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TITLE

**SENTINEL NODE BIOPSY FOR THE CLINICALLY N₊ &
N₀ NECK IN SQUAMOUS CARCINOMA OF THE HEAD
AND NECK**

UNIVERSITY OF CAPE TOWN



**MASTER OF MEDICINE (MMED) IN
OTORHINOLARYNGOLOGY**

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The research in this report is based on independent work performed by the candidate and neither the whole work nor any part of it has been, is being or is to be submitted for another degree to any other university. The same mentioned research has not been published prior to registration for the abovementioned degree.

PART A: PROTOCOL

Sentinel node biopsy for the N+ and N- neck in squamous carcinoma of the head and neck

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INTRODUCTION

The internationally accepted standard of care for clinically palpable neck nodes situated within the lymphatic drainage area of a squamous cell carcinoma of the head and neck is to remove all lymphatic tissue from that side of the neck by means of a comprehensive neck dissection, either radical (RND) or modified (MND). This practice is founded on the following assumptions:

- Palpable neck nodes represent metastases
- The morbidity associated with over-treatment of the clinically overstaged (pN₀) neck is outweighed by the consequences of under-treatment of the pN₊ neck.

FNAC is generally not employed to inform decisions about treatment for the cN₊ neck, as there is concern about the specificity of FNAC, and hence potential for understaging and consequently under treating the occult positive neck.

A number of studies have been published on, and there is ongoing research into, the use of sentinel node biopsy for the N₀ neck, in order to avoid elective neck dissection (END) [1]. Currently, the literature shows it to be feasible for the clinically N₀ neck but alone is insufficient to stage disease accurately [2]. The value of sentinel node biopsy in the N₊ neck has not yet been explored.

The results of a study, published in *The Journal of Laryngology and Otology* in December 2003, by *De Waal, Fagan and Isaacs* at the University of Cape Town (attached) suggest that the 1st assumption, i.e. that palpable neck nodes represent

metastases, does not apply to a Developing World practice such as ours. *Table 1* summarises the positive predictive values (PPV) and false +ve rates of preoperative clinical staging in accordance with nodal staging in 261 neck dissections for squamous cell cancer by *De Waal*.

Preoperative stage	pN+	PPV	False +ve rate
N+	117/172	68%	32%
N ₁	25/47	53%	47%
N _{2a}	23/29	79%	21%
N _{2b}	27/41	66%	34%
N _{2c}	30/44	68%	32%
N ₃	11/11	100%	0%

Table 1

It is apparent that 47% of N₁ necks (single node, <3cms) were pathologically N₀, and had undergone unnecessary MND. The same applied, to a lesser extent, to N_{2b} (multiple ipsilateral nodes), N_{2c} (bilateral nodes), and to N_{2a} (single ipsilateral node) necks.

Likely reasons for clinical overstaging include lymphadenopathy associated with HIV, TB, and inadequately treated dental, oral and venereal disease. With the predicted increase of HIV and TB in Sub-Saharan Africa, it is reasonable to assume that the false +ve rate of clinical N-staging will increase.

Employment of FNAC and/or sentinel lymph node biopsy (SLNB) to improve the specificity of staging for patients with cN+ necks, and hence reduce the number of unnecessary MNDs or RNDs, has not been reported.

SENTINEL LYMPH NODE BIOPSY

Head and neck squamous cell carcinoma (SCC) spreads via lymphatics to the regional draining lymph nodes in the neck. This is thought to be embolic in nature [3]. As the presence of lymph node metastases is an important prognostic factor in Head and Neck cancer (50% decrease in survival) [4], reliable staging is imperative to determine further management. Modalities such as physical examination, ultrasound scanning, computed tomography and magnetic resonance imaging of the neck have not proved to be highly reliable to assess nodal involvement [5].

Extensive research has been done on lymphatic spread in malignant melanoma [6]. The initial node(s) to which tumour has spread can be isolated and are termed sentinel lymph nodes (SLNs). These primary draining nodes are postulated to be representative of the rest of the lymphatic chain in the neck, and if negative on biopsy, would theoretically prevent the morbidity of an unnecessary neck dissection [7].

Sentinel nodes are located using a combination of staining by dye and radiocolloid uptake following peri-tumoural injection prior to surgery.

Lymphoscintigraphy mapping also aids lymphatic channel identification prior to surgery.

AIMS OF STUDY

- To determine the positive (PPV) and negative predictive values (NPV) of sentinel node biopsy of cervical nodal metastasis in squamous cell carcinoma of the head and neck.
- To determine a diagnostic and therapeutic approach to the cN+ neck in a Developing World setting.
- To assess sentinel node biopsy as an indicator of regional lymph node status in the N0 neck.

INCLUSION CRITERIA

- Patients with histologically proven oral or oropharyngeal SCC accessible to injection, and where surgical excision with elective or therapeutic neck dissection is planned.

EXCLUSION CRITERIA

- Pregnancy, lactation, patients with previous surgery or radiotherapy to the neck.

MATERIAL AND METHOD

- Prospective clinico-pathological study
- Institution: Groote Schuur Hospital

- Informed consent from patients
- No change from standard surgical management with regards to type of neck dissection
- Peri-tumoural injection of 0.3 - 1.0ml of 40 - 60MBq ^{99m}Tc-labelled Human Serum Albumin (Nanocoll) in the Nuclear Medicine Department on the morning of surgery, followed by mouthwash immediately afterwards to prevent pooling or swallowing of residual radioactivity by the patient
- Static lymphoscintigraphy performed at 15 and 30 minutes post injection
- After induction in theatre, 1-2ml of blue dye (Methylene Blue) is injected throughout the normal mucosa and submucosa surrounding the tumour
- Standard skin incision for MND and skin flaps raised
- SLN(s) identified using dyed lymphatics and/or gamma probe, resected and radioactivity within the node confirmed *ex-vivo*
- SLN(s) labeled according to their colour, radioactivity and anatomical neck level and sent for histological examination in 10% formalin
- Planned neck dissection continued (levels identified and sent for histological evaluation separately) and primary tumour removed

ANALYSIS OF RESULTS

- Accuracy of techniques (dye vs isotope) to locate the SLN
- Number of cases SLN correctly identified
- Number of SLNs identified in each case and anatomical location

- Could the SLN biopsy correctly predict nodal status? (NB: were there any false negatives)

CONCLUSIONS

1. Can SLN biopsy be used in a Developing World setting to correctly predict the oncologic status of palpable neck nodes in patients with head & neck SCC and therefore prevent unnecessary neck dissections?
2. Reliability of SLN biopsy in clinical & pathological N+ neck vs. that of the clinically N+ / pathologically N0 neck?
3. The role of SLN biopsy in the N0 neck in a Developing World setting?

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PART B: LITERATURE REVIEW

OBJECTIVES

The objectives of the literature review for sentinel lymph node biopsy in head and neck squamous cell carcinoma (SCC), was to determine current understanding of the topic as determined from previous studies and review articles. This was to aid in the formulation of a protocol for this study, to assess where this investigation has been used with success and to identify gaps in current knowledge where this study may prove helpful.

LITERATURE SEARCH STRATEGY

A literature search was undertaken of the Pubmed Medline and Cochrane database for articles in journals that are listed on the Index Medicus. The following keywords were used: SLNB; Head and neck squamous cell carcinoma; lymphatic drainage of the head and neck; Blue dye in SLNB; and fine needle aspiration cytology (FNAC) in head and neck cancer.

Numerous articles were found in the literature pertaining to the above topics. Initially the abstracts were reviewed and assessed according to the questions raised and answered by the paper, the number of patients included in the studies, evidence of statistical significance of the findings and any review articles on the topics. The relevance to this

study was also considered with regard to techniques used and methods of data analysis to assist in the reporting of the data.

Inclusion criteria for articles were: Peer reviewed articles; Prospective studies and review articles on SLNB in the clinically N₀ neck in head and neck SCC; Technical issues relevant to SLNB and articles relevant to the lymphatic drainage pathways in the head and neck region; and prospective and retrospective studies on the accuracy of FNAC in head and neck SCC.

Exclusion criteria included: SLNB in head and neck tumours other than mucosal SCC i.e. malignant melanoma, cutaneous SCC, thyroid carcinoma and salivary gland neoplasms; preliminary studies and studies with very small numbers. However some of these studies were included in the review articles that met the inclusion criteria.

Assessment of quality was based on the levels of clinical evidence. Meta-analyses and review articles were considered as stronger evidence. Studies with larger patient numbers carried greater statistical weight than those with smaller patient numbers. Controlled trials with outcome based results were also sought out as the results of these might provide more significant clinical evidence.

SUMMARY OF THE LITERATURE

It is generally accepted that the future behaviour of a malignancy can be predicted by knowledge of the extent of tumour spread at the time of presentation[1]. This is the premise on which staging systems have been developed. Staging seeks to reflect patient outcome based on survival rates. In head and neck SCC, a key prognostic factor in predicting patient survival is the extent of loco-regional lymphatic spread[2]. The survival rate drops by approximately 50% for the pathologically N₊ as compared to the N₀ neck in these patients[3]. SLNB has been increasingly investigated as a tool in the management of the clinically N₀ neck with a view to preventing morbidity associated with potentially avoidable END [1, 4-7]. Sentinel lymph node sampling by the use of a radioactive isotope, dye or by combining these, has become the standard of care in many centers in the world for the management of patients with cutaneous malignant melanomas and with breast carcinomas[1]. In oral and oropharyngeal SCC, this technique has been shown to have a high degree of sensitivity, to be reliable and reproducible. Reported sensitivity ranges from 89 – 100% with false negative rates of 0 – 12.5%[1]. In a meta-analysis of 19 studies, Paleri V et al reported an overall pooled sensitivity of 0.926 (95% CI, 0.852–0.964) [1, 8].

Despite its reported high sensitivity, SLNB has numerous technical issues that should be taken into consideration. Before discussing this in detail, it might be useful to review the concept of the sentinel node (SN). The SN is the first lymph node in the nodal basin that receives lymphatic drainage from a malignant tumour, and is thus theoretically the first

node to contain any metastases if lymphatic spread was to occur (*Figure 1*). It follows that if a SN was found to be free of metastatic disease then it would suggest that the status of remainder of the nodal basin would be negative. However the drainage pathways in the head and neck region have been shown to be complex and variable and hence tend to be slightly less predictable than this theory would suggest. This is in contrast to the relatively more ordered arrangement of the lymphatic drainage of the breast and other regions of the body [9, 10]. Nodal basins for different head and neck primary tumour subsites are well known. However, evidence of skip lesions are also documented, particularly with primary tumours involving the oral tongue, where metastatic deposits have been demonstrated in level IV only, thus ‘bypassing’ the presumed ‘first port of call’ for metastatic spread, i.e. levels I-III[1, 4, 11, 12]. The potential pitfall with squamous carcinoma of the oral tongue might be that nodes in levels I-III may demonstrate uptake of tracer, blue dye or both and be designated the ‘sentinel nodes’ whereas in fact a metastatic deposit may be overlooked in level IV. Another theoretical problem is that when a lymph node contains metastatic carcinoma, lymphatic flow may be blocked in that lymphatic channel or node and the tracer or dye may be diverted past the true first echelon node(s) to a ‘false SN’ [10].

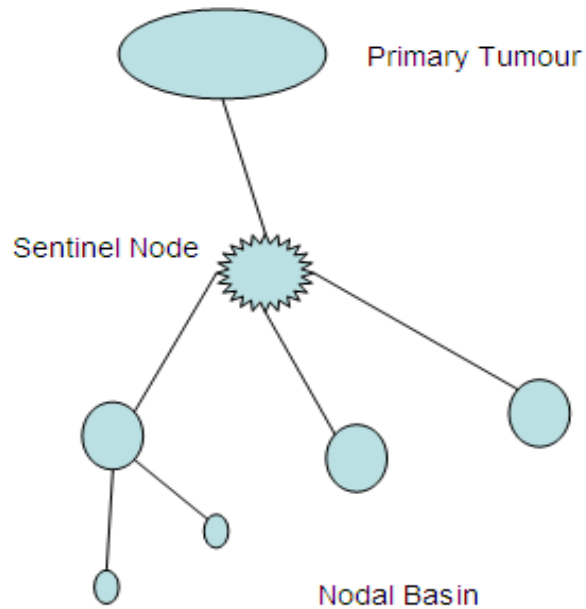


Figure 1: Illustration of the sentinel node concept

The modality used to delineate the sentinel nodes is an issue that also needs to be considered. Lymphoscintigraphy is performed preoperatively with a peritumoral injection of a radioisotope to delineate the sentinel nodes which can then be marked on the skin (*Figure 2*). Intraoperative identification of the nodes with the use of a handheld gamma probe, which detects levels of radioactivity within the tissues sampled, is then undertaken. The commonly used radiotracers are technetium Tc 99m-labelled sulfur colloid and technetium Tc99m-labelled human serum albumin[1].

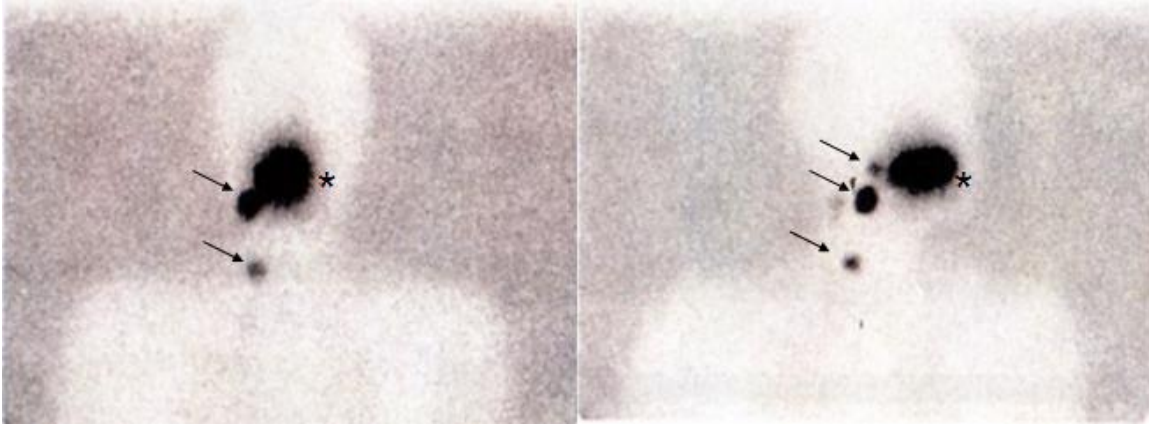


Figure 2: Lymphoscintigraphy; radioactivity seen from injection site around the primary tumour () and the sentinel nodes (arrows).*

A peritumoral injection of dye is also widely used. The dye is taken up by the lymphatics and the sentinel nodes are identified by blue discolouration [1, 4] (*Figure 3*). Various dyes can be used: Methylene blue, isosulvan blue, patent blue and patent blue violet to name a few. All are equally effective in identifying sentinel nodes; however the triphenylmethane group of dyes, to which the latter three belong, carry a significant risk of allergic reactions and anaphylaxis [13]. The accuracy of these techniques differs. Lymphoscintigraphy and the handheld gamma probe are superior to blue dye when used individually. Combining all three techniques has been shown to improve the ability to identify the sentinel nodes [1, 4]. Technical problems may arise with the use of blue dye insofar as that resection of the primary tumour may be hampered by blue staining of the peritumoral tissues and may lead to oncologically inadequate resection margins. The extent of the surgery may also be inappropriately increased with the use of blue dye as a larger area of the nodal basin may need to be exposed in order to visualize the dye in the lymphatics[4].

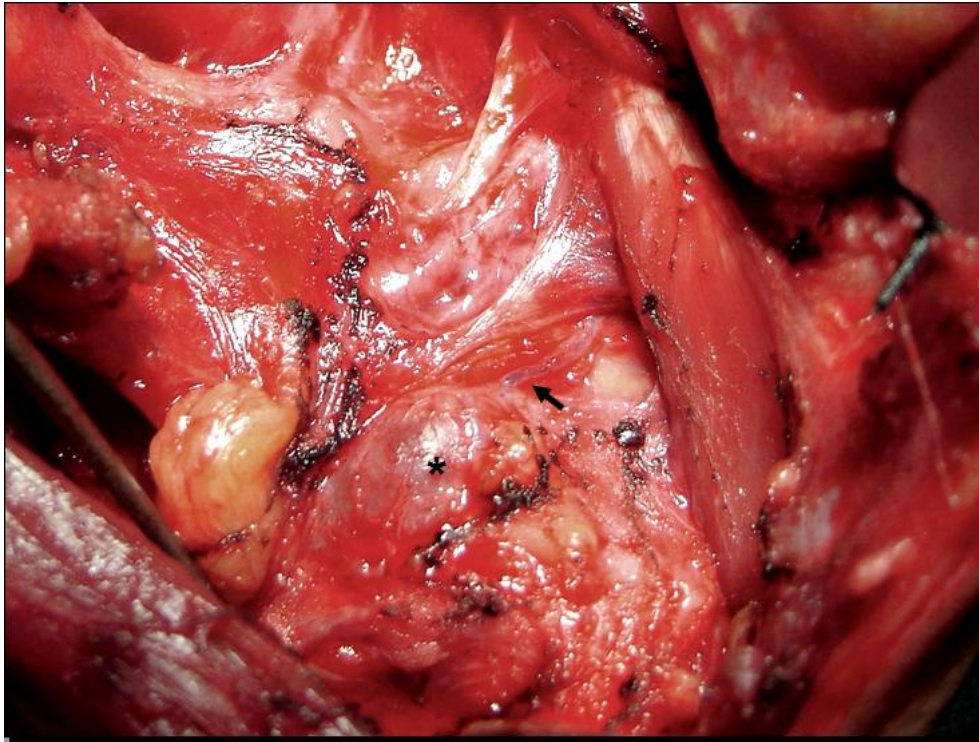


Figure 3: Blue dye identification in lymph node () and lymphatics (arrow)*

Intraoperative localisation of the nodes can be complicated by ‘shine-through artifact’ and needs to be taken into account at surgery. Shine-through refers to the situation when the first echelon nodes are in close proximity to the primary e.g. floor of mouth tumours and first echelon nodes in Level 1 of the neck. Radioactivity emitted by the radiolabelled tracer at the primary tumour site may then obscure detection with the gamma probe of radioactivity emitted by the sentinel nodes and hamper accurate localisation of the SN [6, 12]. In such instances the primary needs to be resected prior to removal of the SN.

The sentinel nodes are defined in the literature as the three nodes with the highest radioactivity. This definition limits the number of nodes that needs to be removed and to obtain an oncologically sound result [5, 14].

The means by which one histologically analyses the sentinel nodes for metastasis is also of importance and is a source of much debate. Intraoperative frozen section analysis would give the surgeon immediate information necessary to make a decision whether to proceed with a comprehensive neck dissection. However frozen section is not recommended as it is not accurate at detecting microscopic deposits of tumour and may lead to underestimating the true status of the neck [1, 5]. Histopathological analysis with or without immunohistochemistry (IHC) is the most reliable method of detecting tumour. Standard analysis of neck nodes harvested by neck dissection is by bisection of the nodes in the longitudinal plane and H&E staining. The literature shows that this routine method misses up to 21% of metastases as this technique only evaluates the central portion of the node, and small metastatic deposits in other areas of the node may be missed[4]. The recommended histological examination of nodes harvested by SLNB is that after bisecting the node, it should be further sectioned into slices of less than 2.5mm. Serial sections are then done at 150 μ m. Out of each four sections, one will be stained by H&E and another by IHC for cytokeratin. The rest of the slices are retained for possible future analysis. This evaluation is considered to be essential if SLNB is used to guide treatment of the neck [4].

When a sentinel node is found to have histopathological evidence of metastatic tumour, then the question arises as to the ideal further management of the patient. A completion neck dissection would add further morbidity and possibly be more technically challenging, depending on the timeframe between the SLNB and the completion surgery. Radiotherapy also carries significant morbidity, along with the fact that once irradiated, patients with recurrences or new primaries in the irradiated field cannot be reirradiated. Another relative contraindication for radiotherapy would be that the rest of the lymphatics in the neck would not be available for pathological analysis, thereby precluding accurate pathological staging of the neck [12]. Intraoperative analysis would be ideal but at present may not be entirely reliable for the reasons already mentioned [5].

If SLNB alone were to be utilised, then removal of the all SNs only would have equal regional control rates of END [5]. As yet there is no evidence in the literature to conclude which approach is best. Paleri V et al in their meta-analysis developed a decision analysis model based on current knowledge to statistically predict outcomes for these management options. A sensitivity analysis concluded that END had a slight advantage over SLNB[8].

From published data and review articles in the literature, certain conclusions have been drawn regarding the use of SLNB in the clinically N₀ neck in head and neck carcinoma. It is suggested that its use should be restricted to early stage, T_{1/2}N₀, SCC of the oral cavity and oropharynx [4]. It has been shown to be feasible, reproducible and to have a high sensitivity [1, 7, 8]. However on its own, it is insufficient for staging of the neck[1]. As

yet its use as a 'standard of care' cannot be supported [1, 12]. Despite the reported high sensitivity, there is no evidence in the form of randomised control trials (RCT) to suggest that the use of SLNB improves patient outcome, rates of local recurrence or survival when compared to END [4]. One European research group has adopted SLNB as part of their management and do not perform neck dissections on patients if the SN is negative in T 1-4 SCC of the oral cavity [12]. According to certain authors, SLNB in head and neck SCC remains an investigational tool pending outcomes of RCT [1, 4]. There is also said to be a significant learning curve associated with SLNB due to technical issues with the procedure and it has been suggested that the technique be standardised [4, 8].

No studies have been reported on the use of SLNB in the clinically N₊ neck. It is presumed that these patients harbour nodal metastases and are candidates for a therapeutic neck dissection[1]. However in Southern Africa and the developing world questions exist regarding the accuracy of clinical staging due to the high prevalence of other causes for palpable lymphadenopathy in patients with a confirmed head and neck mucosal SCC primary tumour. These include HIV, tuberculosis and untreated upper respiratory and dental infections. This would result in overstaging of the neck due to the misdiagnosis of cervical adenopathy as cervical metastases, leading to potential overtreatment of the neck by means of a MND, and hence unnecessary morbidity and expense[15]. De Waal, Fagan and Isaacs reported a false positive rate of 32.0% for the clinically N₊ neck when comparing clinical staging to pathological analysis[15].

Whether FNAC can be used routinely to accurately stage the clinically N₊ neck in patients with a confirmed primary SCC of the upper aerodigestive tract has not been reported in the literature. Fine needle aspiration cytology (FNAC) is widely used as an investigation for masses in the head and neck region [16]. It is often performed blindly in a clinical setting or under image guidance, most often with the use of ultrasound, which improves the diagnostic yield. FNAC has a high level of accuracy [16, 17]. However it is operator dependent and has been shown to be more accurate when performed by an experienced clinician [17]. Cytopathologists have the highest accuracy with this technique and have an added advantage of being able to immediately assess the adequacy of the sample and repeating the procedure if necessary [17]. A systematic review and meta-analysis by Tandon S et al showed the accuracy of FNAC in lymph nodes to be: sensitivity 92.5%, specificity 97.8%, PPV 98.8% and NPV 86.7%. For SCC the sensitivity was found to be 92% [17]. However, a limitation of FNAC is that there is a high rate of inadequate or non-diagnostic aspirates with lymph nodes aspirates [16, 17]. This may lead to multiple aspirations and hence a delay in the diagnosis and management. Howlet DC et al reported that out of a total of 205 patients at five different hospitals, 121 (52%) had non-diagnostic aspirates of neck nodes. Fifty four of these patients had surgery and of these 30 (56%) were found to have malignant cytology [16]. In the United Kingdom, the establishment of combined “one-stop” head and neck lump clinics, where FNAC may be cytologist-led, shows potential in this regard [16]. Other limitations of FNAC include the inability to sub-classify lymphomas, missed diagnoses of low grade lymphomas, the inability to distinguish thyroid follicular adenoma from

carcinoma and difficulty with the diagnosis of salivary gland neoplasms [16, 17]. There is also a rare but reported risk of seeding of tumour along the needle tract [17].

With this reported high degree of accuracy, FNAC may spare patients with cervical adenopathy due to non-oncologic reasons unnecessary neck dissection. The major question that first has to be addressed however is what the risk is of missing metastatic deposits within clinically enlarged lymph nodes when FNAC is done without ultrasound imaging? In our head and neck cancer service, FNAC on neck masses are currently performed by clinicians (specialists or registrars) without the aid of image guidance or immediate cytopathology assessment. With a high rate of non-diagnostic aspirates and lower accuracy without image guidance, relying on this investigation to confirm evidence of lymphatic spread in patients with a known SCC primary and clinically palpable lymph nodes in our setting would seem not be feasible.

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PART C: ARTICLE MANUSCRIPT

(For submission to 'The Laryngoscope')

Sentinel Lymph Node Biopsy in Head and Neck Squamous Cell Carcinoma: The N0 and N+ Neck

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Abstract

Objectives/Hypothesis

The objectives of the study were to determine the accuracy of Sentinel Lymph Node Biopsy (SLNB) in head and neck squamous cell carcinoma (SCC); to determine its role in the approach to the clinically N₊ neck in a Developing World setting; and its accuracy as an indicator of regional lymph node status in the clinically N₀ neck.

Study Design

The study included patients with proven SCC of the oral cavity or oropharynx undergoing surgical resection and neck dissection with clinical stages T₁₋₄ N₀₋₃.

Methods

Sentinel and echelon lymph nodes were identified by means of a combination of lymphoscintigraphy, gamma probe and blue dye identification, were analysed histologically and compared to the rest of the neck dissection specimen to determine accuracy. Patients were grouped into clinically N₀ and N₊ groups.

Results

Thirty three patients were included in the study, 13 in the N₀ and 20 in the N₊ group. The mean age of the patients in the study was 58 years with a male to female ratio of 2.3:1. In the clinically N₀ group a sensitivity of 100% and specificity of 85% was found and in the clinically N₊ group the sensitivity and specificity were 60% and 60% respectively.

Conclusions

The results show that the accuracy of SLNB in the clinically N₊ neck is poor. In the Developing World with the high prevalence of benign lymphadenopathy, treatment of patients with primary SCC of the head and neck and clinically N₊ necks should include

neck dissection, pending a reliable non-invasive method of distinguishing benign from malignant nodal pathology.

Keywords

Sentinel Lymph Node, Head and Neck, Squamous cell carcinoma

Introduction

SLNB is being increasingly investigated as a tool in the management of the clinically N₀ neck with a view to preventing morbidity associated with potentially avoidable elective neck dissection (END) ¹⁻⁵. However no studies have been reported on the use of SLNB in the clinically N₊ neck.

Cervical adenopathy in patients with SCC of the upper aerodigestive tract are usually assumed to represent nodal metastases and is treated as such, usually by means of a therapeutic neck dissection¹. However, particularly in Southern Africa and the Developing World, the accuracy of clinical staging of cervical adenopathy may be confounded by the high prevalence of other causes for lymphadenopathy such as HIV, tuberculosis and untreated upper respiratory and dental infections. This would result in overstaging of the neck due to the misdiagnosis of cervical metastases, leading to overtreatment of the neck by modified neck dissection (MND)⁶. De Waal, Fagan and Isaacs reported a false positive rate of 32% for the clinically N₊ neck when comparing clinical staging to pathological analysis⁶.

Materials and Methods

The study was a clinico-pathological observational study, and was conducted by the Division of Otorhinolaryngology of the University of Cape Town at Groote Schuur Hospital, Cape Town, South Africa between March 2004 and May 2009. The study had been approved by the University of Cape Town Ethics Committee. The aims of the study were to determine the accuracy of sentinel lymph node biopsy (SLNB) in SCC of the

head and neck, i.e. sensitivity, specificity, positive (PPV) and negative predictive values (NPV); to determine whether SLNB can be used in the diagnostic and therapeutic approach to the clinically N₊ neck in a Developing World setting; and to evaluate SLNB as an indicator of regional lymph node status in the clinically N₀ neck.

Inclusion criteria were as follows: Histologically proven oral or oropharyngeal SCC that was accessible to transoral peritumour injection; primary surgical resection; and all T and N clinical stages. Exclusion criteria were pregnancy, lactation and patients who had undergone previous surgery or radiotherapy to the neck. The SLNB findings did not alter the surgical management with regards to the type of neck dissection or type of resection of the primary tumour.

On the morning of surgery, lymphoscintigraphy was carried out in the Department of Nuclear Medicine at Groote Schuur Hospital. A peri-tumoural injection of 99mTc-labelled Human Serum Albumin (Nanocoll) was done. This was followed immediately by a saline mouthwash to prevent pooling or swallowing of the residual radioactivity. Continuous flow lymphoscintigraphy was performed for 30 minutes with a static film at 15 and 30 minutes post-injection. The sentinel lymph nodes (SLN) were then marked on the skin using a radioactive tracer to locate the level of the sentinel nodes found on lymphoscintigraphy. Once in the operating theatre and after induction of general anaesthesia, 1-2ml of Methylene Blue dye was injected in the normal mucosa and submucosa surrounding the primary tumour. Standard neck dissection skin incisions and approaches were used. The SLNs and echelon lymph nodes (ELN) were identified using

combinations of gamma probe localization and identification of blue stained lymphatics and lymph nodes. These nodes were then resected, their radioactivity measured *ex-vivo* and labeled according to their colour, radioactivity and anatomical neck level. These nodes were then sent individually for histological analysis in 10% formalin. The planned neck dissection and primary tumour removal were performed and sent for histological examination. In some cases the primary tumour was removed prior to exploring the neck. This facilitated SLNB where the shine through of radioactivity from the primary interfered with location of the SLN.

The following clinical details were recorded for each patient: age, sex, tumour site, clinical staging, and levels of clinically palpable nodes. The data of the intra-operative stage of the study were entered into a data capture sheet. The number of radioactive-only nodes, the number of blue-only nodes, the number of nodes that were both radioactive and blue stained, the radiation counts of the respective nodes, the background radioactivity and the anatomical levels of the nodes were all documented. The interval time from isotope injection to surgery, the length of time for the SNB, lymph node basins explored and any technical difficulties were also recorded. Histopathology was recorded in the data capture sheet according to pathological stage (TNM), tumour thickness, status of the SLNs and nodal status of the rest of the neck dissection specimens.

Results

Thirty four patients were initially recruited for the study. However one patient (study number: 4) was excluded intra-operatively due to progression of the primary tumour

rendering the patient inoperable. Thus a total of 33 patients were available for analysis.

The mean age of the patients in the study was 58 years (range 42-89) with a male to female ratio of 2.3:1. In the clinically N₀ the staging of the primary tumours ranged from T₁₋₄ and in the clinically N₊ group the staging ranged from T₁₋₄ and N₁₋₃.

The analysis of the results was based on data collected for each patient from the data capture sheet and cross referencing with the histopathology reports. The data is outlined in *Table 1*.

The volume of peri-tumoural injection of 99mTc-labelled Human Serum Albumin (Nanocoll) varied with the size of the primary tumour and ranged from 0.2-0.6ml with a mean of 0.37ml. The dosage range was 29.0-66.0 MBq (mean: 47.2 MBq). Three patients underwent lymphoscintigraphy the afternoon before surgery and the rest of the patients immediately prior to surgery. The time interval between injection and surgery was a mean of 233 minutes (range 91-1185 min).

The accuracy of SLNB to predict the status of the lymph node basin in the neck was calculated separately for the clinically N₀ and clinically N₊ patients. The sensitivity, specificity, positive (PPV) and negative (NPV) predictive value were calculated. The accuracy in each group was subdivided for each individual modality alone and for a combination of the modalities in detecting the sentinel and echelon nodes (*Table 2 & 3*).

The clinically N₀ group comprised 13 patients, 12 of which had ipsilateral and one bilateral END (14 neck dissection specimens). In the N₊ group there were 20 patients, of

which 10 had ipsilateral and 10 bilateral modified radical neck dissections (30 neck dissection specimens).

In the clinically N₀ neck there was a high degree of accuracy with a sensitivity of 100% and specificity of 85% when using a combination of lymphoscintigraphy, gamma probe and blue dye to identify the sentinel nodes. The accuracy in the clinically N₊ group was significantly lower, with sensitivity and specificity of 60% and 60% respectively when combined modalities were used. The accuracy for the individual modalities was poor (*Table 3*).

Discussion

Sentinel lymph node sampling by the use of a radioactive isotope, dye or combinations thereof has become the standard of care in many centers in the world for patients with cutaneous malignant melanoma and breast carcinoma¹. In oral and oropharyngeal SCC, this technique has been shown to have a high degree of sensitivity, to be reliable and reproducible. Reported sensitivity ranges from 89 – 100% with false negative rates of 0 – 12.5%¹. In a meta-analysis of 19 studies, Paleri V et al reported an overall pooled sensitivity of 0.926 (95% CI, 0.852–0.964)⁷. This accuracy was echoed in the results of the clinically N₀ group in our study with a sensitivity of 100%, the numbers albeit small. From published data and review articles in the literature, certain conclusions have been made regarding the use of SLNB in the clinically N₀ neck in head and neck carcinoma. It is suggested that its use should be restricted to early stage, T_{1/2}N₀, SCC of the oral cavity and oropharynx⁴. It has been shown to be feasible, reproducible and to have a high

sensitivity^{1,3,7}. However on its own, it is insufficient for staging of the neck¹. As yet its use as a 'standard of care' cannot be supported and despite the reported high sensitivity, there is no evidence in the form of randomised control trials (RCT) to suggest that the use of SLNB improves patient outcome, rates of local recurrence or of survival when compared to END⁴. One European research group has adopted SLNB as part of their management and do not perform neck dissections on patients if the SN is negative in T₁₋₄ SCC of the oral cavity⁸. According to certain authors, SLNB in head and neck SCC remains an investigational tool pending outcomes of RCT^{1,4}. There is also said to be a significant learning curve associated with SLNB due to technical issues with the procedure and it has been suggested that the technique be standardised^{4,7}.

The SN is the first lymph node in the nodal basin that receives lymphatic drainage from a malignant tumour, and thus theoretically is the first node to contain lymphatic metastasis if spread were to have occurred. It follows that if a SN was found to be free of metastatic disease then it would suggest that the metastatic status of the remainder of the nodal basin would be negative. However the drainage pathways in the head and neck region have been shown to be complex and variable and hence tend to be slightly less predictable than this theory would suggest. This is in contrast to the relatively more ordered arrangement of the lymphatic drainage of the breast and other regions of the body^{9,10}. Nodal basins for different head and neck primary tumour subsites are well known. However, evidence of skip lesions are also documented, particularly with primary tumours involving the oral tongue, where metastatic deposits have been demonstrated in level IV only, thus 'bypassing' the presumed 'first port of call' for metastatic spread, i.e. levels I-III^{1,4,8,11}.

The potential pitfall with SCC of the oral tongue might be that nodes in levels I-III may demonstrate uptake of tracer, blue dye or both and be designated the ‘sentinel nodes’ whereas in fact a metastatic deposit may be overlooked in level IV. Another theoretical problem is that when a lymph node contains metastatic carcinoma, lymphatic flow may be blocked in that lymphatic channel or node and the tracer or dye may be diverted past the true first echelon node(s) to a ‘false SN’⁹.

In our clinically N₊ group, four of the twenty patients were found to be pathologically N₀ despite having clinically palpable lymph nodes. The preoperative clinical staging in these patients was: T₂N₁, T₃N₁, T₃N_{2b} and T₄N_{2c}. Histologically the palpable nodes were generally reactive lymph nodes. These patients had not been routinely tested for HIV and no tuberculosis was found in any of the lymph node specimens. Thus 20% of patients in this group underwent unnecessary neck dissections due to the presumed clinical evidence of nodal metastases. The question arises as to whether these patients could be spared a therapeutic neck dissection, by means of a less invasive, accurate investigation.

From the literature we see that despite its accuracy in the clinically N₀ neck, SLNB has yet to be accepted as a standard therapeutic option. Our results in the clinically N₀ neck confirm this high degree of accuracy, suggesting that the technique was appropriate, and adequate. Hence the suboptimal accuracy of the SLNB in the clinically N₊ necks can be assumed not to be related to technical issues or a “learning curve” associated with the procedure, but reflects the inadequacy of SLNB as a staging tool in the clinically N₊ neck.

Conclusions

The results of our study show that the SLNB is not accurate in the clinically N₊ neck and cannot be relied upon in the therapeutic approach to the clinically N₊ neck.

SLNB in Head and Neck SCC as a therapeutic procedure has not been shown to be superior to END in terms of improving patient outcome in the clinically N₀ neck.

Thus, in the Developing World with the high prevalence of diseases resulting in lymphadenopathy in the neck, treatment of patients with primary SCC of the head and neck region with palpable neck nodes should be based on the assumption of nodal metastases, pending a more reliable non-invasive method of distinguishing these other pathologies from malignancy.

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Table 1: Results of sentinel node biopsy study

Trial No.	Sex	Age	Tumour site	Side	Clinical Stage		Histopathological SCC			
					T	N	Sentinel Nodes		Non-SN Nodes	
							L	R	L	R
1	M	69	Floor of mouth (FOM)	L	2	1	Y		N	
2	M	60	FOM	R	2	1	N	N	N	N
3	M	55	Tongue	R	4	2b		Y		Y
5	M	49	Tongue ant 2/3 & post 1/3	L	3	2a	Y		Y	
6	M	45	FOM	L	1	3	Y	N	Y	N
7	M	65	Tongue ant 2/3 & FOM & Inferior alveolus	R	4	0		N		N
8	F	89	Tongue ant 2/3	L	1	0	N		N	
9	M	54	FOM	L / ML	4	2c	N	N	Y	Y
10	M	51	Tongue ant 2/3 & FOM	L	2	0	Y		N	
11	M	51	FOM & Inferior alveolus	R / ML	4	2c	N	N	N	N
12	F	65	Tongue ant 2/3	L	3	0	N		N	
13	F	59	Buccal & Retromolar trigone	L	4	0	N		N	
14	M	42	Tongue ant 2/3 and post 1/3	L	3	1	N		Y	
15	M	52	Tongue post 1/3 & Soft palate	R	3	2a		N		Y
16	M	59	Tongue post 1/3	L	2	0	N		N	
17	M	52	Tongue ant 2/3 & Post 1/3 & Hard and soft palate	L	4	2a	Y		Y	
18	M	63	Tongue post 1/3	L	2	0	N		N	
19	M	61	FOM	L / ML	2	2b	N	N	Y	N
20	M	65	Buccal & Inferior alveolus	L	4	0	Y		Y	
21	F	49	Tongue ant 2/3	L	3	1	Y		Y	
22	M	63	FOM	R / L	3	2c	N	Y	Y	N
23	M	62	FOM	L / ML	3	0	N	N	N	N
24	M	57	FOM & buccal & Inferior alveolus	R	4	0		N		N
25	F	58	Tongue post 1/3 & buccal	R	2	0		N		N
26	F	57	Tongue post 1/3 & Retromolar trigone & Soft palate	L	3	2b	Y		N	
27	M	65	Tongue ant 2/3	L	3	0	Y		N	
28	M	56	FOM / Inferior alveolus	R / L	4	2c	N	Y	N	N
29	F	57	Tongue post 1/3	R	3	1		N		N
30	F	44	Buccal mucosa	R	3	2b		N		N
31	M	54	Tongue ant 2/3	R	3	2c	Y	Y	N	Y
32	F	82	Buccal & Inferior alveolus	R	4	0		N		N
33	M	61	FOM	R / L	3	2c	Y	N	N	N
34	F	59	Tongue post 1/3 & ant 2/3	L / R	3	2c	Y	Y	Y	Y

ML: midline; Sentinel Nodes = sentinel lymph nodes including echelon nodes; Non-SN

Nodes = all other lymph nodes in the neck dissection specimens; Y = positive for SCC; N

= negative for SCC

Table 2: Accuracy of sentinel node biopsy in N0 group

	Combined	Scintigraphy	Gamma Probe	Blue Dye
PPV	33%	33%	33%	67%
NPV	100%	100%	100%	100%
Sensitivity	100%	100%	100%	100%
Specificity	85%	85%	85%	92%

Combined = Sentinel & echelon nodes by all 3 modalities

PPV = positive predictive value; NPV = negative predictive value.

Table 3: Accuracy of sentinel node biopsy in N+ group

	Combined	Scintigraphy	Gamma Probe	Blue Dye
PPV	60%	88%	64%	50%
NPV	60%	46%	56%	50%
Sensitivity	60%	37%	56%	40%
Specificity	60%	91%	64%	60%

Combined = Sentinel & echelon nodes by all 3 modalities

PPV = positive predictive value; NPV = negative predictive value

PART D: SUPPORTING DOCUMENTS

- DATA CAPTURE SHEET
- CONSENT FORM
- TABULATED DATABASE OF SENTINEL LYMPH NODE BIOPSY RESULTS
- RESEARCH ETHICS COMMITTEE APPROVAL
- INSTRUCTIONS TO AUTHORS: THE LARYNGOSCOPE (PART C)

Patient Name and Hospital #

PATIENT DETAILS

Patient trial #

Age

 yrs

Sex

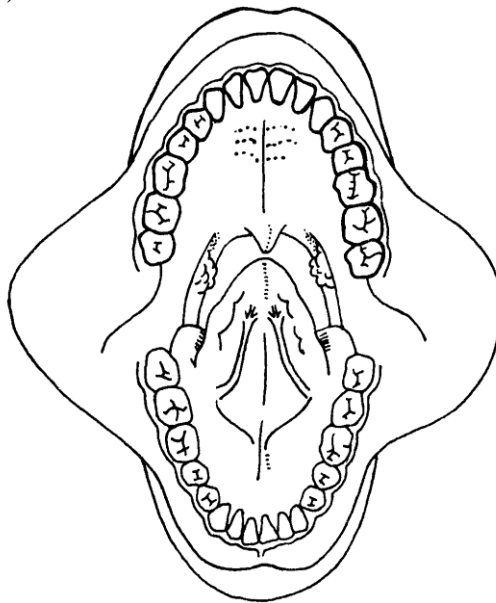
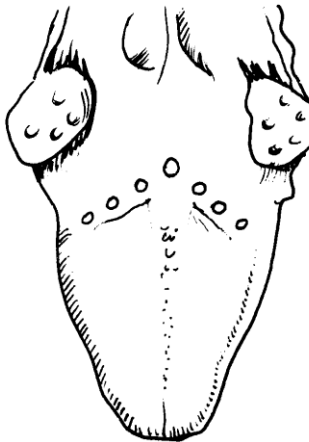
 Male
 Female

Date of sentinel node biopsy

 / /

Tumour site:

(indicate site on diagram)



- Tongue ant 2/3
- Tongue post 1/3
- FOM
- Buccal mucosa
- RMT
- Lower alveolus
- Upper alveolus
- Hard palate
- Soft palate
- Tonsil
- Other.....

Clinical staging

 T N M

Nodal levels, number

	Level 1	Level 2	Level 3	Level 4	Level 5
Left					
Right					

Treatment to primary:

- Excision
- External Beam Radiotherapy
- Interstitial radiotherapy
- Other (state).....

Patient Name and Hospital #

LYMPHOSCINTIGRAPHY

Type of colloid injected Nanocoll Other (state)..... Amount mls

Time of injection h

No of scintigraphy nodes at: 15mins:
30mins:

Levels of nodes: (L) (R)

Nuclear Medicine Clinician

SURGERY

No of radioactive only nodes Surgical team / /

No of blue only nodes Time of skin incision h

No of hot blue nodes Interval time (isotope to surgery) min

Lymph node basins explored Lt neck (levels I-V)
 Rt neck (levels I-V)
 Other (state).....

Any non-sentinel nodes excised How many.....
 Which nodal levels.....

Length of time for SNB: (tick appropriate box) Radiation Count:

<input type="checkbox"/> <15 mins	background	<input type="text"/>
<input type="checkbox"/> 15-30mins	SLN 1	<input type="text"/>
<input type="checkbox"/> 30-45mins	SLN 2	<input type="text"/>
<input type="checkbox"/> 45-60mins	SLN 3	<input type="text"/>
<input type="checkbox"/> >1 hour		

Technical difficulties:

- none and all sentinel nodes removed
- some difficulties but all sentinel nodes removed
- severe difficulties and all sentinel nodes not removed
- abandoned with no neck surgery
- abandoned with neck dissection

Whole procedure of sentinel node biopsy

- satisfactory
- unsatisfactory

PATHOLOGY

Patient Name and Hospital #

FNA cytology

	Node 1	Node 2	Node 3	Node 4	Node 5	Node 6
Left or Right						
Anatomical level						
Malignant cytology						
Benign cytology						
Insufficient for analysis						

Pathological stage: T N M Tumour thickness:.....(mm)

Lymphatic invasion: Y / N Vascular invasion: Y / N Perineural invasion: Y / N

Non-Sentinel nodes: Involved: Y / N

If Yes	Level 1	Level 2	Level 3	Level 4	Level 5
Left					
Right					

Summary of sentinel node information:

	Node 1	Node 2	Node 3	Node 4	Node 5	Node 6
Anatomical level						
Dimensions in mm						
Blue stained?						
Radioactive?						
Histology (SCC,reactive,TB,HIV, sarcoid,syphillis etc)						
Extra-capsular spread (Y/N)						

CONSENT TO ACT AS A SUBJECT IN A CLINICAL STUDY

TITLE: Sentinel lymph node biopsy in oral and oropharyngeal carcinoma

INVESTIGATORS:

Oskar Edkins, Christopher J Hofmeyr, Johannes J Fagan

ADDRESS FOR ALL INVESTIGATORS:

Division of Otolaryngology, Groote Schuur Hospital, Observatory, Cape Town

DESCRIPTION: You have been diagnosed with cancer of the mouth/throat and need an operation to remove the tumour. If there has been spread of the disease already, the most likely site of spread are the glands in your neck. For this reason you may also require removal of these glands at the time of surgery. If enlarged glands are present in your neck prior to surgery, it will be necessary to remove all the glands on that side of your neck in order to determine if the cancer has spread there. Presently we are unable to determine with certainty if there has been spread prior to surgery. In locally advanced tumours without palpable nodes in the neck, we will selectively remove the lymph nodes most likely to be involved, and clear all the neck nodes on that side of the neck if suspicious nodes are found at surgery.

With this in mind we are conducting a clinical study to determine if it is possible to identify the first gland(s) in the neck that cancer spreads to (called the *sentinel lymph node*). Two methods are being tested: (1) blue dye, which when injected around the tumour stains the draining lymphatics and sentinel lymph node blue, and (2) radio labelled isotope, when injected around the tumour spreads to the sentinel lymph node and is picked up by a hand held gamma probe.

This will mean going to the department of nuclear medicine on the morning of your operation for the isotope to be injected and some special scans to be taken. The dye will only be injected once you are asleep in theatre.

There will be no change from standard surgical management with regards to the type of operation performed.

RISKS AND BENEFITS: There are no additional risks and no danger of radiation exposure. The isotope injection is small (0.5mls) and fairly painless. Your participation in this trial will hopefully benefit future patients from having unnecessary neck dissections.

COSTS AND PAYMENTS: There will be no additional costs to you or your family.

CONFIDENTIALITY: The information obtained from this study will be published in the future such that your identity will remain anonymous. Medical records related to this study are confidential, but may be examined by researchers from this institution.

RIGHT TO WITHDRAW: You have the right to refuse to participate in this study at any time, and your decision will not adversely affect your care at this institution.

VOLUNTARY CONSENT: I understand what is stated above and agree to participate in this clinical trial.

Date: _____

Patient signature: _____

Witness: _____

I certify that I have explained to the above individual the nature and purpose, the potential benefits, and possible risks associated with participating in this research study, have answered any questions that have been raised and have witnessed the above signature.

Clinician signature: _____

TABULATED DATABASE OF SENTINEL LYMPH NODE BIOPSY RESULTS

Trial No.	Sex	Age	Tumour site	Clinical Stage				SLN Results					Histopathological Status		Comments
				Side	T	N	Level	Level	Scinti-graphy	Gamma Probe	Blue Dye	Sentinel Nodes	Non-SN Neck Nodes		
1	M	69	FOM	Lt	2	1	Lt L1	Lt L1 Lt L1 Lt L1	N N Y	N Y Y	Y N N	SCC Negative Negative	Lt 0/47		
2	M	60	FOM	Rt	2	1	Rt L1	Rt L1 Rt L1 Rt L1 Rt L2 Rt L2 Rt L2 Lt L1 Lt L1 Lt L1	N Y N Y Y Y Y Y Y N	Y Y Y Y Y Y Y Y Y Y	N Y N Y Y N Y Y Y Y	Negative Negative Negative Negative Negative Negative Negative Negative Negative Negative	Rt 0/21 & Lt 0/26		
3	M	55	T	Rt	4	2b	Rt L2 Rt L2	Rt L2 Rt L1 Rt L1	Y X N	Y X Y	N X N	SCC SCC Negative Negative	Rt 4/15		
4	M	53	T Post 1/3 / BM	Lt										Cancelled: Irresectable Scan done day before surgery	
5	M	49	T Ant 2/3 / Post 1/3	Lt	3	2a	Lt L2	Lt L2 Lt L3 Lt L3	Y Y Y	Y Y Y	N N N	SCC SCC SCC	Lt 12/30		
6	M	45	FOM	Lt	1	3	Lt L1	Lt L4 Lt L3 Lt L3 Lt L1	Y Y Y N	Y Y Y Y	N N Y N	SCC Reactive SCC & Reactive Negative SCC & Reactive	Lt 6/80 & Rt 0/59	Scan done day before surgery	
7	M	65	T Ant 2/3 / FOM / LA	Rt	4	0		Rt L2 Rt L3 Rt L3 Rt L4 Rt L1 Rt L1	Y Y Y Y Y N	Y Y Y Y Y Y	N N N N N N	Negative Negative Negative Negative Negative Negative	Rt 0/44	Scan done day before surgery	
8	F	89	T Ant 2/3	Lt	1	0		Lt L2 Lt L2 Lt L3	N N N	Y Y Y	Y Y N	Negative Negative Negative	Lt 0/16		
9	M	54	FOM	Lt & ML	4	2c	Lt L2	Lt L1 Lt L1	N N	Y Y	N N	Negative Negative	Lt 0/15 & Rt 0/10 Rt SMD Salivary gland SCC	Low radiation counts	
10	M	51	T Ant 2/3 / FOM	Lt	2	0		Lt L1 Lt L2 Lt L2 Lt L2	Y Y N N	Y Y Y Y	N Y Y N	SCC Reactive SCC Reactive	Lt 0/42		
11	M	51	FOM / LA	Rt / ML	4	2c	Lt L1 Rt L1	Rt L2 Rt L1 Rt L1	Y N N	Y Y Y	Y Y Y	Reactive Reactive Reactive	Rt 0/26 & Lt 0/15		

								Rt L3	N	Y	N	Negative	
12	F	65	T Ant 2/3	Lt	3	0		Lt L3	Y	Y	Y	Reactive	Lt 0/27
								Lt L2	N	Y	Y	Reactive	
								Lt L1	N	Y	N	Reactive	
13	F	59	BM / RMT	Lt	4	0		Lt	N	Y	Y	Negative	Lt 0/34
								Lt L1	N	Y	N	Negative	
								Lt	N	Y	N	Negative	
								Lt	N	Y	N	Negative	
								Lt	N	Y	N	Negative	
14	M	42	T Ant 2/3 / Post 1/3	Lt	3	1	Lt L1	Lt L1 A	N	Y	N	Negative	Lt 4/36
								Rt L2	Y	Y	N	Negative	
								Rt L2	Y	Y	N	Negative	
								Lt L2	Y	Y	N	Negative	
15	M	52	T Post 1/3 / SP	Rt	3	2a	Rt L2	—	—	—	—	SCC	Rt 7/119
								Rt L1	N	N	Y	Negative	
16	M	59	T Post 1/3	Lt	2	0		Lt L2	Y	Y	N	Negative	Lt 0/25
								Lt L2	Y	Y	N	Negative	
								Lt L3	Y	Y	N	Negative	
								Lt L3	N	Y	N	Negative	
								Lt L1	N	Y	Y	Negative	
								Lt L1	N	Y	N	Negative	
								Lt Facial	N	N	Y	Negative	
17	M	52	T Ant 2/3 / Post 1/3 / HP / SP	Lt	4	2a	Lt L2	Lt L2	N	Y	Y	SCC	Lt 3/13
								RT L2	Y	Y	Y	Reactive	
								Lt Facial	N	Y	N	Reactive	
								Lt L1	N	Y	N	Reactive	
								Lt Facial	N	Y	N	Reactive	
								Lt L2	N	Y	N	SCC	
18	M	63	T Post 1/3	Lt	2	0		Lt L2	Y	Y	Y	Negative	Lt 0/32
								Lt L3	Y	Y	N	Negative	
								Lt L2	N	Y	Y	Negative	
								Lt L2	N	N	Y	Negative	
19	M	61	FOM	Lt & ML	2	2b	Lt L1/2	—	—	—	—	SCC (L1)	Lt 1/32 & Rt 0/28
								Rt L4	Y	Y	Y	Negative	
								Rt L4	N	Y	N	Negative	
								Rt L1	N	N	Y	Reactive	
								Rt L1	N	N	Y	Reactive	
								Lt Facial	N	N	Y	Negative	
								Lt L3	N	N	Y	Negative	
20	M	65	BM / LA	Lt	4	0		Lt L2	Y	Y	Y	SCC	Lt 10/36
								Lt L2	Y	Y	N	SCC	
21	F	49	T Ant 2/3	Lt	3	1	Lt L2	Lt L2	N	Y	Y	SCC	Lt 1/34
								Lt L2	N	Y	N	SCC	
								Lt L1 SM	N	Y	N	SCC	
								Lt L2	N	N	Y	Negative	
22	M	63	FOM	Rt & Lt	3	2c	Lt L1/1/3	—	—	—	—	Negative	Lt 1/42 & Rt 0/31
								Lt L2	Y	Y	N	Negative	
								Rt L1/2	N	Y	Y	SCC	
								Rt L1	N	Y	Y	Negative	
								Rt L3	Y	Y	Y	Negative	
								Rt L3	N	Y	Y	Negative	
								Lt L1	N	N	Y	Negative	
23	M	62	FOM	Lt & ML	3	0		Rt L2	Y	Y	Y	Negative	Lt 0/25 & Rt 0/26
								Lt L2	Y	Y	Y	Negative	
								Lt L2	N	Y	N	Negative	
								Lt L3	N	Y	Y	Negative	
								Lt L3	N	Y	N	Negative	

								Lt L3	N	N	Y	Negative	
								Lt L2	N	N	Y	Negative	
								Rt L2	N	Y	N	Negative	
								Rt L3	N	Y	N	Negative	
								Rt L1 SM	N	Y	Y	Negative	
24	M	57	FOM / BM / LA	Rt	4	0		Rt L1	Y	Y	Y	Negative	Rt 0/44
								Rt L1 SM	Y	Y	N	Negative	
								Rt L3	Y	Y	N	Negative	
								Rt L3	N	Y	N	Negative	
25	F	58	T Post 1/3 / BM	Rt	2	0		Rt L2	N	Y	Y	Negative	Rt 0/40
								Rt L1	N	Y	Y	Negative	
26	F	57	T Post 1/3 / RMT / SP	Lt	3	2b		Lt L2	Y	Y	Y	Negative	Lt 0/14
							Lt L2	Lt L2	N	Y	Y	SCC	
								Lt L2	N	Y	Y	Negative	
								Lt L4	N	Y	Y	SCC	
								Lt L4	N	Y	Y	Negative	
							Lt L3	Lt L3	N	N	Y	SCC	
27	M	65	T Ant 2/3	Lt	3	0		Lt L2	Y	Y	Y	SCC	Lt 0/25
								Lt L1	N	Y	Y	SCC	
								Lt L2	N	Y	Y	Negative	
								Lt L2	N	Y	Y	Negative	
								Lt L2	N	Y	Y	SCC	
								Lt L3	N	Y	Y	Negative	
								Lt L1 SM	N	Y	Y	Negative	
28	M	56	FOM / LA	Rt & Lt	4	2c	Rt L1	Rt L1	N	Y	Y	Negative	Rt 0/29 & Lt 0/16
							Rt L1	Rt L1	N	Y	Y	SCC	Submental 0/1
								ML SM	N	(weak)	Y	Negative	
								Lt L4	Y	Y	Y	Negative	
								Lt L2	Y	Y	Y	Negative	
							Lt L1	Lt L1	N	Y	Y	Negative	
							Lt L1	Lt L1	N	Y	Y	Negative	
								Lt L1	N	Y	Y	Negative	
								Lt L1	N	Y	Y	Negative	
								Lt L2	N	Y	Y	Negative	
								Lt L2	N	Y	Y	Negative	
29	F	57	T Post 1/3	Rt	3	1	Rt L2	Rt L2	Y	Y	Y	Negative	Rt 0/11
								Rt L1	Y	Y	Y	Reactive	
								Rt L1	N	N	Y	Negative	
30	F	44	BM	Rt	3	2b	Rt L2	Rt L2	Y	Y	N	Reactive	Rt 0/24
								Rt Facial	Y	Y	Y	Reactive	
							Rt L1	Rt L1	N	Y	Y	Reactive	
								Rt L2	N	N	Y	Reactive	
31	M	54	T Ant 2/3	Rt	3	2c	Rt L2	Rt L2	Y	Y	Y	SCC	Rt 2/21 & Lt 0/24
							Rt L2	Rt L2	Y	Y	Y	SCC	
							Rt L2	Rt L2	N	Y	N	Reactive	
								Rt L2	N	Y	Y	SCC	
								Rt L4	Y	Y	Y	SCC	
							Rt L1	Rt Facial	N	Y	Y	SCC	
							Lt L1	Lt Facial	N	Y	Y	Negative	
							Lt L1	Lt Facial	N	Y	Y	SCC	
								Lt L2	N	Y	N	Negative	
32	F	82	BM / LA	Rt	4	0		Rt L1	Y	Y	Y	Negative	Rt 0/43
								Rt L1	Y	Y	Y	Negative	
								Rt L1	Y	Y	Y	Negative	
								Rt L2	N	Y	Y	Negative	
								Rt L3	N	Y	Y	Negative	
								Rt L3	N	Y	Y	Negative	
33	M	61	FOM	Rt &	3	2c		Rt L1	Y	Y	Y	Negative	Rt 0/43 &

				Lt				(SM)						Lt 0/38
								Rt L1						
								(SM)	Y	Y	Y		Negative	
								Rt Facial	N	Y	Y		Negative	
						Rt L1		Rt Facial	N	Y	Y		Negative	
								Rt Facial	N	Y	Y		Negative	
								Rt L1	N	Y	Y		Negative	
								Lt L3	Y	Y	Y		Negative	
								Lt L4	Y	Y	N		Negative	
						Lt L1		Lt Facial	Y	Y	Y		SCC	
						Lt L2		Lt L2	N	Y	Y		Negative	
								Lt L2	N	Y	Y		Negative	
								Lt L2	N	(weak)	Y		Negative	
								Lt L2	N	(weak)	Y		Negative	
								Lt L4	N	Y	Y		Negative	
34	F	59	T Post 1/3 / Ant 2/3	Lt & Rt	3	2c	Lt L1	Rt L2	Y	Y	Y		SCC	Rt 3/41 & Lt 2/29
							Rt L1	Rt L2	Y	Y	Y		SCC	
								Rt L2	Y	Y	Y		Negative	
								Rt L2	Y	Y	Y		SCC	
								Rt Facial	Y	Y	Y		SCC	
								Rt Facial	Y	Y	Y		SCC	
								Rt L4	Y	Y	Y		Negative	
								Rt L3	N	Y	Y		Negative	
								Lt L2	Y	Y	Y		SCC	
								Lt L2	Y	Y	Y		SCC	
								Lt L2	N	Y	Y		SCC	
								Lt L2	N	Y	Y		SCC	
								Lt Facial	N	N	Y		SCC	
								Lt Facial	N	Y	N		SCC	
								Lt L3	N	Y	N		SCC	
								Lt L3	N	Y	N		SCC	
								Lt L1	N	Y	N		SCC	
								Lt Carotid	N	Y	N		Negative	

Table 1:

M (male), F (female), FOM (floor of mouth), T (tongue), BM (buccal mucosa), RMT (retromolar trigone), LA (lower alveolus), HP (hard palate), SP (soft palate), Rt (right), Lt (left), ML (midline). SN (sentinel lymph nodes including echelon nodes), Non-SN (all other lymph nodes in the neck dissection specimens), SCC (positive for squamous cell carcinoma)

Columns 1-3: Patient demographics

Columns 4-8: Clinical details and staging

Columns 9-12: Sentinel and echelon nodes removed; surgical level, whether detected by lymphoscintigraphy, gamma probe or blue dye.

Columns 13-14: Histopathological status of the sentinel and non sentinel nodes (number of positives out of all nodes dissected).

Column 15: Comments

UNIVERSITY OF CAPE TOWN



Research Ethics Committee
Faculty of Health Sciences
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04 June 2003

REC REF: 098/2003

Dr C Hofmeyr
ENT
GSH

Dear Dr Hofmeyr

FINE NEEDLE ASPIRATION CYTOLOGY FOR N+ AND SENTINEL NODE BIOPSY FOR THE N+ AND N- NECK IN SQUAMOUS CARCINOMA OF THE HEAD AND NECK

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Please quote the Reference number in all correspondence.

Yours sincerely

signature removed

PROF T. ZABOW
CHAIRPERSON

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1. Rand NS, Dawson JM, Juliao SF, et al. In vivo macrophage recruitment by murine intervertebral disc cells. *J Spinal Disord* 2001; 14:339–342.

Book chapter

2. Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J, eds. *Frames of Reference for Pediatric Occupational Therapy*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:205–256.

Entire book

3. Webster NR, Galley HF. *Anaesthesia Science*. Oxford, UK: Blackwell Publishing, Ltd.; 2006.

Software

4. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. *Obstet Gynecol* [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

Websites

7. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: <http://www.ama-assn.org/special/hiv/ethics>. Accessed June 26, 1997.

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