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Mapping the Risk: Analysis of Anatomical Nodal Involvement Patterns in Clinically N0 Buccal Squamous Cell Carcinoma

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ABSTRACT

Background: The management of the clinically N0 neck in buccal squamous cell carcinoma (BSCC) remains controversial due to the potential for occult nodal metastasis (ONM). This study aimed to map the anatomical pattern and incidence of ONM in BSCC patients presenting with a clinically negative neck, and to correlate these findings with specific pathological high-risk features. **Methods:** A cross-sectional study was performed on 48 patients with clinically N0 BSCC who underwent Selective Neck Dissection (SND) at a tertiary care center over a nine-month period. Pathological findings were analyzed for overall nodal status (pN), the specific levels of lymph node involvement, the relationship between clinical T-stage and nodal burden, and the presence of perineural invasion (PNI) and lymph vascular invasion (LVI). **Results:** The study demonstrated an extremely high incidence of occult nodal metastasis at 97.9% (47/48 patients), highlighting the clinical unreliability of cN0 staging for this specific site. Analysis of the nodal patterns revealed that metastasis was predominantly confined to the superior cervical regions. Level IIA (48.4%) was the most frequently involved nodal basin, followed closely by Level IB (41.9%) and Level IA (25.8%). Crucially, no isolated skip metastases to Level IIB or Level III were observed. Furthermore, the presence of high-risk pathological features was a definitive predictor of ONM: of cases with Perineural Invasion (PNI) (n=18) and of cases with Lymph vascular Invasion (LVI) (n=14) were pathologically node-positive. Clinical T-stage also correlated with nodal burden, with T4N0MX tumors showing a higher mean number of positive nodes (2.1) compared to T2N0MX (1.6). **Conclusion:** The exceptionally high incidence and predictable pattern of occult nodal metastasis confirm that prophylactic neck management is mandatory for clinically N0 BSCC. The anatomical risk mapping strongly supports performing a Selective Neck Dissection targeting Levels I and IIA. The presence of PNI and LVI serves as an absolute indicator for aggressive regional management.
Keywords: Buccal Squamous Cell Carcinoma, Occult Metastasis, N0 Neck, Selective Neck Dissection, Nodal Mapping, Perineural Invasion, Lymph Vascular Invasion.

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INTRODUCTION

Squamous cell carcinoma (SCC) of the buccal mucosa represents a substantial share of oral cavity cancers globally, with a disproportionate burden in South and Southeast Asia where tobacco chewing and areca nut use are prevalent [1, 2]. Despite advances in imaging, staging, and surgery, regional nodal metastasis remains the single most important adverse prognostic factor in oral cavity SCC, driving both recurrence risk and survival [3]. The clinical challenge is especially sharp in the clinically N0 (cN0) neck, where the imperative to avoid undertreatment must be balanced against the morbidity of elective therapy. In this context, precise mapping of the anatomic distribution of occult nodal disease in buccal SCC is more than an academic exercise it is a practical tool to refine selective neck dissection, optimize adjuvant radiation fields, and individualize care.

Patterns of lymphatic spread in oral cavity SCC are subsite-specific. Classical anatomic and surgical series demonstrate that buccal mucosa cancers most frequently metastasize first to level I nodal basins particularly the submandibular nodes followed by levels II and III, with "skip" metastases to level IV relatively uncommon [3, 4]. These patterns underpin the logic of selective neck dissection templates and radiation target volumes, and they are embedded in contemporary nomenclature and operative planning through standardized neck level definitions [4]. Yet, within this overarching framework, buccal mucosa tumors exhibit heterogeneity: tumor thickness/depth of invasion, perineural and lymph vascular invasion, proximity to the commissure or midline, and margin status all modulate nodal risk and laterality. This heterogeneity argues for more granular, subsite-specific risk maps rather than extrapolation from oral tongue or floor-of-mouth data.

The cN0 neck is notoriously difficult to stage with imaging alone. Micro metastases and small-volume disease regularly evade cross-sectional detection; even with modern modalities, sensitivity for clinically occult metastases remains imperfect [5]. Computed tomography and magnetic resonance imaging provide complementary anatomic detail, while FDG PET/CT adds functional information; however, none reliably excludes microscopic nodal disease in early-stage oral cancers [5]. Sentinel lymph node biopsy (SLNB) has emerged as a staging adjunct that can sample first-echelon nodes and improve pathologic yield, and prospective multi-institutional data suggest SLNB can accurately reflect regional status in early oral cavity cancer [6]. Still, SLNB adoption varies, and many centers continue to rely on selective elective neck dissection (END) in patients at appreciable risk of occult nodal involvement. High-level clinical trial evidence supports proactive management of the cN0 neck. In a landmark randomized trial from an oral cancer–endemic setting, elective neck dissection improved overall and disease-free survival compared with therapeutic neck dissection at nodal relapse in cT1–T2 N0 oral SCC [7]. While practice patterns differ across health systems, this trial sharpened the focus on how to select patients and which neck levels to treat electively. Because most cN0 patients are ultimately pathologically node-negative, the ambition is not simply to treat more, but to treat smarter: to concentrate dissection and/or radiation on levels that truly matter for a given subsite and phenotype, sparing nonessential levels to reduce shoulder dysfunction, lymphedema, fibrosis, and xerostomia.

This study seeks to bridge a crucial knowledge gap by mapping the anatomical distribution of nodal involvement in clinically N0 buccal squamous cell carcinoma (SCC), with careful attention to standardized neck levels. By defining level-specific risks and examining their associations with key clinicopathologic variables, our objectives are threefold: (1) to determine the prevalence and laterality of occult nodal disease in buccal mucosa cancers staged as N0, (2) to distinguish "must-cover" from "low-yield" nodal levels for elective treatment, and (3) to develop subsite-specific, risk-adapted recommendations to guide both surgical and radiotherapeutic decision-making. Ultimately, this data-driven atlas of nodal risk aims to minimize overtreatment while preserving oncologic safety—advancing the principles of precision oncology in harmony with the practical realities of variable resources and the lived experiences of patients with buccal SCC.

OBJECTIVE

This study aimed to map the anatomical pattern and incidence of ONM in BSCC patients presenting with a clinically negative neck, and to correlate these findings with specific pathological high-risk features.

METHODS

Study Design and Seflings

This was a prospective, cross-sectional observational study conducted in the Department of Otolaryngology–Head & Neck Surgery at Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh, over nine months (July 2023 to March 2024). The study commenced after approval by the Institutional Review Board (IRB). Following IRB clearance, the protocol was registered on ClinicalTrials.gov under the BSMMU organizational account. All participants provided written informed consent prior to enrollment.

Study Population

The study population comprised consecutive adult patients presenting with a single primary lesion of the buccal mucosa and a clinically node-negative neck (cN0) at the time of presentation, who were planned for primary surgical treatment. Eligibility required histopathological confirmation of squamous cell carcinoma (SCC) of the buccal mucosa and a cN0 neck based on clinical examination and preoperative contrast-enhanced computed tomography (CECT) performed within 30 days of surgery. Patients were excluded if they declined consent for neck dissection; had extensive disease precluding reliable assessment of the primary buccal site; had pre-malignant conditions or syndromes such as oral submucous fibrosis or dyskeratosis congenita; or had systemic causes of generalized lymphadenopathy (e.g., tuberculosis, non-Hodgkin lymphoma). Sampling was consecutive and non-probabilistic, reflecting the real-world flow of eligible cases within the fixed study window.

Sample Size

A priori sample size estimation targeted 48 participants. This number provided approximately 80% power ($Z\beta \approx 0.84$) to detect an absolute difference of 0.20 from a null proportion (P0) of 0.40 using a two-sided test at $\alpha=0.05$, corresponding to an anticipated occult nodal involvement rate of 0.60 under the alternative hypothesis. All eligible cases within the accrual period were enrolled; the final achieved sample size and precision (95% confidence intervals) are reported alongside the results.

Preoperative Evaluation and Key Definitions

Preoperative evaluation included a detailed clinical history (symptom duration, risk behaviors) and comprehensive head and neck examination, as well as anesthetic fitness assessment. CECT of the head and neck was obtained within one month prior to surgery for tumor measurement and nodal assessment. A cN0 neck was defined by the absence of suspicious lymphadenopathy on palpation and the absence of radiologic criteria for nodal metastasis on CECT (e.g., size thresholds by short-axis diameter, lack of central necrosis, and no features suggestive of extranodal extension). Tumor size was recorded as the largest dimension on CECT. For analytic clarity, lesions were categorized as early (≤4.0 cm) or advanced (>4.0 cm), and clinical staging followed AJCC 8th edition principles where applicable.

Surgical Procedure and Specimen Handling

All patients underwent primary tumor resection with oncologic margins followed by ipsilateral selective neck dissection (SND) encompassing levels I–III. Intraoperative frozen section analysis was used at the surgeon's discretion for suspicious nodal tissue; if positive, the dissection was extended up to level V. Neck dissection specimens were oriented and submitted to pathology as separate, level-specific packets to enable precise mapping. Standardized operating procedures were used for specimen labeling and chain of custody.

Histopathological Assessment and Staging

Histopathological evaluation employed hematoxylin and eosin–stained sections to determine tumor grade (well, moderately, or poorly differentiated) according to World Health Organization criteria, and to assess lymph vascular invasion (LVI), perineural invasion (PNI), margin status, and nodal involvement. For patients with pathologically positive nodes (pN+), the presence of metastasis at each dissected level (I–V, as applicable) was recorded irrespective of the number of positive nodes per level. Extranodal extension, when present, was documented. Pathologic nodal staging (pN) adhered to AJCC 8th edition.

Outcomes and Data Collection

The primary outcome was the prevalence and anatomical distribution of occult cervical nodal metastases by neck level among cN0 buccal SCC patients undergoing SND. Secondary outcomes included the association

between nodal positivity (pN+ vs pN0) and tumor size category (early vs advanced), histopathologic grade, and laterality patterns. Demographic variables (age, sex, occupation), clinical variables (side and subsite within the buccal mucosa, symptom duration, CECT tumor size and nodal assessment), and pathologic variables (WHO grade, LVI, PNI, margins, pN stage, level-specific involvement, extranodal extension) were collected prospectively on standardized case report forms and entered into a coded electronic database.

Statistical Analysis

Descriptive statistics summarized baseline characteristics using means and standard deviations or medians and interquartile ranges for continuous variables, and counts and percentages for categorical variables. Associations between categorical variables (e.g., pN status and tumor size category; level-specific involvement and lesion category) were tested using the chi-square test, or Fisher's exact test where expected cell counts were small. The relationship between histologic grade and nodal positivity was assessed using the Pearson chi-square test; when ordinal trends were of interest or assumptions were not met, Spearman rank correlation was explored. Effect size measures with 95% confidence intervals were reported where appropriate. A two-sided p value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

Ethics, Confidentiality, Quality Assurance, and Monitoring

Confidentiality was maintained through de-identification of all records, secure storage of paper documents in locked cabinets, and password-protected electronic files accessible only to study personnel. No experimental agents or placebos were used. Study conduct adhered to the principles of the Declaration of Helsinki and local regulatory requirements. Quality assurance measures included team training, periodic calibration of imaging measurements, verification of level-specific specimen labeling, and routine cross-checks of data entry. An independent Data and Safety Monitoring Board (DSMB) with expertise in biostatistics, clinical trials, and head and neck oncology conducted periodic reviews of aggregate, de-identified data on accrual, protocol adherence, and safety, and was empowered to recommend protocol modifications or early termination if needed.

RESULTS

Overall Incidence of Occult Metastasis

The study's primary objective was to determine the frequency of occult nodal metastasis in clinically N0 buccal squamous cell carcinoma (BSCC). Pathological evaluation revealed an extremely high incidence, as detailed in Table 1.

Table 1: Overall Pathological Nodal Status in Clinically N0 BSCC Patients

Pathological Nodal Status (pN)	Frequency	Percentage (%)
pN+ (Pathologically Positive)	47	97.9%
pN0 (Pathologically Negative)	1	2.1%
Total	**48**	**100.0%**

This finding highlights the inadequacy of clinical and radiological staging in accurately identifying regional disease for this patient cohort.

Paflern and level of Nodal Involvement

The anatomical distribution of positive lymph nodes was analyzed based on the 31 cases where specific positive nodal levels were clearly documented in the histopathology report. Metastasis was predominantly confined to the superior cervical lymph node regions (Levels I and II). The frequency of involvement for the sub-levels is detailed in Table 2.

Table 2: Anatomical Distribution of Positive Lymph Node Levels in Documented pN+ Cases

Nodal Level	Frequency (Number of Patients Involved)	Percentage of Documented pN+ Cases (%)
Level IIA	15	48.4%
Level IB	13	41.9%
Level IA	8	25.8%
Level IIB	0	0.0%
Level III	0	0.0%

The data clearly demonstrated that Level IIA was the most frequently involved nodal basin, followed closely by Level IB. The sum of frequencies exceeds the number of patients analyzed because multiple nodal levels were involved in several patients. Crucially, no cases of isolated Level IIB or Level III involvement were documented in this sub-cohort, strongly supporting the feasibility of selective neck dissection targeting Levels I and IIA for regional disease control.

Relationship Between Clinical T-Stage and Nodal Burden

While clinical T-stage did not predict the presence of occult metastasis (which was uniformly high), it showed a correlation with the quantity of disease, or the nodal burden. The mean number of positive nodes across different clinical T-stages is presented in Table 3.

Table 3: Mean Nodal Burden (Number of Positive Nodes) by Clinical T-Stage

Clinical T-Stage (cN0)	Frequency	Mean Number of Positive Nodes
T2N0MX	19	1.6
T3N0MX	8	1.7
T4N0MX	21	2.1

This finding suggests that the clinical T-stage can be used to predict the quantity of disease (nodal burden) within the pathologically positive neck.

Correlation of High-Risk Features with Nodal Positivity

The study examined the association between high-risk histopathological features—Perineural Invasion (PNI) and Lymph vascular Invasion (LVI)—and pathological nodal status (pN+). The results confirm that the presence of these features is a definitive predictor of nodal metastasis in this cohort, as shown in Tables 4 and 5.

Table 4: Correlation of Perineural Invasion (PNI) with Pathological Nodal Status

PNI Status	Number of Cases	Percentage of Cohort (%)	Number of Cases	Percentage of Cases
Present	18	37.5%	18	100%
Negative/Not Identified	30	62.5%	29	96.7%
Total	**48**	**100.0%**	**47**	**97.9%**

Table 5: Correlation of Lymph vascular Invasion (LVI) with Pathological Nodal Status

LVI Status	Number of Cases ()	Percentage of Cohort (%)	Number of Cases	Percentage of Cases
Present	14	29.2%	14	100%
Negative/Not Identified	34	70.8%	33	97.1%
Total	**48**	**100.0%**	**47**	**97.9%**

These results provide strong evidence that PNI and LVI are critical indicators of aggressive tumor biology, with 100% of cases exhibiting these features also being pathologically node-positive. This supports heavily

weighting these features in risk stratification for the clinically N0 neck in BSCC.

DISCUSSION

This prospective cross-sectional series underscores three clinically relevant observations in clinically N0 buccal squamous cell carcinoma (BSCC): (1) an extraordinarily high rate of occult cervical metastasis; (2) a highly nonrandom anatomic distribution of nodal disease concentrated in levels I and IIa, with no involvement recorded in sublevel IIb or level III among cases with level-specific data; and (3) a stepwise increase in nodal burden with advancing clinical T stage, alongside universal nodal positivity when perineural invasion (PNI) or lymph vascular invasion (LVI) were present.

Our level-specific pattern aligns with long-standing anatomic and surgical data showing that oral cavity cancers, including buccal mucosa, metastasize first to the submental–submandibular and upper jugular basins (levels I and II), and that "skip" metastases to lower levels are uncommon in the absence of more proximal disease [3, 4]. The predominance of level IIa and level I in our cohort, with no deposits in sublevel IIb or level III among cases with detailed mapping, mirrors the classic drainage pattern and provides pragmatic support for selective neck dissection (SND) templates that prioritize levels I and IIa for cN0 BSCC. While most contemporary SNDs for oral cavity SCC encompass levels I–III, the absence of IIb disease here, together with the low reported prevalence of isolated IIb metastasis across oral cavity cohorts, supports omitting IIb in carefully selected cN0 buccal cases to reduce shoulder morbidity when IIa is clinically/radiologically uninvolved [3, 4]. These findings also inform radiotherapy target design, emphasizing robust coverage of levels I and IIa while considering de-escalation of IIb/III in appropriately staged cN0 buccal primaries. The headline finding—97.9% occult metastasis—exceeds the range reported in most oral cavity cN0 series and highlights the limits of clinical examination and contrast-enhanced CT for excluding microscopic disease [5]. In this context, our data are directionally consonant with high-risk endemic settings and reinforce the rationale for proactive regional management. The randomized trial by D'Cruz *et al*. in an oral cancer–endemic population demonstrated that elective neck dissection at the time of primary surgery improved overall and disease-free survival versus therapeutic dissection at relapse in cT1–T2 N0 oral cavity cancer, establishing a standard of care for at-risk cN0 necks [7]. Where expertise and resources permit, sentinel lymph node biopsy can improve staging yield in early oral cavity cancers and may offer a tissue-sparing alternative to routine neck dissection, though adoption varies and buccal-specific validation is still evolving [6].

The observed increase in the mean number of positive nodes from cT2 to cT4 suggests that while T category did not discriminate presence versus absence of occult disease in this high-prevalence cohort, it did track with the quantity of disease. This is consistent with broader literature: nodal risk and nodal burden escalate with greater local tumor extent, a relationship strongly mediated by depth of invasion (DOI) [3, 8]. The recognized prognostic value of DOI in oral cavity SCC underscores why more extensive local disease tends to harbor multi-node or multilevel metastasis, with implications for the extent of dissection and adjuvant therapy [8]. The tight association of PNI and LVI with nodal positivity echoes robust histopathologic literature identifying both as markers of aggressive biology and regional spread [9]. In our series, all tumors with PNI or LVI were pN+, reinforcing that these features should trigger heightened vigilance for regional disease and may justify intensification of adjuvant treatment when present. Notably, the underlying prevalence of occult metastasis was already very high; thus, PNI/LVI in this dataset serve more as corroborative red flags than as discriminators of who needs neck treatment. Even so, their presence is consistently associated with worse locoregional control and survival across oral cavity cohorts and should be weighted accordingly in multidisciplinary planning [9].

Practical implications follow. First, SND focusing on levels I and IIa appears oncologically sound for cN0 buccal mucosa cancers, with routine inclusion of level III remaining reasonable but potentially de-escalatable in strictly selected cases when preoperative and intraoperative assessments are reassuring. Second, given the limitations of CT for micro metastatic disease, centers may consider integrating ultrasound, ultrasound-guided fine-needle aspiration, or sentinel node techniques to optimize staging where available, recognizing that high-risk buccal primaries in endemic settings will frequently benefit from elective neck treatment regardless [5–7].

Third, PNI/LVI should be systematically reported and incorporated into decisions on adjuvant radiotherapy, with attention to comprehensive coverage of first-echelon basins (levels I–II). Strengths include prospective data capture, uniform surgical management (ipsilateral SND I–III), and level-specific specimen submission enabling granular mapping. Limitations include potential selection bias in a single tertiary center, reliance on CT alone for cN0 designation, level-specific mapping available for a subset of pN+ cases, and a modest sample size that may underpower detection of rare patterns (e.g., isolated IIb or level III). These caveats argue for cautious generalization and external validation. Future work should prioritize larger, multi-institutional buccal-specific cohorts with standardized imaging (including ultrasound and/or PET-CT), mandatory level-specific pathology, and routine DOI measurement to refine risk maps further. Integrating sentinel node ultra staging and molecular assays could sharpen micro metastasis detection and clarify when IIb and level III can be confidently spared. Prospective evaluation of de-escalated neck templates informed by subsite-specific risk could quantify functional gains without compromising oncologic safety.

CONCLUSION

In this prospective cross-sectional cohort of clinically N0 buccal squamous cell carcinoma, we observed an exceptionally high prevalence of occult cervical metastasis (97.9%) despite careful clinical examination and contrast-enhanced CT staging. Nodal spread followed a predictable, first-echelon pattern: metastases clustered in levels I and IIa, with no sublevel IIb or level III involvement documented among cases with level-specific mapping. Nodal burden increased with advancing clinical T stage, and the presence of perineural invasion or lymph vascular invasion was uniformly associated with pathological nodal positivity. These findings reinforce the need for proactive regional management in cN0 buccal primaries in similar practice settings. They support selective neck dissection templates that prioritize levels I and IIa for both surgery and radiotherapy planning, with a strong rationale to omit sublevel IIb routinely when level IIa is not involved, and to consider de-escalation of level III in carefully selected cases. PNI and LVI should be weighted heavily in postoperative risk stratification and decisions regarding adjuvant therapy, recognizing their tight association with regional disease. In practical terms, clinical T stage can help anticipate nodal burden and guide the extent of elective treatment and adjuvant planning.

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