- 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 N_0 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 N_0 neck in these patients[3]. SLNB has been increasingly investigated as a tool in the management of the clinically N_0 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].

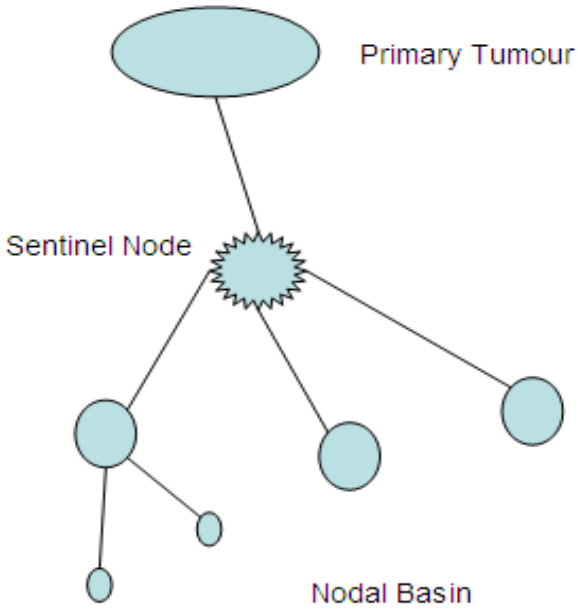

Figure 1: Illustration of the sentinel node concept

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].

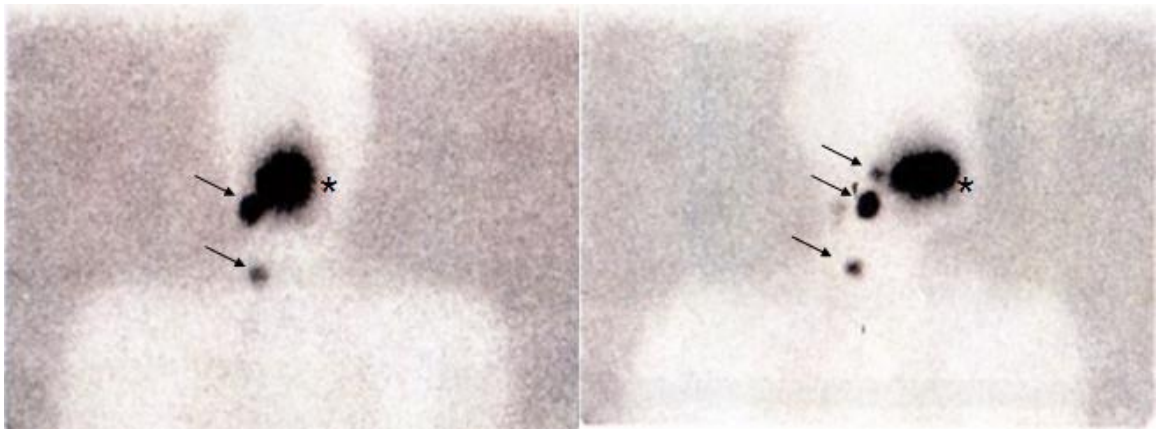

Figure 2: Lymphoscintigraphy; radioactivity seen from injection site around the primary tumour (*) and the sentinel nodes (arrows).

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].

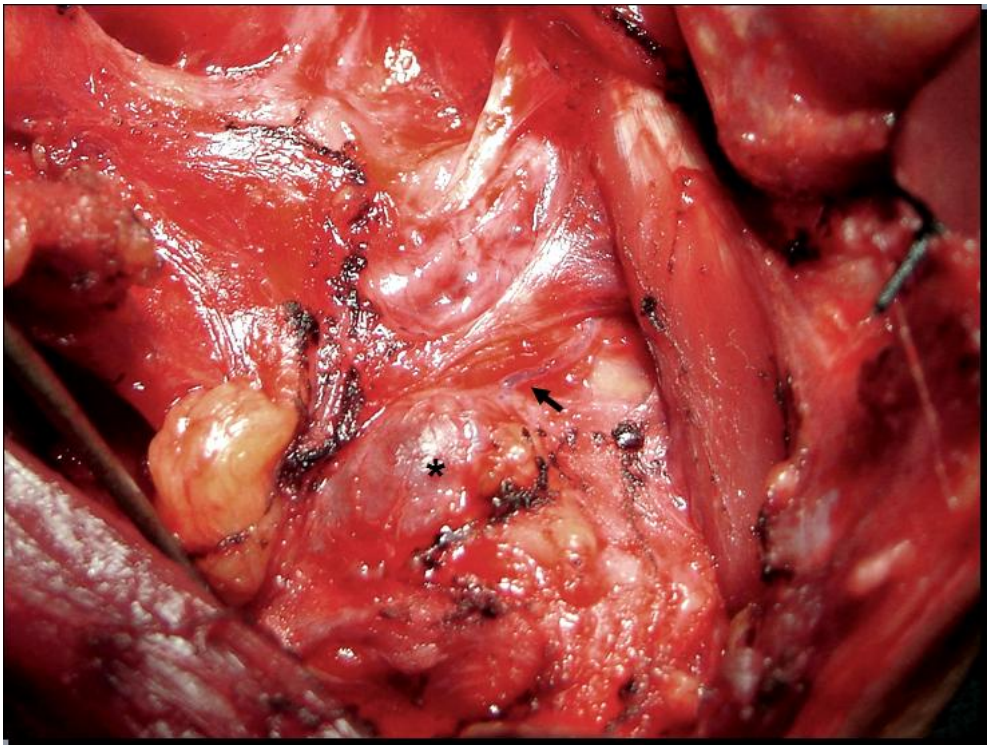

Figure 3: Blue dye identification in lymph node (*) and lymphatics (arrow)

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 150μm. 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 N_0 neck in head and neck carcinoma. It is suggested that its use should be restricted to early stage, $T_{1/2}\,N_0$, 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 N_0 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 T_{1-4} N_{0-3}.

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 N_0 and N_+ groups.

Results

Thirty three patients were included in the study, 13 in the N_0 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 N_0 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 N_0 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 dissection[1]. 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 analysis[6].

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 N_0 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 N_0 the staging of the primary tumours ranged from T_{1-4} and in the clinically N_+ group the staging ranged from T_{1-4} and N_{1-3}.

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 N_0 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 N_0 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 N_0 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 carcinoma[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)[7]. This accuracy was echoed in the results of the clinically N_0 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 N_0 neck in head and neck carcinoma. It is suggested that its use should be restricted to early stage, $T_{1/2}\,N_0$, SCC of the oral cavity and oropharynx[4]. 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 neck[1]. 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 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 [8]. 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 N_0 despite having clinically palpable lymph nodes. The preoperative clinical staging in these patients was: T_2N_1, T_3N_1, T_3N_{2b} and T_4N_{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 it's accuracy in the clinically N_0 neck, SLNB has yet to be accepted as a standard therapeutic option. Our results in the clinically N_0 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 N_0 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			
							Sentinel Nodes		Non-SN Nodes	
					T	N	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 post1/3 & 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

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)

INSTRUCTIONS TO AUTHORS: THE LARYNGOSCOPE

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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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