Exploring the Role of Intraoperative Frozen Section of the Sentinel Lymph Node in the Management of Early-Staged Oral Tongue Cancers

Abstract

Background: The present study aims to explore the role of sentinel lymph node biopsy (SLNB) with intraoperative frozen section in the management of early-staged oral tongue cancers. **Materials and Methods:** Fifty-two patients with clinical stages cT1/2N0 oral tongue cancers were included in the present study. The curative surgery was preceded by the performance of an SLNB using a dual technique. **Results:** The identification rate of sentinel lymph node (SLN) in this study was 98.07%. The sensitivity, specificity, positive predictive value (PPV), and the negative predictive value (NPV) of SLNB were 88.2%, 100%, 100%, and 94.5%, respectively. Further, the sensitivity, specificity, PPV, and the NPV of intraoperative frozen section of the SLN were 70.5%, 100%, 100%, and 87.5%, respectively. **Conclusions:** The addition of intraoperative frozen section could identify 70.5% of patients with occult metastasis. An intraoperative frozen section assessment of sentinel node has the potential to change the overall management of patients with early-oral tongue cancers.

Keywords: *Clinically negative neck, intraoperative frozen section, neck ultrasound, oral tongue cancer, sentinel lymph node biopsy*

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Introduction

The global incidence of lip, oral cavity, and pharyngeal cancers is 529,500, which represents about 3.8% of all the cancer cases. This incidence is predicted to rise by 62% to 856,000 cases by the year 2035 because of changes in demographics.[1] Among the various head-and-neck subsites, global trends suggest, oral tongue as the most common subsite to be affected by squamous cell carcinomas.[2] The status of the cervical lymph nodes is considered to be the single most important factor in determining the staging, management, and prognosis of all patients with oral cavity squamous cell carcinomas. The inaccuracy of clinical examination and imaging to reliably detect occult cervical lymph node micrometastasis, along with the evidence from randomized clinical trials has resulted in elective neck dissections (END) becoming the standard of care for the vast majority of patients with early-stage oral squamous cell carcinomas (OSCCs).[3] However, about 70%–75% of the patients with early-staged OSCCs will not harbor cervical lymph nodal metastases and hence risk being subjected to overtreatment by END. Sentinel lymph node biopsy (SLNB) has over the years emerged as a powerful tool in the management of many cancers, and the same experience has been applied to early-stage OSCCs.[4] Although many studies have assessed the role of SLNB in all oral cavity cancers, only a few have focused on the oral tongue subsite. We share our experience of SLNB in an exclusive cohort of oral tongue cancers in an apex regional cancer center from India along with a special emphasis on the role of intraoperative frozen section.

Materials and Methods

This is a prospective, observational study conducted from November 2016 to May 2018 at an apex regional cancer center in India with due Institutional Review Board clearances. Fifty-two patients with clinical stages cT1/T2N0 oral tongue squamous cell carcinomas were included in the present study. All patients were evaluated by a comprehensive history, physical examination, and a biopsy confirmation of squamous cell carcinoma. The patients then underwent a chest X-ray and neck ultrasound as a part of the staging evaluation. Neck ultrasonography (USG) was performed by an experienced

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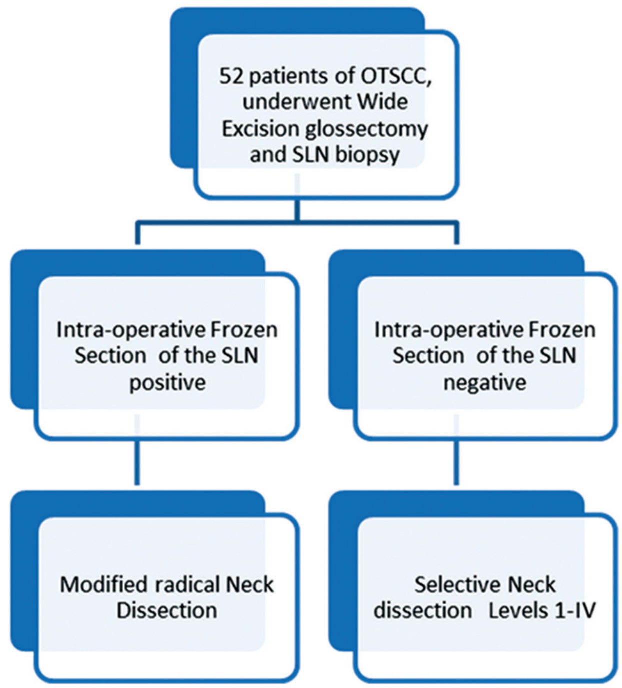
sonologist using a high-frequency 7 MHz transducer. Guided fine-needle aspiration cytology (FNAC) was performed on any indeterminate/suspicious cervical lymph node, and if the node was positive, the patient was not considered for an SLNB.

The selected patients subsequently underwent curative surgery which entailed a wide excision glossectomy and a neck dissection. Prior to the performance of the neck dissection, all the patients underwent an SLNB using a dual technique, i.e., both radionuclide scintigraphy using technetium-99 (Tc-99m) sulfur colloid and blue dye. 1.3 m Ci of unfiltered Tc-99m (0.5–0.6 ml) was injected in the submucosal plane along the superior and inferior margins equally in the nuclear medicine suite, 2 h before the planned surgery. A mouth rinse was advised following the injection to prevent the mixing with saliva and swallowing of residual radioactivity by the patient. A static lymphoscintigraphy in the anterior and lateral views was obtained (256 × 256 matrix, 1500–2000 kilo counts acquired for each image with transmission imaging) around 15–30 min following the injection. At the beginning of surgery, 1 ml blue dye was injected around the primary tumor with the help of insulin syringe. Insulin syringe was used for convenience, as 0.25 ml was to be injected at each of the four sites. A single-photon emission computed tomography study performed only in the initial few patients; however, no significant additional information was obtained from what was observed in the planar imaging.

The radioactivity was initially noted at the background and the site of primary tumor using a hand-held gamma probe (Dual head Infinia G.E Gamma Camera, Gamma probe. [CZT] Scintillator cadmium zinc telluride crystal). Any activity that was ten times more than the background activity was considered as significant. After 5 min of waiting period from the blue dye injection, an incision was first made in the neck at a transverse skin crease, corresponding to the maximum site of activity of the cervical lymph node as imaged on the lymphoscintigraphy. All the sentinel nodes (either hot or blue or both) were identified using a hand-held gamma probe and the visual presence of the blue dye uptake and was sent for frozen section. The nodes were bisected through the hilum, and frozen section was performed on one-half of the nodes, whereas the other half was sent for paraffin section. The neck was rechecked for any abnormal radioactive focus after the removal of all the sentinel nodes. The extent of the neck dissection, i.e., either selective or comprehensive was guided by the result of the intraoperative frozen section of the sentinel lymph node (SLN). If the node was positive for metastasis on frozen section, an ipsilateral modified radical neck dissection was performed, and if the frozen section of the node was negative, ipsilateral END (Levels 1-IV) was performed [Table 1].

Table 1: Study schema



OTSCC: Oral tongue squamous cell carcinoma, SLN: Sentinel lymph node

The primary tumor was then excised with 10-mm margin all around. All the neck nodes were then segregated and sent according to the neck node levels for the paraffin study. Step serial sectioning and immunohistochemistry (IHC) were not done on any of the node. The final histopathology of the neck dissection specimen was considered as the gold standard for statistical analysis.

Results

Fifty-two patients of early tongue cancer (cT1-T2N0) were included in the study. 75% of the patients were male; the mean age in our patient cohort was 49 years. 55.7% of the patients had cT1 tumors, whereas 42.3% of the patients had cT2 tumors. Twenty-seven patients had a lesion on the right lateral border of the tongue and 25 patients had on the left lateral border of the tongue.

On clinical examination, only 5 of the 52 patients had suspicious neck node, but only one patient harbored a positive node on final histopathology. Clinical examination further failed to detect the disease in 16 patients in whom neck node was positive on final histopathology. The sensitivity, specificity, positive predictive value (PPV), and the negative predictive value (NPV) of clinical examination were 5% (0.15–28.69), 88.5% (73.26–96.8), 20% (2.93–67.42), and 65.9% (62.09–69.63). The diagnostic accuracy of the clinical examination was 61.54% (47.02–74.7).

A neck USG was performed in all the patients. Twenty-two patients had suspicious node; however, none of them were positive on a guided FNAC. On correlation with the final histopathology, of the 22 patients, who had suspicious features on the neck USG, seven patients harbored positive nodes, whereas the neck nodes were negative in 15 patients. The sensitivity, specificity, PPV, and the NPV of neck ultrasound were 41.1% (18.44–67.08), 57.1% (39.35–73.68), 31.8% (19.04–48.07), and 66.6% (55.05–76.56), respectively. The diagnostic accuracy of the neck USG was 51.92% (37.63–65.99). The patients who were node positive on a USG-guided FNAC were not considered for SLNB.

The SLN identification rate of in this study was 98.07%. The total number of sentinel nodes identified in all was 153. The average number of sentinel nodes picked up by SLNB was 2.9. In two patients, contralateral sentinel neck nodes were identified, but both of them were negative for metastasis. One patient had a pT2N2M0 SCC Grade III with a depth of invasion of 8 mm and the other patient had a pTx (1) N0M0 SCC Grade II). Neck nodal levels II and III (86.5%) were the most common levels of SLN. Seventeen patients' harboured occult metastasis in the neck nodes, the occult nodal positivity rate was 32.69%.

SLNB had correctly identified 15 of the 17 patients with an occult metastatic neck node. Further, SLNB has correctly identified the negative status of the neck in 35 patients. The sensitivity, specificity, PPV, and the NPV of SLNB were 88.2% (63.56–98.54), 100% (90–100), 100%, and 94.5% (82.64–98.47), respectively. The diagnostic accuracy of SLNB was 96.15% (86.79–99.53). Of 153 SLNs, total of 20 nodes were positive and intraoperative frozen section had correctly identified 17 nodes. Level II neck nodes were the most common positive node, followed by Level I and Level III. In this study, none of the necks showed occult positivity in the Level IV node.

Intraoperative frozen section was able to identify the occult neck positivity in 12 patients; this resulted in change of intraoperative management of neck node from END to therapeutic neck dissection. The sensitivity, specificity, PPV, and the NPV of intraoperative frozen section were 70.5% (44.04–89.69), 100% (90–100), 100%, and 87.5% (77.02–93.06), respectively. The diagnostic accuracy of the intraoperative frozen section was 90.38% (78.97–96.50).

The sensitivity, specificity, PPV, and NPV of all the different diagnostic tools in our cohort are additionally depicted in Table 2.

Discussion

Head-and-neck cancers constitute approximately 25%–30% of all the malignant neoplasms in the Indian subcontinent, in contrast to the proportion being only about 3%–4% in the West.[5] Although the global trends suggest the oral tongue as the most common subsite to be affected by squamous cell carcinomas, cancers of the mouth (alveolus, buccal mucosa, and retromolar trigone) predominate in the Indian subcontinent.[6] Interestingly, many studies, including a study from the authors' center, have suggested that the incidence of tongue cancers is on the rise.[6,7]

The incidence of occult metastasis in this study is 32.69%, which is comparable to many other studies in which it ranges from 20% to 40%.[8-11] The detection of micrometastasis is a very challenging task in the management of early-staged oral cancers. Several imaging modalities, such as ultrasound with or without FNACs, computed tomography (CT) scan, magnetic resonance imaging (MRI), and positron-emission tomography (PET)-CT scans, have been evaluated in this setting with differing sensitivities.[12]

A metaanalysis by Liao *et al*. reported the sensitivity, specificity, PPV, and the NPV of the neck ultrasound to be 66%, 78%, 56%, and 84%, respectively.[12] The updated metaanalysis of by the same authors reported the pooled estimates for sensitivity to be 47%, 56.6%, 48.3%, and 63.3% for CT, MRI, PET scans, and ultrasound, respectively. The pooled estimates for specificity were reported as 88.9%, 82.5%, 86.2%, and 79.1% for CT, MRI, PET, and USG, respectively.[13]

The metaanalysis by de Bondt *et al*. comparing all the imaging modalities reported USG-guided FNAC to have the highest diagnostic odds ratio for staging of the neck, with a pooled sensitivity of 80% and specificity of 98%.[14] The same metaanalysis also reported USG as the most sensitive imaging technique for neck node staging, with a pooled sensitivity of 87% and pooled specificity of 86%, respectively. However, this metaanalysis included studies with both clinically negative and clinically positive necks and was not restricted to oral cavity cancers alone. The only study in this metaanalysis was confined to USG-guided FNAC in the clinically negative neck, and it reported a lower sensitivity of 48%.[15]

The sensitivity, specificity, PPV, and the NPV of the neck USG in our series were lower at 41.1%, 57.1%, 31.8%, and 65.9%, respectively. Many other authors also have reported lower

Table 2: The sensitivity, specificity, positive predictive value, and negative predictive value of all the different diagnostic tools in our cohort

Modalities	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
USG neck	41.1	57.1	31.8	66.6	51.92
Frozen section	70.5	100	100	87.5	90.38
SLNB	88.2	100	100	94.5	96.15

USG: Ultrasonography, SLNB: Sentinel lymph node biopsy, PPV: Positive predictive value, NPV: Negative predictive value sensitivities for neck USG and have hence recommended that USG of the neck is inadequate for decision-making with regard to the management of the cervical lymph nodes in patients with cT1/T2 N0 carcinoma of the oral cavity, including the cancers of the oral tongue.[16-20]

The inaccuracy of clinical examination and imaging to reliably detect occult cervical lymph node metastasis as described above have resulted in END becoming the standard of care (over watchful waiting) for the vast majority of patients with early-stage OSCC. SLNB has been deemed as an alternative staging procedure that can potentially address the controversy of the overkill and the needless morbidity of nearly 70%–75% of the pathologically node-negative patients undergoing END.[4]

SLNB has been introduced as a minimally invasive technique for nodal staging. The SLN is generally believed to be the first lymph node or lymph nodes group which receives lymphatic drainage from the primary tumor. If the SLN is metastasis negative, the non-SLNs in the neighboring regional basins are deemed to be negative of metastases as well. The proposed advantages of SLNB are its ability to identify skip metastases/metastases in unpredictable lymphatic basins, a focused histologic evaluation of the identified nodes at risk, decreased morbidity apart from a better health-related quality of life.[4]

A number of retrospective studies, a few prospective studies, and a few meta-analyses have clearly demonstrated the efficacy of SLNB in the detection of occult cervical lymph node metastases in OSCCs.[4] A recent meta-analysis of 66 studies comprising >3500 patients demonstrated a pooled SLN identification rate of 96.3%, a pooled sensitivity, NPV, and an area under the curve of 0.87, 0.94, and 0.98, respectively.[21] A subgroup analysis from the meta-analysis had shown that the application of IHC increased the sensitivity of SLN detection by about 11%; however, there was no significant difference between the serial step-sectioning group and "no serial-step sectioning" group.[21]

Another recent meta-analysis of SLNB focusing exclusively on oral tongue cancers, including 35 studies (with 1084 patients) reported a pooled SLN detection rate, was 98% (95% CI 97%–100%).[22] The pooled overall sensitivity and NPV of SLNB were 0.92 (95% CI 0.88–0.95) and 0.96 (95% CI 0.94–0.97), respectively. The subgroup analyses demonstrated that studies that recruited a higher number of patients (n = 30) were able to achieve a more stable NPV than the studies with a lower number of patients.[22]

The SLN identification rate of in this study was 98.07%. Further, the sensitivity, specificity, PPV, and the NPV of SLNB were 88.2%, 100%, 100%, and 94.5%, respectively, which very much comparable with what has been reported in the literature as captured in the recent meta-analysis.[21]

A major criticism of the acceptance of SLNB is the physical and psychological concerns resulting due to the necessity for a second-stage completion surgery in patients with positive SLNs.[4] The incorporation of intraoperative frozen section in SLNB protocol can identify the patients with occult micrometastasis at the time of the primary surgery and can potentially avoid a second surgery in the vast majority of the patients.

Very few earlier studies have explored the role of frozen section in the context of an SLNB. In one study, the sensitivity and the NPV of the SLNs were analyzed by fine-sectioned frozen section, i.e., 93% and 94%, respectively.[23] The occult metastasis rate reported in that study was much higher at 45%. The sensitivity, specificity, PPV, and the NPV of intraoperative single-section frozen section analysis of the SLN in our patient cohort were 70.5%, 100%, 100%, and 87.5%, respectively.

It is important to note that although the use of an intraoperative frozen section of the SLN can identify the vast majority of patients with occult metastasis, there remain a fraction of patients with an occult disease which may not be detected. Hence, all the patients in our study, in whom, an SLNB was negative on frozen section, were subjected to an END as per the standard management guidelines. The results of this study with regard to the use of intraoperative frozen section are compelling and can be potentially practice changing. Our study result, however, needs to be validated in a larger cohort of patients, and more importantly, the long-term oncological results of SLNB should be comparable with that of END.

The accuracy of SLNB can possibly be further improved with the incorporation of IHC and serial step sectioning; however, this would considerably add to the costs of the overall procedure, and the later was not found to be effective as well[21] and was, hence, not considered in this study. Further improvement and refinement can be potentially achieved by the incorporation of novel technical innovations aimed at improving the intraoperative SLN localization, including the use of novel radiotracers, improved imaging techniques, molecular assays, and the use of sentinel node navigation surgery.[4] It is possible that with the incorporation of the novel technologies for accurate intraoperative SLN mapping, patients with no metastases on a frozen section assessment could in the near future avoid an END.

Conclusions

This study has demonstrated the feasibility of SLNB in the management of clinically node-negative early oral tongue cancers in a resource-constrained Indian setting. Further, in our study, SLNB emerged as a more accurate staging tool for the detection of occult neck metastases as compared to neck ultrasound. The incorporation of the frozen section of SLNB has the potential to change the management of early-staged tongue cancers and possibly even other subsites of oral cancers.

Ethical issues

All procedures performed in this case report were in accordance with the Ethical Standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Appropriate informed consents have been obtained.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, *et al.* The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin 2017;67:51-64.
2. Thangaraj SV, Shyamsundar V, Krishnamurthy A, Ramani P, Ganesan K, Muthuswami M, *et al.* Molecular portrait of oral tongue squamous cell carcinoma shown by integrative meta-analysis of expression profiles with validations. PLoS One 2016;11:e0156582.
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;373:521-9.
4. Krishnamurthy A. Current status and future perspectives of sentinel lymph node biopsy in oral cancers. Indian J Dent Res 2017;28:239-40.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
6. Elango KJ, Suresh A, Erode EM, Subhadradevi L, Ravindran HK, Iyer SK, *et al.* Role of human papilloma virus in oral tongue squamous cell carcinoma. Asian Pac J Cancer Prev 2011;12:889-96.
7. Krishnamurthy A, Ramshankar V. Early stage oral tongue cancer among non-tobacco users – An increasing trend observed in a South Indian patient population presenting at a single centre. Asian Pac J Cancer Prev 2013;14:5061-5.
8. El-Naaj IA, Leiser Y, Shveis M, Sabo E, Peled M. Incidence of oral cancer occult metastasis and survival of T1-T2N0 oral cancer patients. J Oral Maxillofac Surg 2011;69:2674-9.
9. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:160-7.
10. Kowalski LP, Magrin J, Waksman G, Santo GF, Lopes ME, de Paula RP, *et al.* Supraomohyoid neck dissection in the treatment of head and neck tumors. Survival results in 212 cases. Arch Otolaryngol Head Neck Surg 1993;119:958-63.
11. Shah JP, Andersen PE. The impact of patterns of nodal metastasis on modifications of neck dissection. Ann Surg Oncol 1994;1:521-32.
12. Liao LJ, Lo WC, Hsu WL, Wang CT, Lai MS. Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck – A meta-analysis comparing different imaging modalities. BMC Cancer 2012;12:236.
13. Liao LJ, Hsu WL, Wang CT, Lo WC, Lai MS. Analysis of sentinel node biopsy combined with other diagnostic tools in staging cN0 head and neck cancer: A diagnostic meta-analysis. Head Neck 2016;38:628-34.
14. de Bondt RB, Nelemans PJ, Hofman PA, Casselman JW, Kremer B, van Engelshoven JM, *et al.* Detection of lymph node metastases in head and neck cancer: A meta-analysis comparing US, USgFNAC, CT and MR imaging. Eur J Radiol 2007;64:266-72.
15. Takes RP, Righi P, Meeuwis CA, Manni JJ, Knegt P, Marres HA, *et al.* The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys 1998;40:1027-32.
16. Chaukar D, Dandekar M, Kane S, Arya S, Purandare N, Rangarajan V, *et al.* Relative value of ultrasound, computed tomography and positron emission tomography imaging in the clinically node-negative neck in oral cancer. Asia Pac J Clin Oncol 2016;12:e332-8.
17. Righi PD, Kopecky KK, Caldemeyer KS, Ball VA, Weisberger EC, Radpour S. Comparison of ultrasound-fine needle aspiration and computed tomography in patients undergoing elective neck dissection. Head Neck 1997;19:604-10.
18. Borgemeester MC, van den Brekel MW, van Tinteren H, Smeele LE, Pameijer FA, van Velthuysen ML, *et al.* Ultrasound-guided aspiration cytology for the assessment of the clinically N0 neck: Factors influencing its accuracy. Head Neck 2008;30:1505-13.
19. Byers RM, El-Naggar AK, Lee YY, Rao B, Fornage B, Terry NH, *et al.* Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue? Head Neck 1998;20:138-44.
20. To EW, Tsang WM, Cheng J, Lai E, Pang P, Ahuja AT, *et al.* Is neck ultrasound necessary for early stage oral tongue carcinoma with clinically N0 neck? Dentomaxillofac Radiol 2003;32:156-9.
21. Liu M, Wang SJ, Yang X, Peng H. Diagnostic efficacy of sentinel lymph node biopsy in early oral squamous cell carcinoma: A meta-analysis of 66 studies. PLoS One 2017;12:e0170322.
22. Yang Y, Zhou J, Wu H. Diagnostic value of sentinel lymph node biopsy for cT1/T2N0 tongue squamous cell carcinoma: A meta-analysis. Eur Arch Otorhinolaryngol 2017;274:3843-52.
23. Tschopp L, Nuyens M, Stauffer E, Krause T, Zbären P. The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx. Otolaryngol Head Neck Surg 2005;132:99-102.