e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 551-559

Original Research Article

Feasibility and Diagnostic Performance of Methylene Blue Dye-Only Sentinel Lymph Node Biopsy in Early Oral Cavity Squamous Cell Carcinoma: A Prospective Diagnostic Accuracy Study

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Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026

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Conflict of interest: Nil

Abstract

Introduction: Cervical lymph node status is the single most important prognostic determinant in oral squamous cell carcinoma (OSCC). Elective neck dissection results in overtreatment in a substantial proportion of clinically node-negative patients, whereas sentinel lymph node biopsy (SLNB) using low-cost methylene blue dye offers a feasible, minimally invasive alternative for nodal staging. We prospectively evaluated the diagnostic accuracy of methylene blue dye-only SLNB against formal neck dissection as the reference standard.

Methods: This prospective diagnostic accuracy study enrolled 70 consecutive patients with early oral cavity squamous cell carcinoma (T1–T2, cN0) at a tertiary care centre between March 2023 and September 2024. Methylene blue dye (1 mL) was injected peritumorally 15 minutes before incision as the index test; blue-stained nodes were harvested as sentinel lymph nodes (SLNs) and examined by haematoxylin and eosin staining. All patients subsequently underwent at least a supraomohyoid neck dissection, which served as the reference standard applied uniformly regardless of SLNB result. The primary endpoint was the SLN identification rate; secondary endpoints were sensitivity, specificity, PPV, NPV, false-negative rate, and diagnostic accuracy. Reporting follows the STARD 2015 guideline.

Results: SLNs were identified in 62 of 70 patients (identification rate 88.6%). In total, 131 SLNs were retrieved, with a mean of 2.1 nodes per patient among the 62 successfully mapped cases (1.9 across all 70 patients). SLN positivity was seen in 12 patients; pathological upstaging from cN0 to pN+ occurred in 20 patients (28.6%). Patient-level sensitivity, specificity, PPV, and NPV were 60%, 100%, 100%, and 86.2%, respectively. Overall diagnostic accuracy was 88.6% with a false-negative rate of 40%. The identification failure rate was 11.4% (95% CI: 6.5–22.5%).

Conclusion: Methylene blue dye-only SLNB is technically feasible and highly specific (100%) for nodal staging in early cN0 OSCC, but its 40% false-negative rate precludes standalone use as a decision tool to safely omit neck dissection. Dual-tracer techniques and serial sectioning with immunohistochemistry are recommended to reduce the false-negative burden.

Keywords: Oral Squamous Cell Carcinoma; Sentinel Lymph Node Biopsy; Methylene Blue Dye; Neck Staging; Diagnostic Accuracy; Low-Resource Oncology.

DOI: 10.25258/ijcpr.18.8.86

Introduction

Oral squamous cell carcinoma (OSCC) constitutes a major public health burden worldwide, with a disproportionately high incidence in developing countries owing to widespread tobacco, alcohol, and betel quid consumption. The status of cervical lymph nodes remains the single most important prognostic determinant in OSCC, with nodal metastasis associated with a marked reduction in survival [1,2]. Even in early-stage disease (T1–T2), approximately one-fifth to one-third of patients with a clinically node-negative (cN0) neck harbour occult metastasis, underscoring the limitations of clinical examination and conventional imaging in detecting early nodal involvement [3–5].

Elective neck dissection (END) has long been the standard approach for the cN0 neck; however, it results in overtreatment in a substantial proportion of patients and carries avoidable morbidity, including shoulder dysfunction, sensory deficits, and cosmetic concerns [6,7]. Sentinel lymph node biopsy (SLNB) has emerged as a less invasive staging technique based on the principle that lymphatic spread occurs in a predictable, stepwise fashion from the primary tumor to the first draining node [8]. In validated dual-tracer protocols, a negative sentinel node may reliably predict the absence of further nodal disease, potentially allowing avoidance of END in appropriately selected patients.

Over the past two decades, SLNB has been extensively evaluated in OSCC, with several multicentre studies and meta-analyses demonstrating high negative predictive value and establishing it as an accurate staging tool for early oral cavity cancer [9–11]. Nevertheless, most validated protocols rely on radioisotope tracers, often combined with blue dye, requiring nuclear medicine infrastructure, specialised equipment, and multidisciplinary expertise. These requirements significantly limit routine implementation of SLNB in low-resource settings [12].

Methylene blue dye represents a simple, inexpensive, and widely available alternative tracer. Its use eliminates dependence on radioisotopes and may facilitate broader adoption of SLNB, particularly in resource-constrained healthcare systems. Despite several radioisotope-based studies, methylene blue dye has not been rigorously evaluated for SLNB feasibility in OSCC in such settings. This study addresses that gap by prospectively assessing the diagnostic performance of methylene blue SLNB against formal neck dissection as the reference standard, and by identifying its limitations.

Materials and Methods

Study design and setting: This was a single-centre prospective diagnostic accuracy study conducted in the Department of Surgical Oncology at a tertiary care teaching hospital in India. The index test (methylene blue dye-only SLNB) and the reference standard (formal neck dissection) were both applied to every enrolled patient, and the reference standard was performed and interpreted regardless of the index-test result. The study is reported in accordance with the STARD 2015 guideline for diagnostic accuracy studies.

Ethical Approval: The study was initiated after obtaining ethical clearance from the Institutional Ethics Committee, Government Medical College, Aurangabad (IEC approval number Pharma/IEC-GMCA/203/2023, dated 20 March 2023). Patient enrolment commenced on 22 March 2023, after ethical approval was granted, and continued until 22 September 2024. Written informed consent was obtained from all participants before inclusion.

Sample Size: Previous studies of blue-dye SLNB in oral cavity SCC reported identification rates of 75–90% [13,14]. Assuming an expected identification rate of 85%, with 95% confidence and 8.5% precision using Cochran's formula, a minimum sample size of 70 patients was calculated. Eligible patients were enrolled consecutively until the sample size was reached.

Eligibility Criteria: Patients older than 18 years with well-lateralised oral cavity squamous cell carcinoma, staged T1–T2 with a clinically node-negative (cN0) neck, and willing to give informed consent were included. Patients with cN1–N3 disease, distant metastasis, recurrent lesions, prior radiotherapy or neoadjuvant chemotherapy, known allergy to methylene blue dye, or unwillingness to undergo biopsy were excluded.

Endpoints: The primary endpoint was the SLN identification rate (the proportion of patients in whom at least one SLN was successfully identified using methylene blue dye). Secondary endpoints were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false-negative rate, overall diagnostic accuracy, distribution of SLNs by neck level, and pathological upstaging rate.

Index Test and Reference Standard: All patients underwent detailed clinical evaluation, routine blood investigations, and histopathological confirmation by biopsy, and radiological assessment of the neck using ultrasonography, contrast-enhanced computed tomography, and/or magnetic resonance imaging. Under general anaesthesia, 1 mL of methylene blue dye was

injected submucosally in four quadrants (0.25 mL per quadrant) around the tumor periphery, 15 minutes before surgical incision to allow lymphatic migration (Figure 3A). The neck was explored for blue-stained nodes; an identified blue node was dissected separately and sent for histopathology (Figure 3B). Where no blue node was found, blue-stained lymphatic channels were traced to the draining node, which was considered the sentinel node. All patients then underwent at least a supraomohyoid neck dissection as the reference standard, irrespective of the SLNB result.

All procedures were performed or directly supervised by a single experienced surgical oncologist with more than 10 years of practice in head and neck oncology. A standardised injection and dissection protocol was followed throughout to minimise inter-operator variability. Formal learning-curve analysis was not performed and is acknowledged as a limitation.

Histopathological Examination: Sentinel lymph nodes were examined using routine haematoxylin and eosin (H&E) staining for detection of metastasis. Serial sectioning and immunohistochemistry (IHC) were not performed owing to resource limitations, which is acknowledged as a significant limitation. Where available from the neck dissection specimen, additional parameters including depth of invasion, tumor thickness, lymphovascular invasion, perineural invasion, and extranodal extension were recorded descriptively. All diagnostic performance was assessed at the patient level: a patient was classified as sentinel-node positive if at least one harvested sentinel node (whether single or multiple) showed metastasis, which is the oncologically meaningful unit for nodal staging. The number of sentinel nodes retrieved per patient is reported only as a measure of the technical feasibility of dye-based mapping, not as an oncological endpoint, since node yield does not predict prognosis. A STARD-style diagnostic flow is provided in Figure 1: enrolled = 70; SLN identified = 62; SLN not identified = 8 (mapping failures, reported separately and included as false negatives in the intention-to-diagnose analysis); final pN+ = 20; final pN0 = 50. The diagnostic-analysis denominator was 70 (all enrolled patients).

Statistical Analysis: Data were analysed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation; categorical variables as frequencies and percentages. The Chi-square test of independence was used to assess associations between categorical grouping variables (e.g., pT stage vs SLN positivity, pT stage vs pathological upstaging). Fisher's exact test was applied when any expected cell count was fewer than 5 (e.g., histological grade vs SLN identification, positivity, and upstaging). McNemar's exact (binomial) test was used to assess concordance between SLNB and neck dissection at the patient level, using discordant pairs (FP = 0, FN = 8). The Wilson score method was used for all 95% confidence intervals for diagnostic performance metrics. A p-value < 0.05 was considered statistically significant; all tests were two-tailed.

Results

Baseline characteristics: Seventy patients were included. Age ranged from 27 to 78 years (mean 49.3 ± 11.2 years), and the majority were male (78.6%). Buccal mucosa (44.3%) and tongue (37.2%) were the most common primary sites. Clinically, 70% of patients were staged cT2, while pathological staging revealed pT3 disease in 21.4%. Most tumors (92.9%) were moderately differentiated (G2) (Table 1).

Table 1: Baseline clinical, tumor, and histopathological characteristics (N = 70)

Category	Sub-category	n	%
Gender	Male	55	78.6
	Female	15	21.4
Tumor site	Buccal mucosa	31	44.3
	Tongue	26	37.2
	Retromolar trigone	5	7.2
	Alveolus	3	4.3
	Floor of mouth	3	4.3
	Gingivobuccal sulcus	1	1.4
	Lip	1	1.4
Clinical tumor stage	cT1	21	30.0
	cT2	49	70.0
Pathological tumor stage	pT1	22	31.4
	pT2	33	47.1
	pT3	15	21.4
Pathological node stage	pN0	50	71.4
	pN1	7	10.0

	pN2a	1	1.4
	pN2b	10	14.3
	pN3	1	1.4
Histological grade	G1 (Well differentiated)	5	7.1
	G2 (Moderately differentiated)	65	92.9
	G3 (Poorly differentiated)	0	0.0

Descriptive statistics only. Denominator = 70 for every category.

Sentinel node identification and yield: SLNB using methylene blue dye was successful in 62 of 70 patients (identification rate 88.6%), with an identification failure rate of 11.4% (95% CI: 6.5–22.5%). A total of 131 sentinel nodes were harvested. Node yield is reported only as a measure of the technical feasibility of dye-based mapping, not as an oncological endpoint, since the number of sentinel nodes retrieved does not predict prognosis: on average 1.9 nodes were removed per patient across all 70 patients, and 2.1 per patient among the 62 successfully mapped cases, with the highest mean yield in tumors of the retromolar trigone (2.8) and tongue (2.5).

All diagnostic performance was therefore assessed at the patient level, which is the oncologically meaningful unit for nodal staging: a patient was classified as node-positive when at least one sentinel node showed metastasis, irrespective of how many nodes were retrieved.

Table 2: Sentinel lymph node identification and diagnostic yield (N = 70)

Parameter	Value	95% CI
Patients enrolled	70	—
Patients with SLN successfully identified	62	82.2–93.3%
SLN identification rate	88.6%	—
Patients with SLN mapping failure	8 (11.4%)	6.5–22.5%
Total sentinel nodes harvested	131	—
Mean nodes per patient (all 70)	1.9	—
Mean nodes per patient (62 mapped)	2.1	—

Node yield (total nodes harvested and mean nodes per patient) is reported as a measure of technical feasibility of dye-based mapping, not as an oncological endpoint. All diagnostic performance is assessed at the patient level (Table 5).

Distribution by tumor site: SLN identification was most common in buccal mucosa (26 patients) and tongue tumors (24 patients). Positive SLNs were detected in 12 patients overall, with the highest number in buccal mucosa (5 patients) and tongue (4 patients) (Figure 2).

With respect to nodal levels, metastatic SLNs were most frequently identified at level IIA (11 nodes), followed by level IB (7 nodes). One positive SLN was identified at level III, while none were detected at levels IA, IIB, IV, or V (Table 3).

Table 3: SLN identification and positivity by tumor site

Tumor site	Patients	SLN identified	SLN positive
Buccal mucosa	31	26	5
Tongue	26	24	4
Retromolar trigone	5	5	1
Alveolus	3	3	0
Floor of mouth	3	3	1
Gingivobuccal sulcus	1	1	1
Lip	1	0	0
Total	**70**	**62**	**12**

Chi-square test for SLN positivity across sites: $\chi^2 = 5.38$, df = 5, p = 0.372 (not significant).

T stage, grade, and upstaging: SLN positivity was seen in 1 pT1, 8 pT2, and 3 pT3 cases. Although positivity increased with higher pT stage, the association was not statistically significant ($\chi^2 = 3.26$, p = 0.196). Pathological upstaging from cN0 to pN+ occurred predominantly in pT2 tumors (14 cases), followed by pT3 (5 cases) and pT1 (1 case), for a total of 20 pathologically node-positive patients; this association with pT stage was significant (p = 0.014).

All cases of SLN positivity and pathological upstaging occurred in moderately differentiated tumors (G2); no nodal involvement was seen in well-differentiated tumors (G1). Histological grade was significantly associated with SLN

identification ($p < 0.001$) but not with SLN positivity or upstaging (Table 4).

Table 4: Pathological T stage and histological grade vs SLN status and upstaging

Stratum	N	SLN identified	SLN positive	Upstaged N0→N+	p
pT1	22	18	1	1	
pT2	33	30	8	14	0.014*
pT3	15	14	3	5	
G1 (Well diff.)	5	1	0	0	
G2 (Mod. diff.)	65	61	12	20	
G3 (Poorly diff.)	0	0	0	0	

Chi-square — SLN positivity by pT stage: $\chi^2 = 3.26$, df = 2, p = 0.196 (ns). Pathological upstaging by pT stage: $\chi^2 = 8.48$, df = 2, p = 0.014*. Fisher's exact — grade vs SLN identification: p < 0.001*; grade vs positivity: p = 1.000; grade vs upstaging: p = 1.000. Upstaging totals: pT stratum 1+14+5 = 20; grade stratum 0+20 = 20.

Diagnostic Performance: Pathological nodal metastasis was identified in 20 patients after completion neck dissection. At the patient level, SLNB yielded 12 true positives, 50 true negatives, 8 false negatives, and no false positives; the 8 patients in whom SLN identification failed are conservatively included as false negatives in this intention-to-diagnose analysis. The association between SLNB findings and final histopathology was significant ($\chi^2 = 32.11$, $p < 0.001$).

Sensitivity was 60% (95% CI: 35.7–82.7) and specificity 100% (95% CI: 91.8–100.0); PPV was 100% and NPV 86.2%. The false-negative rate was 40.0% (95% CI: 17.3–64.3), significant on McNemar exact testing (p = 0.008). Overall diagnostic accuracy was 88.6% (95% CI: 77.8–95.3) (Table 5).

Table 5. Diagnostic performance of SLN biopsy — patient-level analysis (N = 70)

SLN result	ND positive	ND negative	Total
SLN positive	12 (TP)	0 (FP)	12
SLN negative / mapping failure	8 (FN)	50 (TN)	58
Total	**20**	**50**	**70**

ND = neck dissection. TP = 12, FP = 0, FN = 8, TN = 50.

Metric	Estimate	95% CI (Wilson)
Sensitivity	60.0%	35.7–82.7%
Specificity	100.0%	91.8–100.0%
Positive predictive value	100.0%	71.5–100.0%
Negative predictive value	86.2%	73.3–94.2%
False-negative rate	40.0%	17.3–64.3% (p = 0.008*, McNemar)
Diagnostic accuracy	88.6%	77.8–95.3%

A sub-analysis restricted to the 62 successfully mapped patients yields sensitivity 60%, specificity 100%, and accuracy 87.1% (TP = 12, FN = 8, TN = 42, FP = 0). * Significant at p < 0.05.

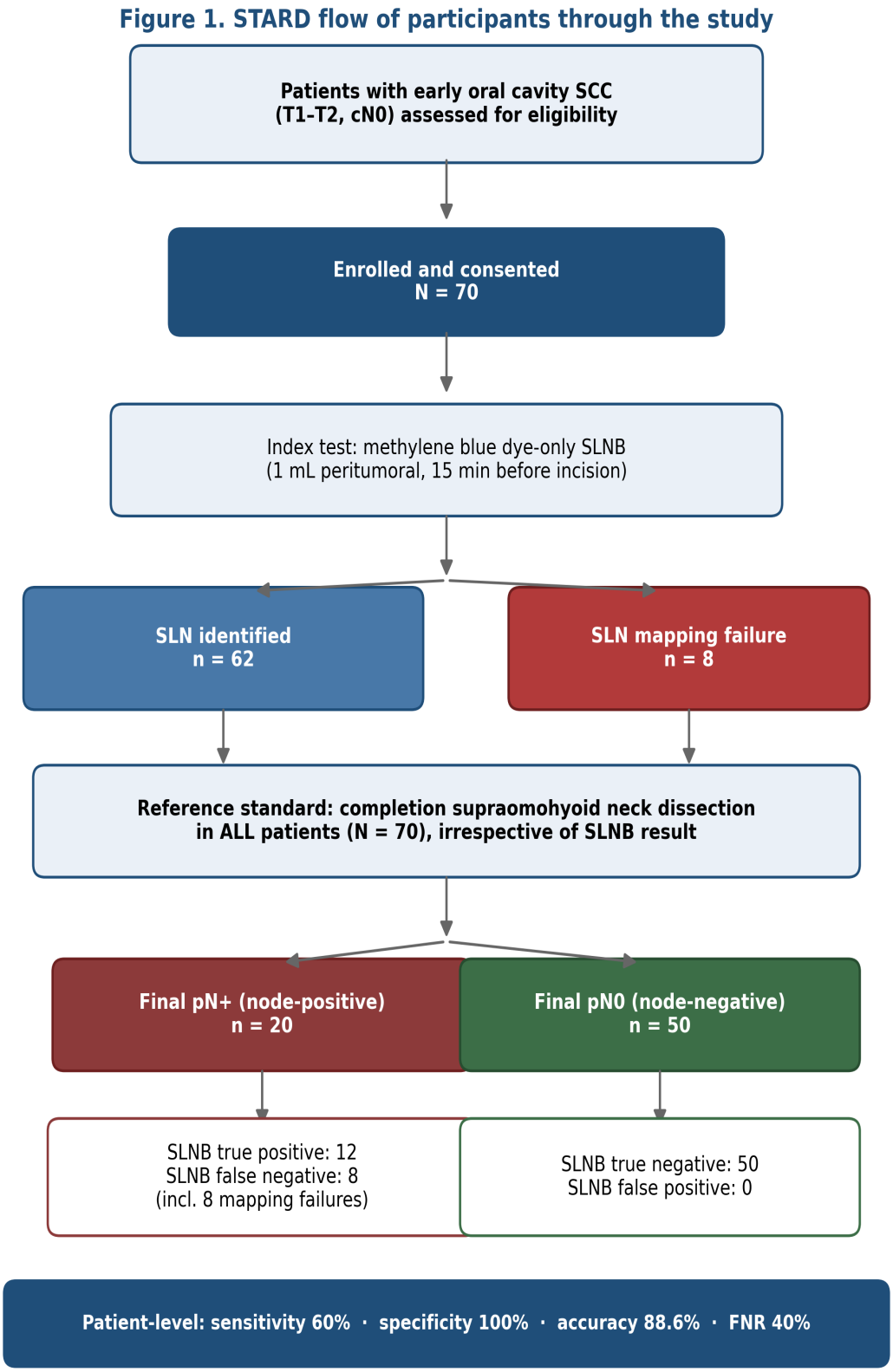

Figure 1: STARD flow of participants through the study. All 70 enrolled patients underwent both the index test (methylene blue dye-only SLNB) and the reference standard (completion supra-omohyoid neck dissection). The 8 mapping failures are conservatively classified as false negatives in the intention-to-diagnose analysis.

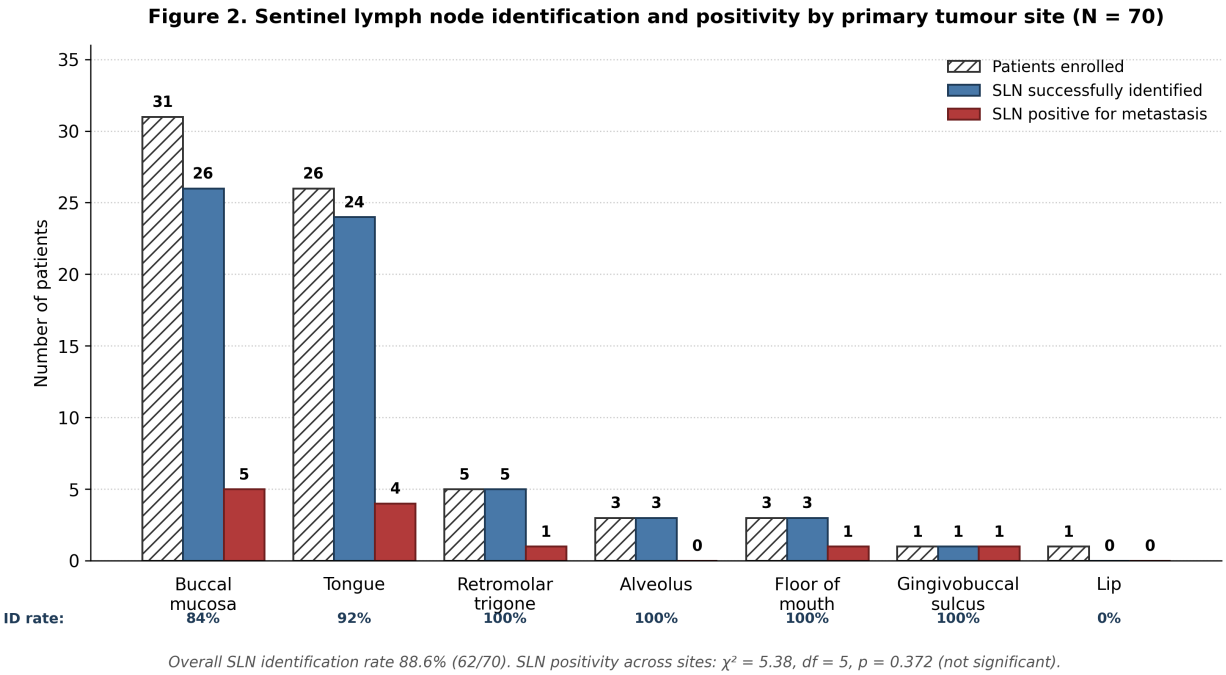

Figure 2: Sentinel lymph node identification and positivity by primary tumor site (N = 70). Bars show patients enrolled, patients with successful SLN identification, and patients with a metastatic SLN, per site. Overall identification rate 88.6% (62/70). SLN positivity across sites: $\chi^2 = 5.38$, df = 5, p = 0.372 (not significant).

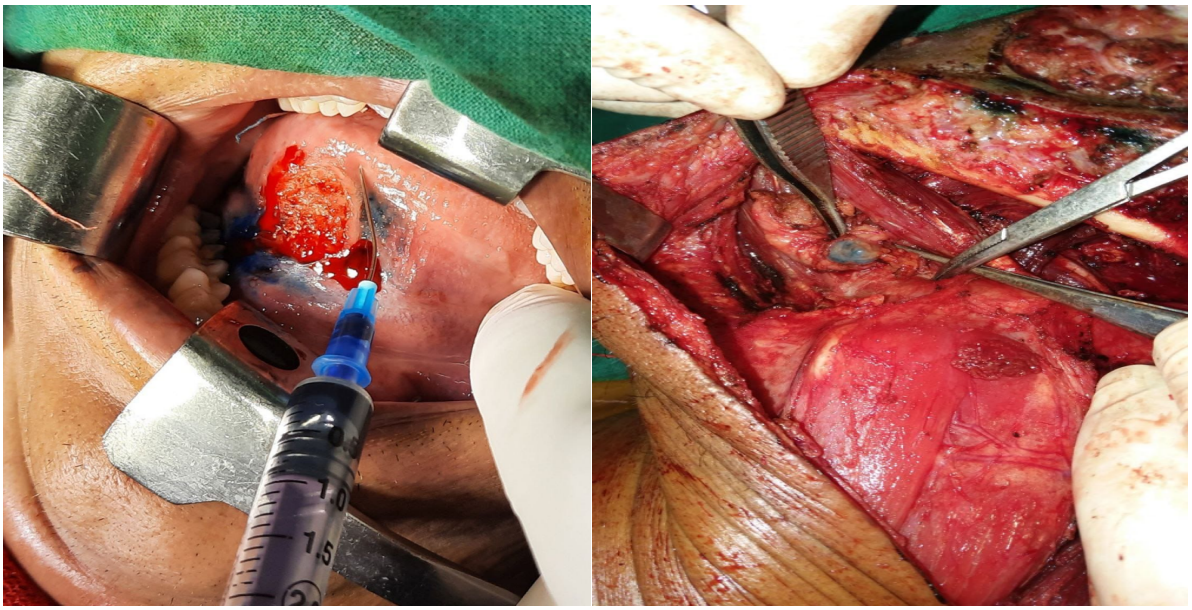

Figure 3: Intraoperative photographs of methylene blue dye-only sentinel lymph node biopsy. (A) Peritumoral submucosal injection of methylene blue dye around the oral cavity primary tumor, showing blue staining of the surrounding mucosa. (B) A blue-stained sentinel lymph node identified in the neck during dissection, harvested separately for histopathological examination.

Discussion

This prospective diagnostic accuracy study evaluated the feasibility and performance of methylene blue dye-only SLNB in early cN0 OSCC. The demographic profile, with a mean age of 49.3 years and male predominance (78.6%), reflects the typical epidemiology of OSCC in India, driven by early and sustained exposure to smokeless tobacco, betel nut, and smoking [6,15]. The predominance of buccal mucosa (44.3%) and tongue lesions (37.2%) aligns with regional carcinogen exposure patterns [16–20].

Most patients had early-stage disease (70% cT2), consistent with the intended use of SLNB in clinically node-negative early OSCC. Pathological upstaging occurred predominantly in pT2 and pT3 tumors, reinforcing the established relationship between tumor burden and occult nodal metastasis

[21–24]. Nodal evaluation revealed that 71.4% of patients were pathologically N0, yet 28.6% harboured occult metastasis, highlighting the clinical importance of elective staging [25]. The predominance of moderately differentiated (G2) tumors was comparable with earlier Indian and international reports and indicates that conventional grading alone has limited predictive value for cervical metastasis [26].

The SLN identification rate of 88.6% is acceptable for dye-based SLNB but lower than radiotracer or combined techniques, reflecting the technical limitations of methylene blue in complex oral lymphatics [27]. Diagnostic performance was assessed exclusively at the patient level, which is the oncologically meaningful unit for nodal staging; a patient was considered node-positive when at least one sentinel node harboured metastasis, irrespective of the number of nodes retrieved. On this basis the technique was highly specific, with no false positives [28,29]. Node yield (mean 1.9 per patient, higher in retromolar trigone and tongue) reflects the staining efficiency of methylene blue and is reported as a feasibility descriptor only; it is not itself oncologically significant and does not predict prognosis [30].

Although higher pT stage was significantly associated with upstaging ($p = 0.014$), SLN positivity by pT stage did not reach significance ($p = 0.196$). This divergence highlights a biological limitation of SLNB: it may not fully capture the complexity of lymphatic dissemination in progressively invasive tumors. Similar concerns have been raised where tumor thickness, depth of invasion, and perineural spread were stronger predictors of occult metastasis than SLN mapping alone [18,26,31,32]. Histological grade did not influence positivity or upstaging, although it significantly affected identification ($p < 0.001$); the lack of association with nodal status likely reflects the predominance of G2 tumors (92.9%), limiting statistical variability [13,30].

Clinical implications of the false-negative rate

The overall false-negative rate of 40% (8 of 20 node-positive patients missed by SLNB) is clinically significant and warrants explicit discussion. Although comparable rates of 10–30% have been reported depending on technique and experience [13,30], the higher rate here reflects limitations inherent to dye-only mapping and H&E-only pathology. Crucially, none of these 8 missed patients suffered a missed diagnosis: because the study protocol mandated completion supraomohyoid neck dissection in every patient regardless of SLNB result, the occult disease in all 8 was intercepted by the neck dissection specimen and treated appropriately. In other words, the diagnostic accuracy reported here was measurable only because the reference standard was applied to all patients.

This distinction is the central safety message of the study. When SLNB is used clinically in the manner ultimately intended — to spare a node-negative patient from neck dissection — that safety net disappears. Under a real-world decision rule of "negative SLNB, no neck dissection," the 8 false-negative patients in this cohort would have been left with an untreated, undissected neck harbouring occult metastatic disease. The significant McNemar test ($p = 0.008$) confirms systematic under-detection of nodal disease by SLNB relative to formal neck dissection. Combined radiotracer and dye techniques significantly reduce false-negative rates by improving lymphatic visualisation and reducing dependence on operator experience [12,30]. On this evidence, dye-only SLNB without completion neck dissection cannot currently be regarded as safe for OSCC staging.

The perfect specificity and PPV indicate that a positive SLNB reliably confirms nodal disease, consistent with multi-center trials [9,33,34]. However, the relatively low sensitivity means SLNB missed a substantial proportion of occult metastases — clinically important because missed nodal disease directly affects survival [35,36].

The discrepancy between SLN findings and final pathology may be explained by aberrant lymphatic drainage, skip metastasis, and multicentric nodal spread, well documented in oral cavity cancers [14,37], which challenge the foundational assumption of SLNB that spread follows a predictable sequential pathway [4,34]. The preferential drainage to levels IB and IIA observed here is consistent with established mapping patterns [18,34], but the level III and skip drainage reinforce the complexity of lymphatic spread.

When compared with larger meta-analyses reporting pooled sensitivities of 80–90% [38], the present results again highlight the impact of technique selection and institutional experience, and are consistent with the view that SLNB reduces morbidity but its diagnostic variability limits replacement of END in routine practice [10].

Limitations

This single-centre study has limited generalisability, and the relatively small sample ($n = 70$) may have influenced the precision of accuracy and NPV estimates. Methylene blue was used alone, without radioisotope guidance; combined dual-tracer protocols are established to reduce false-negative rates. Sentinel nodes were examined by H&E only — serial sectioning and IHC were not performed owing to resource constraints, which is likely the primary contributor to the high false-negative rate, as micrometastases

detectable on serial sections or IHC may have been missed. Although all procedures were performed by a single experienced surgeon following a standardized protocol, formal learning-curve analysis was not performed and inter-operator variability remains unquantified.

The identification failure rate of 11.4% (8 patients) was conservatively treated as false-negative in the intention-to-diagnose analysis. Finally, the study lacks long-term follow-up for survival, regional recurrence, and oncological outcomes.

Conclusions

In this prospective diagnostic accuracy study, methylene blue dye-only SLNB achieved an identification rate of 88.6% and demonstrated 100% specificity and PPV in a resource-limited setting, confirming that a positive result reliably indicates nodal disease.

However, a false-negative rate of 40% indicates that a negative result cannot reliably exclude occult nodal disease when methylene blue is used as the sole agent.

These findings support the technical feasibility of methylene blue SLNB in appropriate centres but do not support its standalone use to safely omit formal neck dissection. Future studies should incorporate dual-tracer techniques with radioisotope guidance and serial sectioning with immunohistochemistry to reduce the false-negative burden.

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