis published by Alex *et al.*[12] indicates that the gamma-probe reading for the sentinel lymph node in situ should be at least three times the background count. In the literature on malignant melanoma and breast cancer, a 10-fold elevated count ex situ is required for sentinel lymph node biopsy.[13] In our cohort, all sentinel lymph nodes met both criteria; after excision, the count activity dropped to background levels, proving excision of the sentinel lymph node.

The use of Patent Blue V dye in the identification of the sentinel lymph node remains debatable. Centres in favour of its use report that it aids identification of such nodes, although it is accepted that this dye is most useful in combination with radiocolloid.[7] Because the use of Patent Blue V dye, radiocolloid and pre-operative lymphoscintigraphy is now an integral part of the sentinel node biopsy procedure in both melanoma and breast cancer cases, it seems reasonable to recommend this triple diagnostic approach for head and neck tumours. Ross *et al.*[10] stated that, for oral cavity and oropharyngeal tumours, blue dye does not seem to interfere with surgical margins, and they reported no side effects from the injection process. Our experience with the use of blue dye differed. We found that the identification of adequate margins around the primary tumour was very difficult when using the dye, although no margins in this study were positive following resection of the primary tumour. Also, of the two cases in which a blue sentinel lymph node was found, only one was positive for metastatic disease. For these reasons, we would not recommend the use of blue dye in sentinel lymph node mapping, and we would place more emphasis on use of the gamma probe for identification of the sentinel lymph node, combined with pre-operative lymphoscintigraphy.

- **Sentinel lymph node evaluation in node-negative (N_0) squamous cell carcinoma of the oral cavity and oropharynx is feasible, and seems to predict the presence of occult neck disease**
- **Sentinel lymph node biopsy is minimally invasive, causes minimum morbidity, and combines radiological and pathological techniques in order to stage the neck**
- **Sentinel lymph node biopsy alone can be used to stage the N_0 neck for the majority of early tumours of the oral cavity and oropharynx**

Sentinel lymph node pathology did not reflect that of the remaining neck dissection in one of our cases, thus giving us one false negative result. This patient had a large, T_3, floor of mouth tumour. Shoaib *et al.*[14] stated that, in such large (T_3/T_4) floor of mouth tumours, the small volume of radiocolloid used may be insufficient to completely surround the metastasising edge of the tumour. However, the senior author would recommend a modified radical neck dissection in all T_3/T_4 floor of mouth tumours, and their exclusion from sentinel lymph node studies, due to the high rate of regional disease associated with these tumours. The numbers of false negative and false positive sentinel lymph node biopsies occurring in studies involving head and neck SCC are too small to be statistically significant.[9–12] If we as a specialty keep awaiting large, multi-centre trials with adequate numbers, the procedure of sentinel lymph node mapping and biopsy will be abandoned. It is the opinion of the senior author that sentinel lymph node biopsy adds greatly to the management of early disease of the oral cavity and oropharynx. We would recommend the referral of all early tumours to one centre, thus increasing numbers and allowing accurate statistics on false positive and false negative rates, hence improving treatment outcomes.

The use of positron emission tomography (PET) as a prerequisite for staging a patient clinically N_0, in combination with sentinel node biopsy as the sole

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pathological staging tool, could potentially be an advancement in the treatment of oral cavity and oropharyngeal tumours. Kovacs *et al.*[15] assessed 62 patients with T_1–T_3 SCC of the oral cavity or oropharynx. Patients without uptake on PET then underwent sentinel lymph node biopsy, and the results were correlated with the histopathological analysis. Kovacs *et al.* found a sentinel lymph node in all 38 patients who were PET-negative for neck disease. They stated that PET should not be used in place of sentinel lymph node biopsy, because micrometastases are beyond the scope of PET resolution. They recommend that PET results should not be compared with sentinel lymph node results, but rather that PET should be used as a prerequisite for sentinel lymph node biopsy.

Conclusion

Sentinel lymph node evaluation in cases of N_0 SCC of the oral cavity or oropharynx is feasible, and seems to predict the presence of occult neck disease. Sentinel lymph node biopsy is minimally invasive, causes minimum morbidity, and combines radiological and pathological techniques in order to stage the neck.

Much debate has surrounded the management of early oral cavity tumours, regarding whether to adopt a 'wait and see' approach or to proceed to a neck dissection. Sentinel lymph node biopsy would seem to answer this debate, and to remove the risk of poor clinical outcome with salvage surgery in those patients in whom a failed 'wait and see' approach has previously been adopted.

It would seem from the literature that sentinel lymph node biopsy alone can be used to stage the N_0 neck for the majority of early tumours of the oral cavity and oropharynx. Floor of mouth tumours must be approached with more caution, as they are more difficult in terms of both sentinel lymph node identification and harvesting.

We recommend referral to a specialist centre for all cases of early stage oral cavity and oropharyngeal tumours, in order to obtain accurate statistics on treatment outcomes. The ongoing wait for multicentre trials could see the abandonment of sentinel lymph node biopsy in the management of head and neck cancers.

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Address for correspondence:
Mr Paul Burns,
31 Woodview,
Blackrock,
Co Dublin, Ireland.

E-mail: pburns@rcsi.ie.

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