Original Article

Role of Sentinel Lymph Node Drainage Mapping for Localization of Contralateral Lymph Node Metastasis in Locally Advanced Oral Squamous Cell Carcinoma – A Prospective Pilot Study

Abstract

Aim/Background: Sentinel lymph node biopsy (SLNB) has become the standard of care for nodal staging in early-stage oral squamous cell carcinoma (OSCC) as an alternative to elective neck dissection. However, the role of sentinel lymph node (SLN) and lymphatic drainage mapping with image-guided surgery has not been studied in locally advanced OSCC. Therefore, this study was undertaken to evaluate the role of lymphatic drainage mapping in the identification of contralateral cervical lymph node metastasis in locally advanced OSCC (Stage III-IVb). **Materials and Methods:** We have prospectively analyzed treatment-naïve patients of locally advanced, lateralized OSCC (n = 20). All patients underwent SLN imaging using peritumoral injection 0.5–1.0 mCi of 99 mTc-Sulfur colloid (Filtered) and intraoperative identification of contralateral neck nodes using a handheld gamma probe (Crystal Photonics). **Results:** A total of 20 patients (18 males and 2 females) with a median age of 52.5 (33–70 years) were included. Ipsilateral SLN was localized in 18 (90%) patients. Bilateral cervical nodes were visualized only in 7 (35%) patients on lymphoscintigraphy (LSG). Out of the seven patients, 5 patients underwent bilateral neck dissection and 2 patients had unilateral neck dissection with LSG-guided exploration of contralateral cervical node and intraoperative frozen section examination. Six out of these seven patients had one or other risk factor for contralateral metastasis (patients had either primary in the tongue, involvement of floor of mouth, or tumor thickness >3.75 mm). On postoperative HPE, only 1/20 (5%) patient showed metastasis in the contralateral cervical lymph node. **Conclusion:** Correct identification of metastatic disease in contralateral neck directly influences clinical management, as it can reduce contralateral neck failure rate and limit the morbidity associated with unnecessary contralateral neck dissection, and it is also crucial in radiotherapy planning in locally advanced OSCC. In the current study, lymphatic drainage mapping showed a metastatic rate of 5% in the contralateral neck nodes in locally advanced, lateralized OSCC. However, the role of SLNB and lymphatic drainage mapping in this subgroup of OSCC needs to be studied in larger population to validate these findings.

Keywords: *Head-and-neck squamous cell carcinoma, oral squamous cell carcinoma, sentinel lymph node, sentinel lymph node biopsy*

Parneet Singh, Pallvi Kaul[1], Tejasvini Singhal, Amit Kumar[2], Pankaj Kumar Garg[1], Manishi L. Narayan

Departments of Nuclear Medicine and [2]Otorhinolaryngology (ENT), All India Institute of Medical Sciences, Rishikesh, [1]Department of Surgical Oncology, Shri Guru Ram Rai Institute of Medical and Health Sciences and Shri Mahant Indiresh Hospital, Dehradun, Uttarakhand, India

Introduction

Cancers are considered one of the modern epidemics and now rank the leading cause of mortality, more so in age <70 years. The incidence of cancer is growing at a continuous rate and thus there is an increasing prevalence of mortality related to cancer.[1] Head-and-neck squamous cell cancer (HNSCC) rank the sixth most common type of cancer in the world and constitute 90% of all head-and-neck cancers.[2]

The prevalence of HNSCC has a high variation among different geographical regions and has generally been attributed to exposure to tobacco-derived carcinogens, excessive alcohol consumption, or both.[3] Developing nations contribute to three-fourths of the affected population.[4] In India, lip-and-oral cavity cancers rank second in terms of incidence and third in mortality with an overall incidence of 10.3%. The incidence among males is 14.8%, while in females it is 4.6%.[5]

Clinical stage of the disease and metastatic nodal involvement remains the most important prognostic factor for oral squamous cell carcinoma (OSCC). Presence of regional nodal involvement decreases the

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Address for correspondence: *Prof. Manishi L. Narayan, Department of Nuclear Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India. E-mail: manishi.ln@gmail.com*

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5-year survival from 82% (N0) to 53%.[6] The incidence of occult metastasis in patients with clinically N0 OSCC is reported to be >30%.[4]

Head-and-neck region has rich lymphatic connections, and this makes OSCC susceptible to cross midline. The frequency of contralateral cervical lymph node metastases in squamous cell carcinoma of the oral cavity varies between 0.9% and 36%.[7] The presence of contralateral lymph node metastasis decreases the 5-year survival rate in patients with OSCC, from 70% to 41.2%.[8] The risk of contralateral metastasis increases with increase in the size of primary, the dimensions of tumors crossing the midline. If tumors cross the midline by less than 1 cm, the risk of contralateral spread is of approximately 16%, which increases to 46%, and if tumor has crossed the midline by more than 1 cm.[9]

Sentinel lymph node biopsy (SLNB) has become the standard of care for staging of nodal metastatic spread in various malignancies including OSCC in early stage (Stage I and II). It can prevent unnecessary neck dissection and associated morbidity, thus ultimately affecting the prognosis of the patient.[10,11]

Use of preoperative lymphoscintigraphy (LSG) with single photon emission computed tomography/computed tomography (SPECT/CT) provides precise three-dimensional localization of tumor draining lymph nodes, while handheld gamma probe (GP) provides real-time identification of lymph nodes during surgery and ensures their removal, which are at times difficult to be separated from fatty tissue by visual inspection.[12] Newer techniques involve use of positron emission tomography/CT in identifying the sentinel nodes with more precision.[12]

In general, SLNB is indicated for patients with biopsy-proven early-stage OSCC (Stage I, II) with clinically and radiologically N0 neck nodes. However, limited studies are available in literature utilizing LSG and image-guided surgery in locally advanced oral cancer.

In developing nations, patients usually present in late stages of disease as opposed to the West. In India, about 70% of cases present with locally advanced disease (American Joint Committee on Cancer, Stage III-IV), thus making correct identification of contralateral nodal metastasis very important.[13] Correct identification of metastatic disease in contralateral nodes will have direct impact on the extent of surgery being planned, reduce and defines the extent of C/L neck dissection, dictates the need for postoperative radiotherapy. Recent surgical consensus guidelines (2019) on SLNB in patients with oral cancer also emphasised the exploration of navigation-guided SLNB to stage C/L neck in locally advanced disease.[12] Therefore, there is need to comprehensively evaluate diagnostic utility of LSG with intraoperative GP procedure in locally advanced oral cavity cancer.

Materials and Methods

This is a prospective, observational study. Histopathologically proven, treatment naïve patients, >18 years with locally advanced oral cancer (Clinical Stage III to IVb disease, American Joint Committee on Cancer 8th edition) who were planned for upfront surgery, were prospectively enrolled for the study. All eligible patients underwent LSG to identify sentinel lymph node (SLN) and lymphatic mapping. LSG was performed 1 h before the surgery using approx. 1 mCi/37MBq 99mTc-Sulphur colloid (filtered). Peritumour injection of tracer *(250–500 microCi in 0.4–0.5 ml volume of filtered Sulphur colloid solution)* was given superficially (submucosally or intradermally) in the four cardinal points around the tumor at 3,6,9 and 12 o'clock positions. Patients were advised to rinse the oral cavity immediately after the injection without swallowing, in order to reduce oral uptake. Lignocaine 10% spray or gel was used locally to reduce the injection site pain.

Initial dynamic, sequential static and SPECT/CT images of the neck were acquired using GE NMCT 670 dual head Gamma Camera. Dynamic imaging was done in supine position immediately after injection (30s/frame in 128 × 128 matrix) anterior view, followed by static images and SPECT/CT at 15 min and 60 min. postinjection.

Images were analyzed by an experienced Nuclear Medicine Physician, for visualization of lymphatic ducts directly draining from the injection site to lymph nodes, bilateral or unilateral drainage, number and intensity of uptake of first echelon nodes, number of second echelon nodes and additional lymph nodes appearing on delayed images in other basin.

SPECT/CT images were analyzed for identification of SLN and for lymphatic drainage pattern with reference to anatomical landmarks (vessels and muscles). CT images helped in better localization of a nodal cluster behind a single hot spot seen on planar images. Location of SLN with respect to the surgical neck levels (I to VII right and left), additional findings including enlarged nodes, cluster of nodes, incidental finding and other abnormalities were also analyzed with SPECT-CT and documented.

All qualitative imaging parameters including number, uptake intensity, and anatomical localization of tumor draining contralateral cervical lymph node station, anatomical/surgical level, and order of appearance of nodes were assessed and documented. Preoperative patient marking for location of SLN was based on SPECT/CT image findings with respect to anatomical landmarks. The lymph node identified first, which is closest to the primary tumor and brightest in intensity, was considered as SLN. Second echelon lymph nodes that were visualized after the first node were considered as having a low-probability SLN.

Table 1: Clinical details of patients included in the study

Characterstics	N
Median age (years)	52.5 (33-70)
Sex (%)	
Male	18 (90)
Female	2 (10)
Risk factor (tobacco)	
Smokeless	17
Smoked	11
Both	7
Presenting complaints	
Ulcerative	7
Ulcero-proliferative	9
Proliferative	4
Sub-site	
Buccal mucosa	7
Bucco-alveolar complex	5
Tongue	4
Lip	4
Clinical stage	
"TNM" stage	
T2N1M0 (Stage III)	2
T2N2bM0 (Stage IVa)	1
T3N0M0 (Stage III)	4
T3N1M0 (Stage III)	1
T3N2bM0 (Stage IVa)	1
T3N2cM0 (Stage IVa)	1
T4aN1M0 (Stage IVa)	2
T4aN2bM0 (Stage IVa)	3
T4aN3bM0 (Stage IVb)	2
T4bN2bM0 (Stage IVb)	1
T4bN3bM0 (Stage IVb)	2

*AJCC 8th edition Clinical Stage III – 7 cases, Stage IVa – 8 cases and Stage IVb – 5 cases. AJCC: American Joint Committee on Cancer, TNM: Tumour, node, and metastasis[25]

Intraoperative GP *(SG-04 Model: MK482HN/A, Crystal Photonics)* was used for the localization of radioactive lymph nodes. All the radioactive nodes identified were removed. Lymphnode with highest count rate was considered as the first echelon node. Histopathological diagnosis of lymph nodes served as the standard of reference.

Results

This was a time-bound, prospective pilot study to establish the feasibility of sentinel node biopsy and lymphatic drainage mapping in locally advanced OSCC. We have prospectively analyzed treatment-naive, histopathologically proven patients with locally advanced OSCC, who were planned for primary surgical management, enrolled from February 2020 to June 2021. A total of 20 patients (18 males and 2 females) with a median age of 52.5 (33–70 years) were included. Owing to the pandemic restrictions and less number of patients visited the hospital and only twenty patients with locally advanced oral cavity squamous cell carcinoma, who fulfilled the inclusion criteria, qualified for the final analysis. The demographic details of these patients are described in Table 1.

Clinical details

Operative details

Majority of the patients 16/20 (80%) underwent composite resection with a circumferential margin of 1 cm, while the remaining 4/20 (20%) patients underwent hemi-glossectomy. Only ipsilateral neck dissection was performed in 12/20 cases [Table 2], and 8/20 patients underwent bilateral neck dissection as per the institutional management guidelines [Table 3] based on characteristics such as site of primary, distance from midline, involvement of floor of mouth, and clinical or radiological nodal involvement.

In well-lateralized tumors, only ipsilateral neck was addressed; however, for primary lesions which were approaching or crossing the midline, contralateral neck was also addressed (selective neck dissection [SND] in cases with cN0 and modified radical neck dissection [RND] in cN + cases).

Lymphoscintigraphy

All the patients recruited in the study underwent preoperative mapping of sentinel nodes with planar and SPECT/CT LSG on Discovery NM CT 670 (16 slice), followed by intraoperative identification of lymph nodes using SG-04 Model: MK482HN/A GP (Crystal Photonics).

Planar (LSG) imaging identified sentinel lymph in 15/20 (75%) patients and no draining node could be localized in 5/20 (25%) patients up to 60 min post injection. Of these five patients, three had SLN near the primary tumor (1b/II) identified on SPECT-CT Imaging and GP*,* while 2/5 patients SLN could not be identified on imaging. Additional draining lymph nodes were identified in 9/20 (45%) patients.

On SPECT/CT evaluation, SLN on the ipsilateral side was localized in 18/20 (90%) patients. In the remaining 2/20 patients, no sentinel node on ipsilateral neck could be identified. Additional draining lymph nodes were identified in 14 (70%) patients. Lymphatic drainage to contralateral neck node was visualized only in 7/20 (35%) patients. Of these seven patients, 6 had one or other risk factors for contralateral nodal metastasis (patients had either primary of tongue, involvement of floor of mouth, or large lesion approaching/involving midline and one patient had poorly differentiated tumor). However, no high-risk feature was seen in one of these seven patients. Additional draining lymph nodes on contralateral side were identified in 5/7 (71.4%) patients. In these seven patients, only 5/7 patients underwent bilateral neck dissection and 2/7 had unilateral neck dissection with LSG-guided exploration of contralateral cervical node and frozen section examination. The details of the patients who underwent bilateral neck dissection are described in Table 3.

Table 2: Details of patients who underwent ipsilateral neck dissection

Name	Diagnosis	Clinical Stage (AJCC 8th Edn.)	Neck Dissection	SPECT & GP				Ipsilateral ND
				Nodes Identified		Metastases found on HPE		
				I/L	C/L	I/L	C/L on frozen section	All Neck Nodes Dissected & Metastases found on HPE
RFN-1	Ca. Rt. Lower Lip	cT3N2bM0 (IVa)	Rt. MND Type 3	IB, II	-	Negative	NA	Negative
AKR-2	Ca. Rt. Border of Tongue	cT2N2bM0 (IVa)	Rt. RND	II	-	II- 2/3	NA	Positive II (2/3)
SDN-3	Ca Rt. Buccal Mucosa	cT4aN2bM0 (IVa)	Rt. MND Type 3	IIB/IB	-	IB- 2/5	NA	Positive IB (2/5)
MNH-4	Ca Lt. Lower Alveolus	cT4aN2bM0 (IVa)	Lt. MND Type 3	IB (V. Faint)	-	IA+ IB-4/7	NA	Positive IA+IB-4/7
GPL-30	Ca Lt. Lower Alveolus	cT4aN3bM0 (IVb)	Lt. MND Type 3	IB	-	Negative	NA	Negative
NTU-26	Ca Rt. Buccal Mucosa	cT4bN3bM0 (IVb)	Rt. MND Type 1	IA	-	IA- 3/3	NA	Positive IA-3/3, II-1/3
VSK-27	Ca Lt. Buccal Mucosa	cT4aN1M0 (IVa)	Lt. MND Type 3	IB	-	Negative	NA	Negative
YSN-35	Ca Lt. Border of Tongue	cT3N0M0 (III)	Lt. SND (I-IV) Rt. SLN (F.S)	II, IV	II	Negative	Negative	Negative
KJt-38	Ca Rt. Lower Lip	cT3N0M0 (III)	Rt. MND Type 3	IB	-	IL-IB-2/5	NA	Positive IB-2/39
PMC-39	Ca Lt. Border of Tongue	cT2N1M0 (III)	Lt. MND Type 3	IB	IB	I/L-IB-1/1	Negative	Positive IB-1/54
ZMH-40	Ca. Rt. Lower Lip	cT2N1M0 (III)	Rt. MND Type 3	IB	-	Negative	NA	Negative
MDN-41	Ca Lt. Buccal Mucosa	cT3N1M0 (III)	Lt. MND Type 3	IB, II	-	I/L-IB-2/2	NA	IB -1/22

Unilateral neck dissection group

A total of 12 out of 20 patients underwent unilateral neck dissection. SLN was identified on the ipsilateral side in these 12 patients who underwent unilateral neck dissection, while lymphatic drainage to the contralateral node was visualized only in 2 out of the 12 patients [Table 2] on LSG. In these two patients, frozen section of the identified node on the contralateral neck was sent for HPE and was found to be negative for metastasis.

Bilateral neck dissection group

A total of 8/20 patients underwent bilateral neck dissection. Lymphatic drainage to contralateral cervical nodes was visualized in 5/8 (62.5%) patients. In 4 out of these five patients, both sentinel and rest of the dissected contralateral lymph nodes were negative for metastasis on HPE [Figure 1]. While in 1/5 patient, contralateral cervical node identified on LSG was positive for metastasis (sensitivity – 100% and specificity – 100%) [Figure 2]. In this patient, a total of 2/55 nodes dissected were positive for the presence of metastasis on the contralateral side. In this study group, we were able to accurately identify the presence of contralateral nodal metastasis on LSG procedure.

Of 8/20 patients who underwent bilateral neck dissection, ipsilateral SLN was identified in six patients. A total of 3/6 patients had no metastasis in the ipsilateral side and rest of the dissected neck on final HPE, while in the remaining 3/6 patients, ipsilateral sentinel node showed the presence of metastasis [Table 3]. Two patients in which ipsilateral sentinel node could not be identified had very large size of the primary lesion and presence of lymphovascular invasion on HPE which can explain the nonvisualization of sentinel node of ipsilateral side due to blockage of lymphatic channels by tumor cells. In one of these two patients, there was visualization of lymphatic streaking adjacent to the primary; however, no nodes were found on HPE at that location. The visualized streaking was possibly due to the visualization of lymphatic vessels draining the primary prior to the obstruction.

Intraoperative gamma probe localization

On intraoperative GP assessment, SLN could be identified in 14 (70%) patients. Among the remaining 2/6 patients, SLN nodes that were identified on SPECT/CT got excised along with the primary. However, in 4/6 patients, SLN could not be identified separately with intraoperative GP. This could possibly be due to the proximity of nodes with the primary lesion. Out of the six patients showing contralateral drainage on SPECT/CT, we were able to localize contralateral nodes with GP in 6/8 (75%) patients.

On final HPE, 12/20 (60%) patients were positive for ipsilateral nodal metastasis. Out of eight patients who underwent bilateral neck dissection, only 1/8 (12.5) patient had metastasis in the contralateral neck. The metastasis was seen in 42/738 (5.7%) of ipsilateral nodes identified, while contralateral lymph nodal metastasis was seen in 2/230 (0.87%) nodes identified, with an overall 44/968 (4.5%) nodes dissected showing tumor deposits.

Survival outcomes

In the present study, the mean follow-up period was 12.2 months (±11.3 months) with a range of 1–29 months.

Table 3: Details of patients who underwent bilateral neck dissection

SLN Code	Diagnosis	Clinical Stage (AJCC 8th Edn.)	Neck Dissection		SPECT & GP				MND	
					Nodes Identified		Metastases found on HPE		All Neck Nodes Dissected & Metastases found on HPE	
			I/L	C/L	I/L	C/L	I/L	C/L	I/L	C/L
TSM-9	Ca Lt. Border of Tongue	cT3N0M0 (III)	MND type 3	SOHND	IL-II	IB	Negative		Negative	Negative
SDK-19	Ca Lt. Lower BAC	cT4aN3bM0 (IVb)	MND type 2	SND (I-III)	-	III	Negative		Present IA (1/3), IIA (1/3), II B (5/9)	Negative
MNU-21	Ca Rt. BAC	cT4aN2bM0 (IVa)	MND type 2	SOHND	(Streak)	-	Negative		IB (4/8), IIA (1/12)	Negative
SHD-31	Ca Lt. Lower Lip	cT3N0M0 (III)	MND type 3	MND type 3	IB	IB	Negative		Negative	Negative
SNS-32	Ca Rt. BAC	cT3N2cM0 (IVa)	MND type 3	MND type 3	IB	II	1/5	1/5	IB-1/5, IIA (1/3), III (1/1)	IB (1/6), IIA (1/5)
RHK-33	Ca Rt. Buccal Mucosa	cT4bN3bhgnb ,,M0 (IVb)	MND type 2	SND (I-III)	IB	-	4/4	Negative	IB- 4/4	Negative
MAS-36	Rt. Buccal Mucosa	cT4bN2bM0 (IVb)	MND type 3	SND (I-III)	II	II	II- 2/9	Negative	IA-(2/3), IB-(2/2), IIA-(2/9), III-(1/2)	Negative
HRM-37	Lt. Buccal Mucosa	cT4aN1M0 (IVa)	MND type 3	MND type 3	II	-	Negative		Negative	Negative

All except two patients were alive and disease free during the last follow-up visit. Both the patients who died had primary malignancy as carcinoma left lower alveolus. Out of these two patients, one patient (pT3N2b) developed metastatic disease at 14th month of follow-up, was advised chemotherapy, but the patient denied further treatment and died 3 months later. The other patient (pT4aN3b) got COVID-19 infection 7 months post surgery and died 1 month later due to viral pneumonia.

Discussion

SLNB is a well-established modality for nodal staging in a wide range of tumors such as breast cancer, penile cancer, melanoma, and early-stage OSCC. It is based on the fact that the lymphatic spread of tumor occurs in a stepwise manner. SLN acts as a representative for the subsequent draining lymph nodes, making the examination of SLN a surrogate to determine the status of regional lymph nodes.

In early OSCC, SLNB is recommended as an alternative to elective neck dissection (END) and prevents neck dissection-related higher morbidity without affecting the overall survival. The present study extends the same concept of lymphatic drainage mapping in locally advanced OSCC.

Oral cancer has been a major public health problem in India, especially in low-income groups. Major risk factors for OSCC include tobacco (both smoked and smokeless) and alcohol. The annual incidence of oral cancer in South-East Asia is about 180,000 cases, approximately 90% of which can be attributed to tobacco smoking or chewing habits.[14]

The tumor sub-site varies widely globally. In the West, the most common subset was reported to be tongue (61.9%) followed by floor of mouth (16.2%).[15] While in India, the most common subset was buccal mucosa (35.5%), followed by alveolus (28%), tongue (17%), and gingivo-buccal cavity (10%) as reported by Krishna *et al*.[16] This might be due to the high incidence of tobacco chewing (Gutka, Paan) in the Indian population. In the present study, buccal mucosa was the most common sub-site involved by the tumor accounting for 7 (35%) patients. Other sub-sites include bucco-alveolar complex in five patients (25%), tongue in four patients (20%), and lip in remaining four patients (20%).

In developing countries like India, most of the patients present in late stages of cancer, as described by Singh *et al*. in their retrospective study on clinical profile and epidemiological factors of oral cancer. This study included 479 patients, of which 135 patients (28.2%) presented with Stage III disease, while 307 (64.1%) patients presented with Stage IV disease.[17] Similar trend was observed in the present study where 7/20 patients (35%) had Stage III disease, 8 (40%) patients had Stage IVa, and 5 (25%) patients had Stage IVb disease.

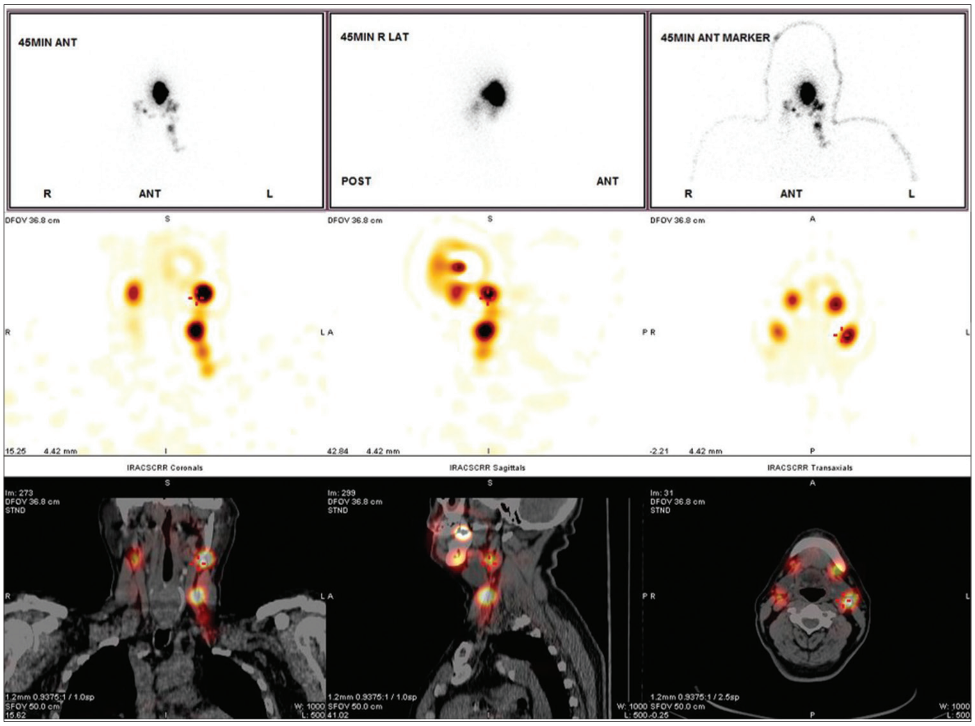

Figure 1: Lymphoscintigraphy (LSG) images obtained after peritumour injection of 99mTc-Sulphur Colloid, in a patient was carcinoma of left lateral border of tongue cT3N0M0. Planar and SPECT/CT images show bilateral drainage from the primary. The sentinel node identified at Level II on ipsilateral side and tumor draining contralateral node was identified at Level Ib cervical station.This patient underwent ipsilateral MND Type 3 with contralateral SOHND. Final HPE showed bilateral neck free of metastasis. SOHND: Supraomohyoid neck dissection, SPECT/CT: Single photon emission computed tomography/ computed tomography, MND: Modified neck dissection HPE: Histopathological examination

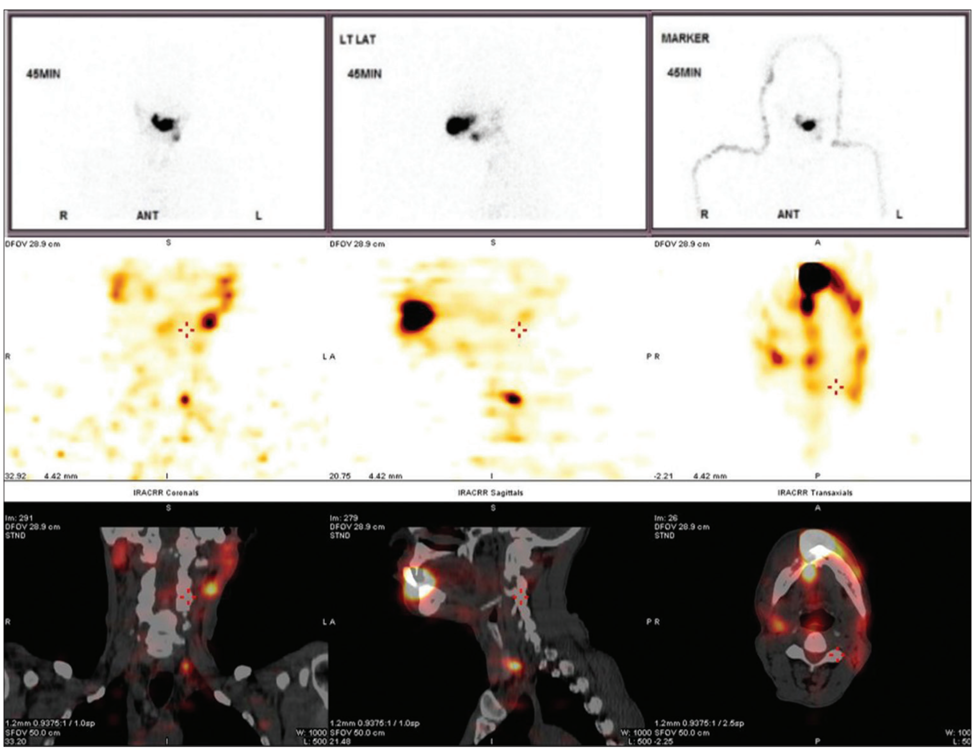

Figure 2: Lymphoscintigraphy (LSG) planar & SPECT-CT images obtained in a patient with carcinoma of right lower bucco-alveolar complex cT3N2cM0. The images show bilateral drainage from the primary. The sentinel node was identified at Level IB on ipsilateral side and tumor draining contralateral node was identified at Level-II cervical station. This patient underwent bilateral MND Type 3 and final HPE showed the presence of metastasis in bilateral tumor draining nodes and some additional nodes on ipsilateral side

In our study, 16 (80%) patients underwent composite resection with a circumferential margin of 1 cm, while the remaining four (20%) patients underwent hemi-glossectomy. All patients underwent adjuvant locoregional radiotherapy. Ipsilateral modified neck dissection (MND) was done in 18/20 patients, ipsilateral radical neck dissection(RND) in 1/20, and ipsilateral selective neck dissection (SND) in remaining one patient, considering the same as standard of care. Contralateral neck dissection was done only in case, where tumor was approaching the midline or in cases with clinically involved contralateral neck (n = 8; 40%). Out of eight patients undergoing contralateral neck dissection 3 (37.5%) patients underwent SND, 3 (37.5%) patients underwent MND, and in remaining 2 (25%) patients supraomohyoid neck dissection was performed. The surgical approach followed was in accordance with the standard management recommended by NCCN guidelines (2021) and Indian clinical practice consensus guidelines for the management of oral cavity cancer (2021).[11,18]

All the patients recruited in the current study underwent preoperative mapping of sentinel nodes with planar and SPECT LSG on Discovery NM CT-670 (16 slice). SLN was identified in 18/20 (90%) patients on the ipsilateral side. However, contralateral neck nodes were visualized only in 7 (35%) patients. No studies have been reported in literature till date that evaluated the role of preoperative contralateral tumor draining lymph node identification in late stages of tumor. However, drainage patterns have been well studied in early-stage OSCC (T1/T2) in a large multicenteric SENT trial by Schilling *et al*., where the author encountered contralateral drainage in 12.4% of patients with well-lateralized tumor.[19] Thus, the results of present study were in line with the previously published studies, which showed that the incidence of contralateral neck drainage varies between 0.9% and 36%, with increased risk in advanced clinical stages of tumor, as included in the present study.[7,19-21]

In the present study, ipsilateral SLN was identified in 18/20 (90%) patients by SPECT/CT. However, SLN was identified only in 14 (70%) patients by intraoperative GP. Majority SLN missed on intraoperative GP was from Level I and II located very near to the primary tumor, possibly be due to greater spillover of counts from the primary site. This finding was in agreement with the existing literature, where SLN identification rate was higher with preoperative LSG than with intraoperative GP.[22] Plausible explanations for the same might be that the sentinel node sometimes contains so little radioactivity that it cannot be picked up by a probe through the intact skin and also the nodes in vicinity of the primary tumor are likely to be overlooked due to shine through of the counts from the injection site. Nieweg *et al*. also reported the same findings and suggested that preoperative LSG imaging increases the likelihood of identification of the sentinel nodes.[22]

Contralateral lymphatic drainage was identified in 7 (35%) patients only. Out of seven, 6 patients had one or other risk factors for contralateral nodal neck drainage as described by Fan *et al*. in their study.[20] Of the seven patients who had contralateral drainage, four patients had primary of tongue, while 4 had involvement of floor of mouth, and all of these six patients had tumor thickness >3.75 mm.

The concept of SLNB can also be used to define the extent of radiotherapy in patients with HNSCC. This has been studied by de Veij Mestdagh *et al*. in T1-3N0-2bM0, HNSCC in their proof-of-principle trial. They have established the feasibility, safety, and clinical benefit of SPECT/CT-guided elective neck irradiation (ENI) over bilateral ENI. They have studied the use of lymphatic mapping with SPECT/CT to limit radiotherapy to ipsilateral side in patients with negative contralateral sentinel node on HPE. They concluded that SPECT/CT-guided ENI reduces significantly the incidence of dysphagia, feeding tube placement, and late xerostomia and improved the health-related quality of life.[23]

One similar trial, SUSPECT-2, is being conducted by de Veij Mestdagh *et al*. at Netherlands Cancer Institute. Their aim is to correctly localize lymphatic drainage using SPECT/CT and to give bilateral ENI only to patients with histopathologically confirmed metastasis in contralateral tumor draining node. Patients with no evidence of contralateral drainage or metastasis, will be given unilateral ENI only.[24]

Contralateral neck dissection was done in a total of 8 (40%) patients in our study. Out of these eight patients, five patients had bilateral drainage on LSG and the other 3 had high clinical Stage (IVa or IVb). Out of the five patients who showed bilateral drainage, only 1 (20%) patient was found to have metastatic deposits in contralateral lymph nodes on HPE. This patient had 2 lymph nodes positive for metastasis and one of these was Level 1b, which was the tumor draining lymph node of the contralateral side as identified by LSG. Thus, reinforcing the hypothesis that if management would have been decided based on LSG-guided SLNB and frozen section analysis, then contralateral neck dissection could have been avoided in four patients [Figure 3].

We hereby also acknowledge the fact that in advanced cancer, there may be nonvisualization of nodes due to obstruction of lymphatic capillaries by tumor cells, thus leading to misinterpretation or false negative results on LSG, due to absent contralateral drainage. Therefore, we would like to propose that standard surgical plan should not be changed, in cases where contralateral lymphatic drainage is not visualized, especially in advanced cancers.

The major limitations of the current study were small sample size and limited follow-up period to establish the oncological safety of the procedure. Thus, larger studies should be performed to evaluate the role of LSG and SLNB in locally advanced OCSCC.

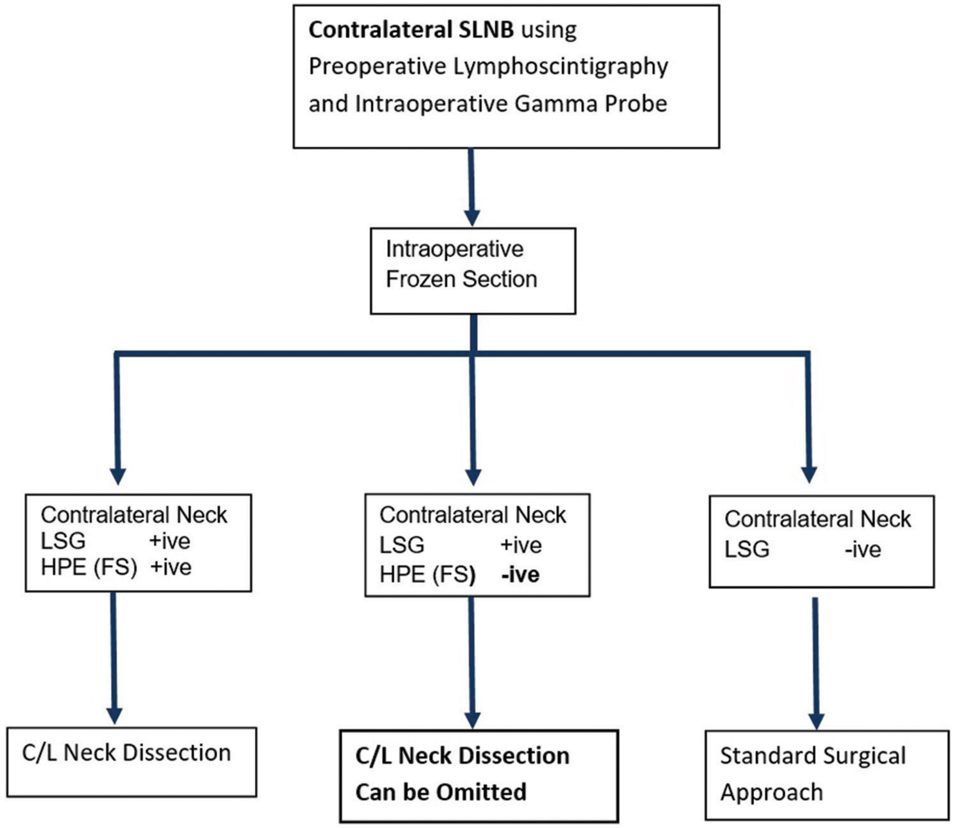

Figure 3: Proposed plan for surgical management in locally advanced OSCC, based on lymphatic drainage mapping using LSG

Conclusion

Correct identification of metastatic disease in contralateral neck directly influences clinical management, as it can reduce contralateral neck failure rate and limit the morbidity associated with unnecessary contralateral neck dissection, and it is also crucial in radiotherapy planning in locally advanced OSCC.

It is a well-established fact that ipsilateral SLN, when identified, is representative of metastatic spread to the rest of neck on ipsilateral side due to stepwise spread of metastasis. This concept of SLN identification and lymphatic drainage mapping using 99mTc-Sulphur colloid could possibly be extended to assess the contralateral neck nodal status in locally advanced OSCC, to identify the first draining lymph node for both ipsilateral and contralateral drainage. SPECT-CT-guided approach can additionally be extremely useful for accurate localization and staging contralateral neck nodes in locally advanced OSCC.

In the current study, lymphatic drainage mapping of contralateral neck correctly identified the presence (n = 1) or absence (n = 4) of metastatic disease in contralateral neck on imaging and intraoperative probe-guided lymph node biopsy procedure in surgically explored bilateral neck dissection group with a sensitivity and specificity ~100%. A metastatic rate of 5% was noted in contralateral neck nodes in locally advanced, lateralized OSCC, in total patient population currently studied.

However, if the sentinel node is not visualized, this could possibly be due to blockage of lymphatics, as seen in 2/20 patients in our study. In both of these patients, HPE revealed lymphovascular space invasion by the primary tumor, which explains the nonvisualization of nodal drainage.

Hence, we hypothesize that identification of tumor draining node and lymphatic drainage mapping can be used to guide modified, tailored approach for the management of the contralateral neck, in locally advanced OSCC as it can accurately identify the patients with presence or absence of contralateral metastasis. Thus, END can selectively be offered only in patients with presence of metastasis in the contralateral neck, while END and associated morbidity can be safely avoided in patients when contralateral neck is free of metastasis. It can serve as a potential decisive tool to provide an adaptive, approach in RT planning and for surgical management in advanced OSCC.

Owing to small sample size in the present study, we also propose that the role of LSG and (SLNB) in locally advanced OSCC should be evaluated in larger population to validate these findings.

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Conflicts of interest

There are no conflicts of interest.

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