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Outcome of Single Tracer Sentinel Lymph Node Biopsy in Early Oral Cavity Squamous Cell Carcinoma

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Abstract
Purpose: *Cervical nodal status is one of the most important denominator of prognosis in oral cavity squamous cell carcinoma. Management of clinically negative cervical node is controversial and practice varies from institution to institution. But in most of the institutions Early oral malignancy with negative neck nodes is usually managed with elective neck dissection. Sentinel node biopsy can reduce the adverse events of neck dissection. Purpose of current study is to assess outcome of the procedure in our setup.*
Materials and Method: *This single institutional observational study was carried out in a tertiary care centre in north India Prior approval from hospital's Scientific and Ethical committee. Total 40 Patients with early OSCC [clinical T1, T2, N0] were included over a period of 20months. Single tracer SLNB using unfiltered 99mTc-sulfur colloid were performed followed by selective neck dissection. Nodal status determined on haematoxylin and eosin testing. Data analysed at the end of study period.*
Results: *Sentinel nodes were successfully harvested in 92.5 % cases. Average 2.4 sentinel nodes were harvested per person. In 42 % cases nodes were found in neck level II. A false negative rate of 0.11, accuracy of 0.89 and NPV of 0.86 were recorded. Highest number of false negative rate recorded in clinical stage T1 and in tongue respectively. In all three FOM cases detection of SLN failed due to shine through effect of radio colloid.*
Conclusion: *Results showed that SLNB is technically feasible in a centre like us where sentinel lymph node biopsies are already being performed. The outcome of the procedure is comparable to the existing literature.*
Keywords: *Sentinel Lymph node biopsy, Oral squamous cell carcinoma, Elective neck dissection.*

Introduction

Oral cavity cancer is the most common cancer in men and third most common cancer in women in India accounting for 75000 to 80000 new cases every year[1,2]. This is because of the typical behaviour of tobacco and betel nut chewing. Prognosis largely depends upon lymph-node status and survival dropped by 50 % with involvement of neck nodes. Current practice for management of node negative disease is elective neck dissection with its attending morbidity in a significant proportion of patients who are virtually over treated[3] In the past decade, the SLN-technique has been increasingly used for other malignancies, including head and neck carcinomas. Technical developments and a gain in experience have led to a wider use of SNB, even in the complex lymphatic

system of the head and neck region[4,5]. Multiple single institution studies, few multicentric trials and also some metaanalysis was done till date showing a detection rate of > 95 % and NPV of > 90 %.[6,7]. But no direct comparison of END and SLND has been performed. Due to lack of long term follow up data and RCTs the oncological safety is not established and hence SLNB for OSCC is not a standard practice in most of the institutions. The purpose of the current study is to investigate the results of sentinel lymph node biopsy in our setup.

Aim and Objectives

Aim of this study is to investigate the reliability of sentinel lymph node biopsy in predicting the staging of neck for early oral cancer [T1-T2, N0]. Primary objective was to ascertain whether a negative hematoxylin and eosin (H& E) finding from the SLNB procedure accurately predicted the negativity of the other cervical lymph nodes (LNs) which will be represented by NPV. Secondary objective is to calculate the accuracy and false negative rate.

Methods

Total 40 patient of early oral malignancy [T1,T2 N0] with significant risk of neck metastasis were enrolled in the study after taking informed consent. Approval was obtained from Scientific and Ethics Committee of the hospital. Since all patient ultimately underwent completion ND, we sought to define a group at low, but significant, risk of developing lymphatic metastasis. Therefore, minimally invasive lesions(invasion on imaging < 4mm) and lesions smaller than 6mm in diameter were excluded from the study. Prior neck surgery, trauma, radiation, diseases which might have alter the lymphatic drainage or recent cancer history led to exclusion.

Clinical staging performed by physical examination and neck imaging [CECT and CE MRI]. Patients received primary site injection with unfiltered 99Tc-sulfur colloid within 18hours of the surgical procedure. Injection was performed late the day before, or on the morning of the procedure. Dosage was 300 to 400 micro curies in 5 aliquots of 0.1 mL in patients injected less than 8 hours before the procedure. Dosage was 1 mCi for patients injected the afternoon before surgery. Serial nuclear imaging was then acquired at 15 min, 30 min and 60 min. Radioactive lymph nodes were identified with handheld gamma probe (Europhobe). SLNB was done through as small an incision as possible within the planned incision for selective ND and completion ND with removal of levels I, II (including IIB), III, and IV was done subsequently. All SLNs identified using the gamma probe were removed, including any LN exhibiting10%or more of the radioactivity of the most radioactive node. Routine H&E histopathology was used at the clinical sites to evaluate the SLN(s) and non-SLN(s). The sentinel lymph nodes were fixed in 10 % neutral buffered formalin and then bisected through there long axis at 2-3 mm interval. One hematoxylin and eosin (H & E) stained slide was prepared from each block and examined for possible metastasis. The relative performance of the test was evaluated using a negative-predictive value (NPV). False Negative Rate and Accuracy for evaluation of performance of a test were also calculated.

Results and Discussion

Table No. 1 Demographic characteristics and clinical data

Sex	**Frequency**	**Percent**
Female	9	23%
Male	31	78%
Age	**Frequency**	**Percent**
<60 years	28	70%
>60 years	12	30%
Tumour Location	**Frequency**	**Percent**
BUCCAL MUCOSA	8	20%
FOM	3	7%
RMT	4	10%
TONGUE	25	63%
Clinical Stage	**Frequency**	**Percent**
T1	24	60%
T2	16	40%
Level of Sentinel LN Identified	**Frequency**	**Percent**
I	11	27%
II	17	42%
III	9	23%
NOT DETECTED	3	8%
Imaging	**Frequency**	**Percent**
CECT	6	15%
CEMRI	34	85%
HPE	**Frequency**	**Percent**
MDSCC	17	43%
WDSCC	23	58%

Total 40 patient enrolled in the study. The drainage of radio colloid was found at least in one sentinel

lymph node in 37 patients. A sentinel lymph node cannot be detected in 3 patients. The identification rate was 92.5 %. In all the three patients where sentinel lymph node was not detected, no metastasis was found on final histopathological examinations. The mean number of sentinel nodes removed per patient was three 2.375 +/- 1.14774. Identification of sentinel node was failed in all the three floor-of-mouth lesion.]. The mean number of node harvested was 26.8 +/- 11.8; mean depth of tumour invasion was 11.1mm+/- 4.0 mm. On histopathological study out of 40 patient there were 8 patients (22%) who had showed metastasis in the sentinel node/nodes or both sentinel node/nodes and other cervical node/nodes. On further breakdown of the positive results sentinel node only positive cases are 4(11%) in number where rest of the neck nodes were negative. In 4 (11%) occasions we have found metastasis in other cervical nodes also. 25 (68%) cases showed true negative results where the sentinel lymph node/ nodes and rest of the cervical nodes showed no metastasis. In 4 (11%) cases a false negative sentinel node was obtained where sentinel lymph nodes were negative for metastatic deposit on H &E stain, but on further examination of cervical nodes a positive result was found. So the accuracy of the procedure was 0.89, negative predictive value of the procedure was 0.86 and false negative rate of the procedure was 0.11. The 95 % confidence interval of NPV was 0.68 to 0.96. The 95 % confidence interval of accuracy is 0.74 to 0.92[shown below].

Table No. 2- Table is showing the overall results. Overall accuracy of the procedure was 0.89 (95 % CI 0.74 to 0.92), negative predictive value of the procedure was 0.86 (95% CI 0.68 to 0.96) and false negative rate of the procedure was 0.11.

Clinical Status	Frequency	Percent
True Negative		68%
False Negative	4	11%
Total Positive	8	22%
Positive Breakdown		
SN only (Fp)	4	50%
SN & On Positive (TP)	4	50%
Accuracy	0.89(0.74,0.92)	
FNR	0.11	
NPV	0.86 (0.63, 0.96)	

Table No. 3- Table showing the results of sentinel lymph node biopsy procedure in respect of clinical T stage. The NPV, accuracy and False negative rate was 0.82 (95 % CI 0.60 to 0.95), 0.82 (95 % CI 0.70 to 0.88) and 14.29% respectively for T1 stage. The NPV, accuracy and False negative rate for T2 lesion were 0.87 (95% CI 0.47 to 1.00) ,0.94 (95% CI 0.70 to 0.88) and 0.06 respectively.

	T1		T2	
CLINICAL STATUS	**NO**	**%**	**NO**	**&**
True Negative	18	82%	7	44%
False Negative	4	18%	1	6%
Total Positive	0	0%	8	50%
Positive Breakdown				
SN only (FP)	0	0%	4	50%
SN & ON Positive (TP)	0	0%	4	50%
Accuracy	0.82 (0.70,0.88)		0.94(0.64,0.99)	
NPV	0.82 (0.60,0.95)		0.87 (0.47,1.00)	
FNR	0.18		0.06	

Table No. 4-table showing the results of accuracy, NPV and FNR of sentinel lymph node biopsy procedure with 95% confidence interval in respect to site of the tumours. NPV, accuracy and false negative rate for tongue was 0.86 (95% CI 0.65 to 0.97), 0.88 (95% CI 0.72 to 0.94) and 0. 12 respectively. The NPV, accuracy and false negative rate for buccal mucosal site was 0.80 (95% confidence limit 0.28 to 0.99), 0.87 (95% CI 0.42 to 0.90) and 0.125 respectively. the NPV, accuracy and false negative rate for RMT was 1 (95% CI 0.09 to 1.00), 1 (95 % CI 0.42 to 0.90) and 0 respectively.

	TUMOUR LOCATION					
	TONGUE		BUCCAL MUCOSA		OTHER	
CLINICAL STATUS	**NO**	**%**	**NO**	**%**	**NO**	**%**
TRUE NEGATIVE	19	76%	4	50%	2	50%
FALSE NEGATIVE	3	12%	1	13%	0	0%
POSITIVE	3	12%	3	38%	2	50%
POSITIVE BREAKDOWN						
SNONLY POSITIVE	1	33%	2	67%	1	50%
SN & ON POSTIVE	2	67%	1	33%	1	50%
ACCURACY	0.88 (0.72,0.94)		0.87 (0.42,0.90)		1 (0.3,1.0)	
NPV	0.86 (0.65,0.97)		0.80 (0.28,0.99)		1 (0.09,1.00)	
FNR	0.14		0.2		0	

Discussion

There are a number of studies focusing on the use of SLN in SCC. Butonly few studies do have a homogenous clientele with only small tumours and a clinical N0 neck in which the SLN is of importance. In addition the majority of these studies did not focus on a specific region (oral cavity vs.

oropharynx. The detection rate of sentinel lymph nodes by single dye technique in current study is 92.5 % (37/40) which compares favourably with the rate of sentinel node identification in patients undergoing SNB for head and neck cancer[8,9]. Literature showed that there is an established role of experience of the surgeon in determining the NPV and false negative rate, which reflects the significant learning curve[10].

Sentinel lymph node biopsy is technically challenging, particularly in head and neck area and difficulties may be encountered during lympho-scintigraphy as well as during surgery; sentinel lymph node may be too close to the primary injection site to be discernible by the gamma camera, and this is particularly troublesome for sentinel nodes in submental and submandibular region (level I) for a primary tumour located in the floor of the mouth. Infact the three occasions where we are unable to retrieve the sentinel node the primary injection site was floor of mouth. It is indeed noted in some previous studies that SNB is less reliable for tumours in the floor of mouth presumably due to the close proximity of the injection site to the primary draining nodes (58). Although use of lead shields and software masking may suppress the shine –through effect of primary site in floor of mouth, some would recommend routine exploration of level I lymph node station in all cases of floor of mouth primary. Blue dye visualization may be the primary means of identifying lymph nodes in level I, with the hand-held probe being used to confirm the presence of radio colloid within the lymph node ex-vivo. Last, removal of the primary tumour does not remove all radioactivity from the injection site, despite adequate tumour resection margins, although the reduction in radioactivity within the primary site can aid in the subsequent identification of hot lymph nodes close to the primary tumour.

Frozen section analysis was not used in this study, thus avoiding a further variable and ensuring that all the material was available for pathological analysis. The accuracy of frozen section has been questioned in melanoma and breast cancer[11,12]. Some studies have recommended serial sectioning of the SLNs at interval of 1-mm and immunohistochemical staining for keratin with pancytokeratin to reveal occult micrometastases. A study has suggested that serial sectioning, immunohistochemistry, and molecular methods may help to identify smaller metastatic deposits. The SLN biopsy has the benefit of concentrating only on the relevant nodes for pathological examination. This selection allows a more in depth evaluation of the small number of sentinel nodes, using step serial sections and immunohistochemistry[13]. However, if there are multiple SLNs at different levels, the number of SLNs that should be removed for the examination remains unknown. The majority of studies recommend the removal of at least 2-3 SLNs to reduce the possibility of false negative results[14]. In the present study, an average of 2.3 SLNs was detected per patient. The NPV is the closest equivalent to the clinical situation in a patient with low to moderate risk of harbouring cervical metastases and represents true-negatives as a fraction of total negatives. It answers the following question: If the sentinel node is negative, what is the percentage of risk that there is occult cancer in the neck?

NPV of current study is 86 % which is little inferior than the values mentioned in literature. Nonetheless the true NPV can only be determined by a trial where negative SLNBs will be observed without complete neck dissection, with several years of follow up. The false negative rate of current study is 11 % which is similar to that reported in a meta-analysis of 25,000 melanoma patients (12.5%) (38) and better than which is reported in 10-year follow-up of the Multicentre Selective Lymphadenectomy Trial (MSLT) inmelanoma [20 %][15]. However, our aim is to reduce this to the 7% FNR, accepted in breast cancer which reasonably corroborating with previous literature. The identification of aberrant drainage patterns is a huge advantage which in fact giving rise to currently emerging concept of gamma probe guided neck dissection.

The disadvantage of blanket ipsilateral END is illustrated in the study of pN0 necks treated by END[16]. In this series, the regional recurrence rate

of 18% seems high but it is worth noting that in over one third of patients (39%) recurrence occurred in the contralateral neck. One further advantage of SNB is that because the tissues have not been significantly disturbed, comprehensive salvage surgery is possible if a recurrence is detected promptly. At the present time, SNB is not widely recognized as standard care in early oral and oropharyngeal cancer. However, increasingly it is gaining utility in Europe and in some countries, such as Denmark, it is integrated into the standard care pathway.

Conclusion

The results of our prospective study are consistent with those of previous multicentre studies, which demonstrate that sentinel lymph node biopsy technique is a valid alternative to elective neck dissection in pathological staging of early oral malignancy with the exception perhaps of floor of mouth squamous cell carcinoma. A negative sentinel node on hematoxylin and eosin study predicted the negativity of the rest of the neck with high NPV for squamous cell carcinoma of the oral cavity. Successful application of SLNB technique for oral SCC requires surgical experience and technical devices including preoperative lympho-scintigraphy and intraoperative gamma probe. More over dynamic lympho-scintigraphy would appear to show the lymphatic stream from the primary tumour and could thus allow selective neck dissection to be tailored reducing the related morbidity.

References

1. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J ClinOncol Off J Am SocClinOncol. 2013 Dec 20;31(36):4550–9.
2. Byakodi R, Byakodi S, Hiremath S, Byakodi J, Adaki S, Marathe K, et al. Oral cancer in India: an epidemiologic and clinical review. J Community Health. 2012 Apr;37(2):316–9.
3. D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med. 2015 Aug 6;373(6):521
4. Stefanicka P, Profant M, Duchaj B, Valach M, Gal V, Dolezal P, et al. Sentinel lymph node radiolocalization and biopsy in oral cavity and oropharynx mucosal squamous cell carcinoma. Bratisl Lekárske Listy. 2010;111(11):590–4.
5. Trivedi NP, Ravindran HK, Sundram S, Iyer S, Kekatpure V, Durah S, et al. Pathologic evaluation of sentinel lymph nodes in oral squamous cell carcinoma. Head Neck. 2010 Nov;32(11):1437–43.
6. Ross GL, Soutar DS, Gordon MacDonald D, Shoaib T, Camilleri I, Roberton AG, et al. Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial. Ann SurgOncol. 2004 Jul;11(7):690–6.
7. Schilling C, Stoeckli SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. Eur J Cancer OxfEngl 1990. 2015 Dec;51 (18):2777–84.
8. Antonio JK, Santini S, Politi D, Sulfaro S, Spaziante R, Alberti A, et al. Sentinel lymph node biopsy in squamous cell carcinoma of the head and neck: 10 years of experience. ActaOtorhinolaryngol Ital OrganoUff Della Soc Ital Otorinolaringol E ChirCerv-facc. 2012 Feb;32(1):18–25.
9. Thompson CF, St John MA, Lawson G, Grogan T, Elashoff D, Mendelsohn AH. Diagnostic value of sentinel lymph node biopsy in head and neck cancer: a meta-analysis. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-LaryngolSoc EUFOS AffilGerSoc Oto-Rhino-Laryngol - Head Neck Surg. 2013 Jul;270(7):2115–22.
10. Alkureishi LWT, Ross GL, Shoaib T, Soutar DS, Robertson AG, Thompson R, et al. Sentinel node biopsy in head and neck

squamous cell cancer: 5-year follow-up of a European multicenter trial. Ann SurgOncol. 2010 Sep;17(9):2459–64.

11. Koopal SA, Tiebosch AT, Albertus Piers D, Plukker JT, SchraffordtKoops H, Hoekstra HJ. Frozen section analysis of sentinel lymph nodes in melanoma patients. Cancer. 2000 Oct 15;89(8):1720–5.
12. Weiser MR, Montgomery LL, Susnik B, Tan LK, Borgen PI, Cody HS. Is routine intraoperative frozen-section examination of sentinel lymph nodes in breast cancer worthwhile? Ann SurgOncol. 2000 Oct;7(9):651–5.
13. Werner JA, Dünne AA, Ramaswamy A, Dalchow C, Behr T, Moll R, et al. The sentinel node concept in head and neck cancer: solution for the controversies in the N0 neck? Head Neck. 2004 Jul;26(7):603–11.
14. Atula T, Shoaib T, Ross GL, Gray HW, Soutar DS. How many sentinel nodes should be harvested in oral squamous cell carcinoma? Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-LaryngolSoc EUFOS AffilGerSoc Oto-Rhino-Laryngol - Head Neck Surg. 2008 Jul;265 Suppl 1:S19-23.
15. Valsecchi ME, Silbermins D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: a meta-analysis. J ClinOncol Off J Am SocClinOncol. 2011 Apr 10;29(11):1479–87.
16. Ganly I, Goldstein D, Carlson DL, Patel SG, O'Sullivan B, Lee N, et al. Long-term regional control and survival in patients with "low-risk," early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumor thickness. Cancer. 2013 Mar 15;119(6):1168–76.