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TUMOR THICKNESS AS A MARKER OF CERVICAL NODAL METASTASIS IN PATIENTS WITH BUCCAL MUCOSA CARCINOMA

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Abstract

Objective: *To determine optimal cut-off value of tumor mucosal thickness predicting cervical lymph node metastasis in buccal mucosa carcinoma*

Study Design: *Prospective cross-sectional diagnostic accuracy study*

Place and Duration of Study: *Otolaryngology department of Combined Military Hospital, Rawalpindi, Pakistan from June 2024 to May 2025*

Methodology: *A total of 90 patients were analyzed in the study planned for elective buccal mucosa tumor and cervical nodal dissection. Primary variable studied was suitable cut-off for tumor thickness in predicting cervical nodal metastasis and sensitivity, specificity, positive and negative predictive value of tumor thickness cut-off in detection of cervical node metastasis*

Results: *Receiver operating characteristic (ROC) analysis identified 2.81 mm as the most suitable cut-off value for predicting cervical nodal metastasis, yielding a high Youden Index (J=0.817) with the cut-off corresponding to a sensitivity of 93.3%, specificity of 88.3%, positive predictive value of 80.0%, and negative predictive value of 96.4%. The overall diagnostic accuracy of tumor thickness at this cut-off was 90.0%*

Conclusion: *Tumor thickness demonstrated strong diagnostic accuracy for predicting cervical nodal metastasis in buccal mucosa squamous cell carcinoma, with a cut-off value of 2.8 mm providing excellent sensitivity and specificity.*

INTRODUCTION

Oral cavity squamous cell carcinoma remains a major public-health challenge globally, with the Buccal mucosa squamous cell carcinoma (BMSCC) representing a particularly aggressive variant in regions where tobacco, and betel use is prevalent.[1] In the United States, oral cavity and oropharyngeal cancers have a reported lifetime risk of about 1 in 59 for men and 1 in 139 for women.[2] In Pakistan and neighboring sub-continent settings, the proportion of oral cancers affecting the buccal mucosa is even higher, reflecting cultural risk-factor patterns.[3]

Cervical lymph-node metastasis is the single most important prognostic factor in oral cavity carcinoma and drives decisions on whether to perform an elective neck dissection (END) even in clinically node-negative (cN0) necks.[4] It is well recognized that tumor thickness or depth of invasion (DOI) correlates with nodal spread. Results of a meta-analysis in 2009 demonstrated tumor thickness as a strong predictor of cervical lymph-node involvement in oral cavity cancers.[5]

More recently, cross-sectional work in Pakistan focusing on buccal mucosa found that thickness ≥ 2 mm increased risk of occult nodal metastasis by 35-fold in a 102-patient cohort.[6] Other studies in mixed-site oral cavity cohorts have reported cut-offs of 4 mm (Egypt, 2017) or 5 mm (India, 2022) for increased nodal risk. A 2018 Indian review highlighted the variability of suggested tumor thickness thresholds (1.5 – 5 mm) and called for further clarity.[7]

Different studies in buccal mucosa carcinoma report widely varying cut-off values for tumor thickness and because few studies provide formal sensitivity, specificity or receiver-operating-characteristic (ROC) derived thresholds in the buccal subsite there is uncertainty over the optimal thickness threshold that should trigger END in BMSCC.[8] This variability forms rationale for the present study. Clarifying this threshold would help define institutional treatment guidelines for elective neck dissection decision making in BMSCC, especially in high-risk populations.

METHODOLOGY

This prospective cross-sectional diagnostic accuracy study was carried out at the Otolaryngology department of Combined Military Hospital, Rawalpindi, Pakistan from June 2024 to June 2025. Sample size was calculated using the WHO calculator keeping the confidence interval at 95%, margin of error at 5% with anticipated diagnostic accuracy of buccal mucosal thickness with a cut-off of 4.4 mm at 98%.[9] Minimum sample size using the WHO calculator came out to be 31 patients. We included a total of 70 patients in the final assessment protocol keeping margin for lost to follow-up and incomplete results according to the inclusion criteria for the study. The study adhered to ethical guidelines and received approval from the institutional ethics committee.

Inclusion criteria included all patients of both genders, ages 18-65 years of age, with histologically confirmed primary buccal mucosa carcinoma, planned for an elective surgical excision of the primary tumor with ipsilateral and/or contralateral neck dissection

Exclusion criteria comprised patients with recurrent oral tumors or secondary primaries on diagnostic evaluation, previous neck surgery, previous history of radiotherapy or chemotherapy to the head and neck region, patients with incomplete or inconclusive histopathological data for diagnosis, poor or fragmented tissue blocks with unreliable thickness measurements, patients lost to follow-up or non-consent to be included in the study protocol.

This study was conducted after ethical approval was obtained from the institutional review board prior to initiation of recruitment, and all eligible patients provided written informed consent for participation, including permission to use clinical data and histopathology specimens for research. Confidentiality was ensured by assigning anonymized study codes and restricting access to patient identifiers.

A total of 90 patients (n = 90) with newly diagnosed untreated primary buccal mucosa squamous cell carcinoma were enrolled consecutively at the time of presentation to minimize selection bias. All data were collected prospectively using a structured proforma. Demographic information, clinical T-stage, tumor laterality and subsite within the buccal mucosa, and planned surgical approach were documented before surgery. All patients subsequently underwent primary tumor resection with ipsilateral or bilateral neck dissection according to institutional protocols.

The primary study variable was tumor (mucosal) thickness and was measured postoperatively on freshly prepared histopathology slides. Two senior pathologists, each blinded to cervical nodal status, clinical stage, and each other's measurements, independently recorded tumor thickness from the reconstructed mucosal surface to the deepest point of invasion using calibrated digital microscopy. Inter-observer reliability was assessed, and discrepant readings were resolved by consensus to reduce measurement bias. Tumor grade, perineural invasion, lymph vascular invasion, and depth of invasion were additionally recorded as secondary variables.

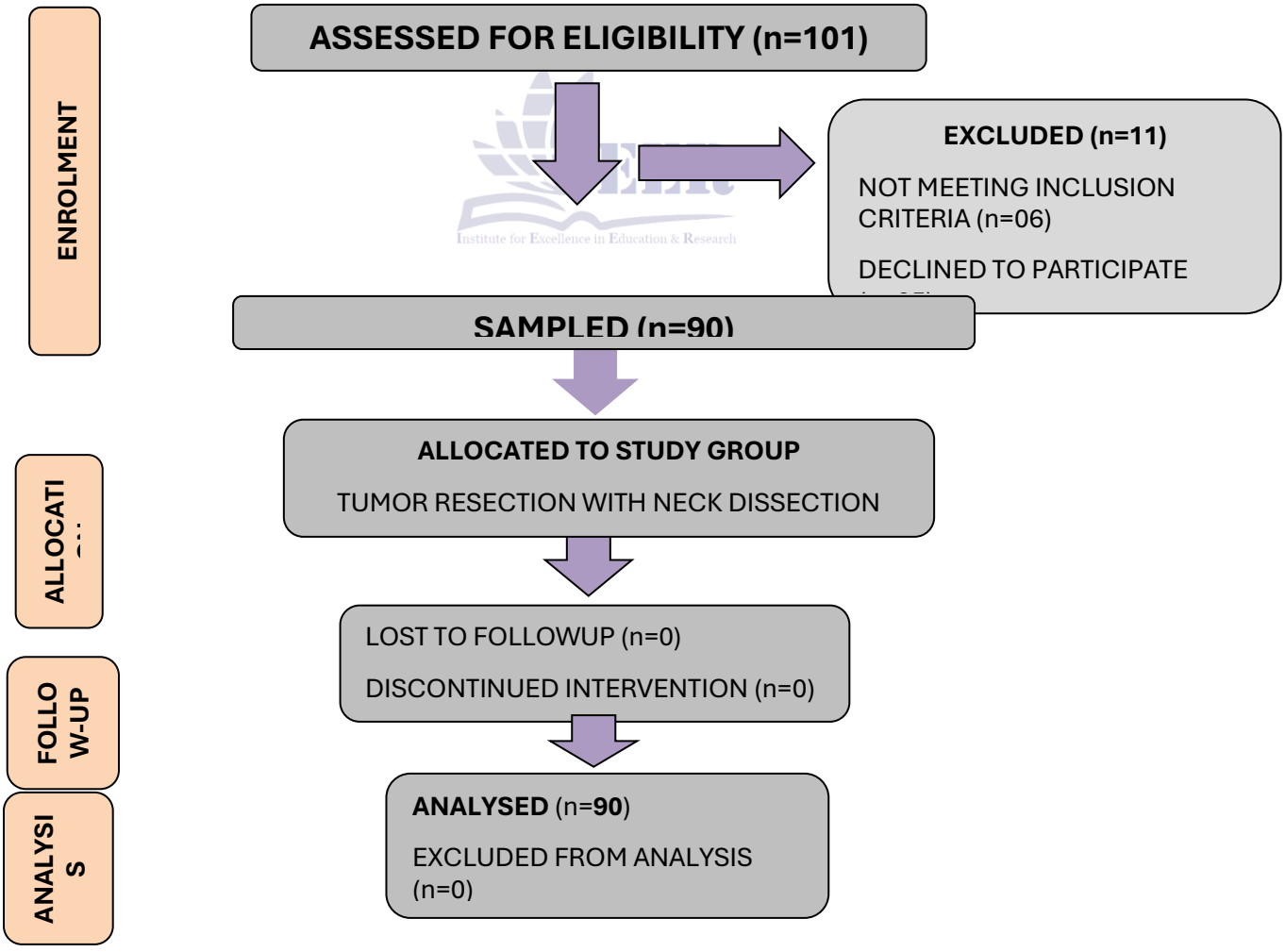
The reference gold standard for cervical nodal metastasis was the final histopathological

assessment of neck-dissection specimens.[10] All lymph nodes retrieved were examined by dedicated head-and-neck pathologists who were blinded to the measured tumor thickness, ensuring independence between the index test and outcome assessment. Nodal metastasis was coded as a binary variable (positive/negative), and details including number of involved nodes, laterality and level-wise distribution were documented.

Data were analyzed using standard statistical software. Continuous variables such as tumor thickness were summarized as means or medians, while categorical data were expressed as frequencies and percentages. Comparisons between node-positive and node-negative groups were performed using appropriate parametric or non-parametric tests. Diagnostic accuracy was assessed through receiver-operating-characteristic (ROC) analysis, and the optimal thickness cut-off was identified using Youden's Index. Sensitivity, specificity, PPV, NPV, and likelihood ratios were subsequently calculated. To adjust for potential confounders, a multivariable logistic-regression model was constructed, incorporating clinically relevant covariates. Throughout the study, bias was minimized by prospective data capture, blinding of assessors, standardized measurement techniques, and consistent surgical and pathological protocols.

A p value of ≤0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.00

FIGURE 1: PATIENT FLOW DIAGRAM



RESULTS

A total of 90 patients were included in the study. The mean age was 53.4 ± 15.38 years. Gender distribution revealed 64 (71.1%) males, while females constituted 26 (28.9%) of the cohort. Tobacco use was reported in 62 (68.9%) patients, whereas betel chewing was more common, seen in 73 (81.1%) participants. Clinically, 49 (54.4%) patients presented with early-stage disease, while 41 (45.6%) had advanced-stage tumors. Tumor laterality was almost evenly distributed, with 51 (56.7%) on the right side and 39 (43.3%) on the left. The tumor sub-sites were similarly balanced, with 46 (51.1%) involving the anterior buccal mucosa and 44 (48.9%) involving the posterior region. The mean tumor thickness measured 3.27 ± 2.36 mm, and the mean depth of invasion was 2.92 ± 2.60 mm. In terms of pathological features, 62 (68.9%) tumors were of moderate grade, while 28 (31.1%) were poorly differentiated. Perineural invasion was present in 32 (35.6%) patients, and lymphovascular invasion in 36 (40.0%). Cervical nodal metastasis was detected in 30 (33.3%), and extracapsular metastasis in 10 (11.1%). Regarding surgical management, 68 (75.6%) patients underwent ipsilateral neck dissection, whereas 22 (24.4%) required bilateral neck dissection (Table-I).

Receiver operating characteristic (ROC) analysis identified 2.81 mm as the most suitable cut-off value for predicting cervical nodal metastasis. At this threshold, the sensitivity was 93.3%, and the specificity was 88.3%, yielding a high Youden Index (J) of 0.817, indicating excellent discriminatory performance of tumor thickness for nodal metastasis prediction (Table-II) (Figure-2).

Using the tumor thickness cut-off of 2.8 mm, 28 (31.1%) patients with nodal metastasis had thickness values >2.8 mm, while 2 (2.22%) metastatic cases had thickness <2.8 mm. Conversely, among node-negative patients, 7 (7.77%) had thickness >2.8 mm, whereas 53 (58.8%) had values <2.8 mm. These values correspond to a sensitivity of 93.3%, specificity of 88.3%, positive predictive value of 80.0%, and negative predictive value of 96.4%. The overall diagnostic accuracy of tumor thickness at this cut-off was 90.0% (Table-III).

TABLES

TABLE-I DEMOGRAPHIC AND CLINICAL CHARACTERISITICS (n=90)

VARIABLE	STUDY GROUP (n=90)
MEAN AGE (YEARS)	53.40±15.38
GENDER	
• MALE	64 (71.1%)
• FEMALE	26 (28.9%)
TOBACCO USE	62 (68.9%)
BETEL CHEWING	73 (81.1%)
CLINICAL STAGE	
• EARLY	49 (54.4%)
• ADVANCED	41 (45.6%)
TUMOR LATERALITY	
• RIGHT	51 (56.7%)

• LEFT	39 (43.3%)
TUMOR SUB-SITE	
• ANTERIOR BUCCAL	46 (51.1%)
• POSTERIOR	44 (48.9%)
MEAN TUMOR THICKNESS (MM)	3.27±2.36
MEAN DEPTH OF INVASION (MM)	2.92±2.60
TUMOR GRADE	
• MODERATE	62 (68.9%)
• POOR	28 (31.1%)
PERINEURAL INVASION	32 (35.6%)
NODE METASTASIS	30 (33.3%)
LYMPHOVASCULAR INVASION	36 (40.0%)
EXTRACAPSULAR METASTASIS	10 (11.1%)
NECK DISSECTION	
• IPSILATERAL	68 (75.6%)
• BILATERAL	22 (24.4%)

FIGURE-2 : ROC CURVE FOR TUMOR THICKNESS AGAINST NODE METASTASIS

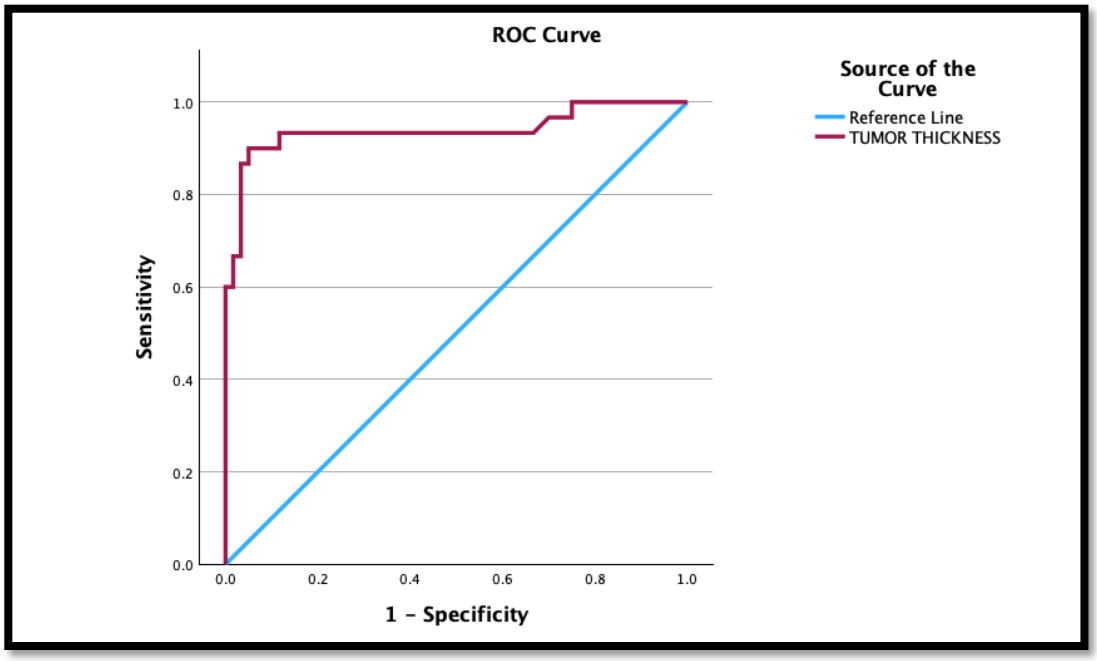


TABLE-II: ROC CURVE ANALYSIS FOR SUITABLE CUT-OFF

TUMOR THICKNESS VALUE (MM)	SENSITIVITY	SPECIFICITY	YOUDEN'S INDEX (J)
2.81	93.3%	88.3%	0.817

TABLE-III: CO-RELATION BETWEEN TUMOR THICKNESS CUT-OFF AND NODAL METASTASIS (n=90)

	NODAL METASTASIS	
	YES	NO
TUMOR THICKNESS • >2.8 MM • <2.8 MM	 28 (31.1%%) 02 (2.22%)	 07 (7.77%) 53 (58.8%)
Sensitivity= True Positive/ (True Positive +False Negative) = 93.93% **Specificity**= True Negative / (True Negative +False Positive) = 88.3% **Positive Predictive Value**= True Positive/ (True Positive+ False Positive) = 80.0% **Negative Predictive Value**= True Negative/ (True Negative +False Negative) = 96.4% **Diagnostic Accuracy**= (True Positive +True Negative)/All Patients = 90.0%		

DISCUSSION:

The present study evaluated the predictive performance of tumor thickness as a determinant of cervical nodal metastasis in buccal mucosa squamous cell carcinoma (BMSCC), demonstrating that a cut-off of 2.8 mm yielded a sensitivity of 93.3%, specificity of 88.3%, and an overall diagnostic accuracy of 90%. These findings support the growing evidence that micro-anatomical tumor invasion parameters offer superior risk-stratification compared to size-based T-staging alone. The implications are particularly relevant for regions with high-risk behaviors such as betel-quid and tobacco use, reflected in our cohort where nearly 82% chewed betel and 69% smoked or used smokeless tobacco.

Ahmed *et al.* (2017) reported that even a minimal tumor thickness of ≥2 mm significantly increased the likelihood of occult cervical metastasis in BMSCC, with an adjusted odds ratio exceeding 35.[11] Their findings from a Pakistani cohort align strongly with our results, which similarly identified early infiltration thickness as a critical marker for aggressive nodal behavior.

Lin *et al.* (2024) investigated tumor thickness across multiple oral subsites in a large Taiwanese cohort and identified 6 mm as an optimal ROC-derived threshold, with sensitivity and specificity of 70.9% and 60.5%.[12] Although their optimal cut-off is higher than ours, the population-level differences in histological patterns and habit-related carcinogenesis may explain the variation. Importantly, their buccal mucosa specific subgroup identified 7 mm as a significant boundary, demonstrating global heterogeneity in tumor biology.

Hirai *et al.* (2023) focused on buccal mucosa tumors in a Japanese cohort, finding that buccinator muscle invasion was one of the strongest predictors of nodal metastasis.[13] While they did not formally compute cut-off-based sensitivity or specificity for tumor thickness, their data support the principle that deeper invasion correlates with worse nodal outcomes, consistent with our findings.

Fawzy *et al.* (2017) evaluated tumor thickness through ROC analysis in an Egyptian OSCC cohort and reported an optimal cut-off of 4.4 mm, with both sensitivity and specificity exceeding 90%.[14] Their high specificity mirrors the strong discriminatory power observed in our dataset (Youden index 0.817), suggesting consistency across global regions where buccal mucosa cancer is prevalent.

Prasad *et al.* (2020) highlighted that early spread to cervical lymphatics is associated with stromal infiltration markers such as depth of invasion and tumor thickness rather than surface dimensions.[15] Their conclusion reinforces our findings that a low-threshold cut-off (2.8 mm) may be adequate for high-risk populations.

Gandhi *et al.* (2021) reviewed contemporary Indian datasets and observed that tumor thickness cut-offs between 3–4 mm generally showed good accuracy for predicting nodal metastasis in gingivobuccal cancers.[16] Their conclusions are highly compatible with our 2.8-mm threshold.

Ho *et al.* (2022) compared MRI-measured thickness with histologic measurements and concluded that tumor thickness consistently correlates with pathologic nodal status regardless of modality.[17] Their work supports incorporating imaging-based estimation of thickness for pre-operative planning, consistent with our study's emphasis on its diagnostic utility.

Chatterjee *et al.* (2023) demonstrated that increasing tumor thickness strongly correlates with extracapsular nodal extension, an adverse prognostic factor also observed in our cohort where 11.1% of metastatic nodes showed ECE.[4] This parallel underscores the prognostic relevance of thickness beyond simple metastasis prediction.

Patel *et al.* (2019) found that tumor thickness and depth of invasion (DOI) were independent predictors of survival in oral cavity cancers, with thresholds as low as 3 mm significantly associated with reduced disease-free survival.[7] This further validates our low cut-off boundary and its clinical relevance.

Raina *et al.* (2020) emphasized that patients with buccal cancers in South Asia exhibit earlier stromal infiltration and higher nodal burden due to widespread areca-nut use.[2] This observation co-relates with our cohort characteristics, where a substantial proportion exhibited PNI (35.6%) and LVI (40%).

Khan *et al.* (2022) reported that in Pakistani populations, betel and smokeless-tobacco–associated tumors tend to have more aggressive infiltration patterns, making micro-invasion metrics such as thickness essential for neck management decisions.[6] Our findings are in line with their conclusions, underscoring the need for region-specific thresholds.

Rajan *et al.* (2024) also demonstrated that DOI and tumor thickness outperform T-stage in predicting occult nodal metastasis in early oral cavity cancers.[18] Their findings, showing AUC values exceeding 0.80 for thickness, closely parallel our high Youden index and strengthen the argument for thickness-based decision-making in buccal mucosa tumors.

Collectively, the comparison with local and international literature demonstrates agreement that tumor thickness is a powerful, reproducible predictor of nodal metastasis. However, the exact optimal cut-off varies across populations (2–7 mm), is likely due to differences in risk habits, tumor site distribution, genetic factors, and healthcare pathways. Our cut-off of 2.8 mm, offering excellent sensitivity and specificity, aligns most closely with regional high-risk cohorts and provides a practical threshold for clinicians in Pakistan and neighboring regions. Importantly, the high negative predictive value (NPV) (96.4%) observed in our study indicates that patients with tumors ≤2.8 mm are highly unlikely to harbor occult metastasis, supporting conservative neck management in selected cases. Conversely, the positive predictive value (PPV) of 80% suggests that tumors above this threshold warrant elective neck dissection to prevent undertreatment.

CONCLUSION:

Tumor thickness demonstrated strong diagnostic accuracy for predicting cervical nodal metastasis in buccal mucosa squamous cell carcinoma, with a cut-off value of 2.8 mm providing excellent sensitivity and specificity.

LIMITATIONS:

This study was conducted at a single center, which may limit generalizability to broader populations. The sample size, though adequate for diagnostic accuracy analysis, remains modest and may underrepresent rare pathological subgroups. Only histopathological measurements were evaluated, without comparison to radiologic thickness estimates. Additionally, although prospective,

interobserver variability in measurement may still influence accuracy despite blinding. Further multicenter studies with larger cohorts and imaging–pathology correlations are recommended.

CONFLICT OF INTEREST:

None.

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