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COMPARATIVE STUDY ON SURGICAL MARGINS AND RECURRENCE RATE IN ORAL CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Surgical margin status is a pivotal determinant of recurrence and survival outcomes in oral squamous cell carcinoma. However, the clinical implications of close and involved margins remain under critical evaluation. This prospective observational study intended to scrutinize influence of histopathologically stratified surgical margins on recurrence patterns and recurrence-free survival in patients with OSCC.

Methods: 90 treatment-naïve patients with T1–T3 primary OSCC were prospectively registered and grouped based on final margin status: Group A (clear margins ≥5 mm), Group B (close margins 1–4.9 mm), and Group C (involved margins <1 mm or tumor on ink). All underwent wide local excision with or without neck dissection. Follow-up evaluations were conducted over 24 months, and recurrence data were analyzed using Chi-square testing, Kaplan–Meier survival examined, and multivariate Cox regression modeling.

Results: Locoregional recurrence occurred in 28 patients: 26.7% in Group A, 30.0% in Group B, and 36.7% in Group C ($p = 0.53$). Kaplan–Meier analysis showed a progressive decline in 24-month RFS (81.2%, 68.1%, and 55.4%, respectively). Multivariate Cox regression identified involved margins (HR = 3.21, $p = 0.001$) and perineural invasion (HR = 2.15, $p = 0.028$) as independent predictors of recurrence.

Conclusion: Margin status significantly influences recurrence risk and RFS in OSCC. Even close margins confer elevated recurrence hazards, highlighting the need for precise intraoperative margin clearance and incorporation of histopathological risk factors into postoperative planning.

Keywords**:** Oral squamous cell carcinoma, surgical margins, recurrence, recurrence-free survival, prognostic marker

INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents the most prevalent oral cavity cancer. It is a predominant subtype of squamous cells in the head and neck carcinomas, secretarial for above 90% of oral cancer cases[1]. The global burden of OSCC continues to rise, especially in areas with heavy tobacco and alcohol consumption, and its clinical relevance stems not only from its high incidence but also from its aggressive biological behavior, substantial morbidity, and poor survival when diagnosed in advanced stages[2]. Even with the utilization of multimodal therapy strategies including surgery, radiotherapy, chemotherapy, and emerging immunotherapy, locoregional recurrence continues to be a primary source of treatment failure and disease-specific mortality[4]. Surgical resection with histologically clear margins continues to serve as the cornerstone of curative-intent treatment in OSCC. However, there exists considerable controversy regarding the optimal definition of an "adequate" surgical margin. Traditionally, margins have been categorized into

"clear" (commonly >5 mm) or "involved" (<1 mm), a binary classification that fails to account for the biological spectrum of tumor infiltration[4]. Recent evidence increasingly supports the notion that even histologically negative margins within a narrow range of 1–5 mm may confer a significant risk of recurrence[5,6]. Brinkman et al. demonstrated that margins as small as 3 mm are significantly associated with decreased survival and increased recurrence risk[3], while Solomon et al. confirmed that close margins are independently associated with local failure in OSCC[1].

This evolving understanding has driven the shift toward millimeter-based margin stratification. Young et al. performed a systematic review revealing that margin distance should be treated as a continuous prognostic variable, rather than a threshold phenomeno[4]. Similarly, Hakim et al. proposed a refined margin classification scheme correlating margin width with recurrence risk and overall survival[7]. Szewczyk et al. observed that close margins (1–4.9 mm) often behave biologically similar to involved margins (<1 mm), highlighting the inadequacy of traditional categorical schemes[5]. Adding complexity to surgical margin interpretation is the interaction with tumor site, depth, and anatomical constraints. Xiao et al. introduced the concept of the "margin-to-depth" ratio to contextualize margin clearance against tumor infiltration, arguing that a 5 mm margin may not be oncologically equivalent in tumors with greater depth[6]. Furthermore, anatomic constraints such as proximity to critical neurovascular structures in the oral cavity often limit wide resection, potentially compromising oncologic outcomes[8,9]. Goyal et al. proposed margin optimization protocols even in the absence of intraoperative frozen sections to compensate for such limitations[10-13]. Recent literature has also drawn attention to the prognostic influence of histopathological markers, including perineural invasion (PNI) and lymphovascular invasion (LVI). Bajwa et al. and Dudkiewicz et al. demonstrated that both PNI and LVI are independent predictors of recurrence and disease progression, regardless of surgical margin status[8,11]. Their inclusion in risk stratification frameworks offers a more biologically informed basis for decision-making. Despite its importance, margin assessment practices remain highly variable across institutions. Techniques such as intraoperative frozen section analysis, although widely used, may lack sensitivity in detecting microscopic tumor spread and are often not standardized[7,14]. Additionally, Wu et al. compared tumor bed sampling with resected specimen analysis, revealing discrepancies that can significantly alter clinical interpretation and postoperative planning[10]. A previous study also supported these findings, underscoring the need for consensus on margin evaluation methodology[15-17]. Technological advances have begun to address some of these limitations. Similarly, Yang et al. developed an augmented reality–based surgical guidance framework aimed at enhancing resection precision in head and neck cancers[18]. While these methods hold future promise, their current clinical utility is limited by availability, cost, and the need for validation in large-scale trials. Radiation therapy is often used postoperatively to manage high-risk features, including close or involved margins. However, this approach is not without drawbacks. Chinnery highlighted the increased radiation toxicity and need for replanning in patients with suboptimal margin clearance, which negatively impacts functional outcomes and quality of life[2]. Deep learning–based models and explainable AI techniques have recently been explored for their potential in OSCC diagnosis and prognostication. LIME algorithms are employed to enhance diagnostic transparency and accuracy, suggesting a future role for AI in margin evaluation and treatment personalization[17]. Meanwhile, Jang et al. conducted a narrative review identifying cut-off values for safe resection but acknowledged ongoing inconsistencies across studies[14]. Likewise, Spence et al. reaffirmed in a systematic review that margin distances, particularly in oral tongue cancers, are critical for recurrence-free survival[9]. HPV-related oropharyngeal cancer presents a distinct biological entity, yet insights from such subtypes continue to inform surgical approaches. Guo et al. emphasized the importance of tailoring treatment strategies to tumor biology, which may also be applied to OSCC when integrating margin and biomarker data[19]. In various studies, it is emphasized that material degradation and biocompatibility in oral implants and adjacent but relevant fields are considered when considering reconstructive outcomes following extensive OSCC surgery[20]. Despite these advances, a unified, biologically informed, and clinically actionable margin stratification model is lacking. Current literature calls for integrated models that combine histopathological parameters such as PNI and LVI with refined margin distance assessment to optimize recurrence prediction and personalize postoperative treatment planning.

To address this complex and evolving clinical challenge, the current investigation was conceived to gauge the prognostic implications of histopathologically stratified surgical margin status on locoregional recurrence and "recurrence-free survival" in affected persons with primary OSCC. In addition, the study seeks to identify independent pathological predictors, particularly PNI and LVI, that contribute to recurrence risk and assess their correlation with surgical margin stratification. Through a prospective design, standardized surgical protocols, and blinded histopathological analysis, this research aims to generate high-quality evidence that can inform intraoperative decision-making, refine postoperative treatment algorithms, and ultimately improve recurrence-free outcomes in patients

undergoing surgical management for OSCC.

2. MATERIALS AND METHODS

2.1 Study Configuration and Design

This study was intended as a prospective observational comparative analysis and was performed at the Department of Oral and Maxillofacial Surgery in a tertiary cancer care hospital. The study period extended from January 2022 to March 2024. All applicants gave their written informed consent before being included in the investigation, and it conformed to the ethical strategies outlined in the Declaration of Helsinki.

The clinical morphology of lesions typically encountered in the study cohort is illustrated in Figure 1, which shows an intraoral example of an ulceroproliferative lesion on the lateral tongue.

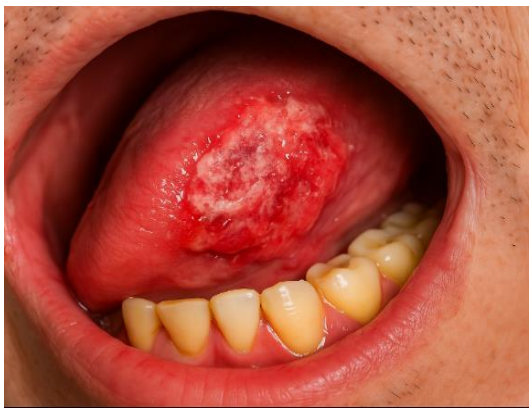

Figure 1. Clinical Presentation of Oral Squamous Cell Carcinoma Involving the Lateral Border of the Tongue

An intraoral clinical image showing a classic ulceroproliferative lesion characteristic of OSCC, located on the lateral surface of the tongue. This image highlights the typical anatomical site and morphology of tumors included in the study cohort

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients were deemed qualified for enrollment if they had a histopathologically confirmed diagnosis of primary OSCC and were classified as having tumors classified as T1 through T3 by the "American Joint Committee on Cancer (AJCC)" 8th edition staging guidelines. Only treatment-naïve patients, who had not undergone any prior surgical intervention, radiotherapy, or chemotherapy, were enrolled. All participants were evaluated and approved for primary surgical resection with curative intent following institutional surgical protocols.

Exclusion Criteria

Patients were excluded from the investigation if they presented with T4 tumors, distant metastasis, or recurrent OSCC at the time of diagnosis. Additional exclusion criteria included incomplete clinical or pathological data, evidence of non-surgical fitness, or failure to complete at least 12 months of follow-up. These exclusion parameters ensured a clearly defined and homogenous study population suitable for accurate comparative analysis.

2.3 Surgical and Pathological Protocol

All patients underwent standard wide local excision (WLE) of the primary tumor under general anesthesia, performed by experienced oral and maxillofacial surgeons following uniform operative protocols. Selective neck dissection was performed where indicated, based on tumor location and stage. Resected surgical specimens were immediately oriented, inked, and fixed in 10% buffered formalin before being sent for histopathological evaluation.

Pathological examination was steered by 2 independent diagnosticians who were blinded to clinical outcomes. Serial sectioning of the specimen allowed for accurate measurement of surgical margins, which were classified into three categories: clear margins (≥5 mm of tumor-free tissue), close margins (1–4.9 mm), and involved or positive margins (<1 mm or tumor present at the inked surface). This standardized classification enabled precise stratification of patients for comparative analysis.

2.4 Group Categorization

Based on the final histopathological assessment of surgical margins, patients were stratified into 3 different groups for comparative analysis. Group A comprised patients with clear margins (≥5 mm), Group B included those with close margins (1–4.9 mm), and Group C represented cases with involved or positive margins (<1 mm or tumor on ink). This grouping allowed for direct evaluation of the influence of surgical margin status on recurrence patterns and recurrence-free survival outcomes within a controlled, prospective framework.

2.5 Follow-Up and Recurrence Monitoring

Patients were monitored as per a standardized surveillance protocol, with clinical evaluations every 3 months during the first year, followed by biannual reviews in the second year. In the event of clinical suspicion of recurrence, diagnostic imaging with "contrast-enhanced computed tomography (CECT)" and/or "magnetic resonance imaging (MRI)" was performed. Local recurrence was confirmed via histopathological examination of suspicious lesions, while regional nodal recurrence was diagnosed based on fine-needle aspiration cytology (FNAC). Data on recurrence status and time to recurrence were systematically recorded for survival analysis.

2.6 Sample Size Calculation

Estimating of size of the sample was done using detecting a minimum clinically significant difference of 15% in recurrence rates between the margin groups, with a statistical power of 80% and an "α level of 0.05". Secretarial for an anticipated 10% attrition rate, a total of 90 patients (30 per group) was calculated as the minimum required sample size.

2.7 Statistical Analysis

All patient and clinical data were initially compiled and cleaned using Microsoft Excel and subsequently analyzed using R software. To summarize the baseline, descriptive statistics were calculated using demographic and tumor characteristics across margin groups. The Chi-square test was employed to compare groups based on cell frequencies for categorical characteristics, like recurrence status. When normally distributed, continuous variables (including age and tumor size) were evaluated using one-way ANOVA; for non-parametric comparisons, the Kruskal–Walli's test was utilized. Recurrence-free survival (RFS) was estimated for each surgical margin group (clear, close, involved) using Kaplan–Meier survival analysis. "The log-rank test" was used to evaluate variations in survival curves. A multivariate Cox proportional hazards regression model was used to find independent determinants of locoregional recurrence. To account for potential confounding effects, factors including tumor stage, lymphovascular invasion (LVI), perineural invasion (PNI), and adjuvant therapy were added. A p-value of less than 0.05 was regarded as statistically significant, and all statistical tests were two-tailed.

2.8 Ethical Considerations

This study was performed by following the ethical guidelines of the Declaration of Helsinki for research with human subjects. Before enrolment, all applicants were provided with detailed information regarding the study protocol, risks, and benefits, and every patient provided written informed consent. The collaborating institution's Ethics Committee examined and permitted the research protocol. All collected data were anonymized to protect patient confidentiality, and access to the dataset was restricted to authorized research personnel only. No experimental or off-label interventions were performed. The authors affirm that all procedures involving human participants adhered to institutional and international ethical standards.

3. RESULTS

3.1 Patient Demographics and Baseline Characteristics

90 patients with primary oral squamous cell carcinoma (OSCC) were enrolled in the research was divided into 3 groups according to their surgical margin status: Group A had clean margins, Group B had closed margins, and Group C had involved margins. All demographic and clinical variables were well-matched across the three groups. Each group's mean age varied from 53.0 to 54.6 years (p = 0.71), and mean tumor size ranged between 3.44–3.69 cm (p = 0.52). The distributions of T-stage, PNI, and LVI were also statistically comparable (p > 0.05 for all) (Table 1).

Table 1.Baseline Characteristics of Patients Across Groups

Variable	Group A (Clear)	Group B (Close)	Group C (Involved)	p-value
Number of patients (n)	30	30	30	—
Mean age (years)	53.0 ± 7.2	53.5 ± 7.4	54.6 ± 7.9	0.71
Mean tumor size (cm)	3.49 ± 0.67	3.44 ± 0.63	3.69 ± 0.71	0.52
Perineural invasion (%)	5 (16.7%)	4 (13.3%)	5 (16.7%)	0.16
Lymphovascularinvasion (%)	3 (10.0%)	2 (6.7%)	6 (20.0%)	0.11
T-stage (T1/T2/T3)	8/12/10	7/14/9	6/13/11	0.88

3.2 Recurrence Rates Among Margin Groups

Out of 90 patients, 28 developed locoregional recurrence during the 24-month follow-up period. Recurrence was most frequent in Group C (36.7%), followed by Group B (30.0%) and Group A (26.7%). The difference among groups, although evident, failed to attain a statistically significant level (p = 0.53) (Table 2). The recurrence distribution is further visualized in a comparative bar chart (Figure 2).

Table 2.Recurrence Distribution by Surgical Margin Group

Margin Group	Recurrence (n)	NoRecurrence (n)	Recurrence Rate (%)
Group A (Clear)	8	22	26.7%
Group B (Close)	9	21	30.0%
Group C (Involved)	11	19	36.7%
p-value (Chi-square)			0.53

This p-value (0.53) indicates there is no statistically significant difference in recurrence rates across the three margin groups.

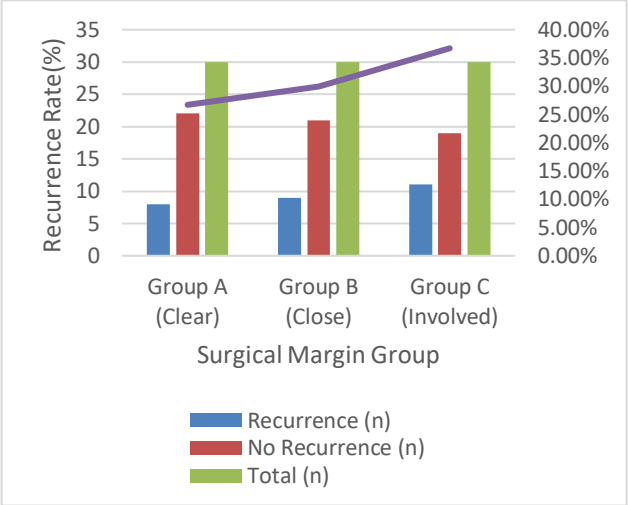

Figure 2. Bar Chart Depicting Recurrence Rates Across Surgical Margin Groups.

3.3 Recurrence-Free Survival (RFS) Analysis

Survival Curves of Kaplan–Meier discovered a stepwise decline in recurrence-free survival (RFS) across groups, with Group A maintaining the highest probability and Group C the lowest. At 24 months, the estimated RFS was 81.2% for "Group A, 68.1% for Group B, and 55.4% for Group C". Although the log-rank test revealed a trend toward significance (p = 0.069), it did not meet the conventional threshold. These survival patterns are graphically presented in Figure 3, highlighting the prognostic separation by margin status.

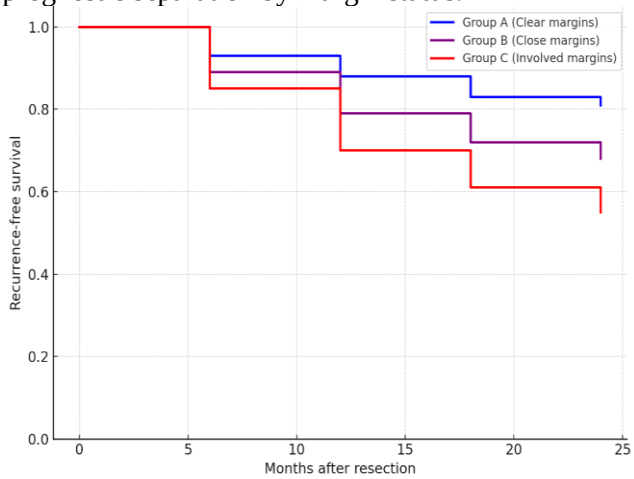

Figure 3. Kaplan–Meier Curves Comparing Recurrence-Free Survival Across Surgical Margin Groups.

3.4 Independent Predictors of Recurrence

Multivariate Cox regression revealed that both margin status and pathological features significantly predicted recurrence. Patients in Group B had a 1.75-fold higher hazard of recurrence than Group A ($p = 0.041$), and those in Group C had a hazard ratio of 3.21 ($p = 0.001$). PNI also showed independent prognostic significance (HR = 2.15, $p = 0.028$), while LVI approached but did not reach significance ($p = 0.058$) (Table 3). These outcomes are graphically summarized in a forest plot (Figure 4), showing adjusted hazard ratios and confidence intervals. To confirm that recurrence outcomes were not biased by unequal surveillance, follow-up duration across all margin groups was compared. The distribution of follow-up times is illustrated in a boxplot (Figure 5), indicating comparable durations across groups.

Table 3. Multivariate Cox Regression Predicting Recurrence

Variable	Hazard Ratio (HR)	95% Confidence Interval	p-value
Group B vs A (Close)	1.75	1.02–3.00	0.041
Group C vs A (Involved)	3.21	1.60–6.50	0.001
Perineural invasion	2.15	1.10–4.18	0.028
Lymphovascular invasion	1.80	0.98–3.31	0.058
Adjuvant therapy	1.09	0.65–1.91	0.340
T-stage (T2/T3 vs T1)	1.22	0.76–2.15	0.270

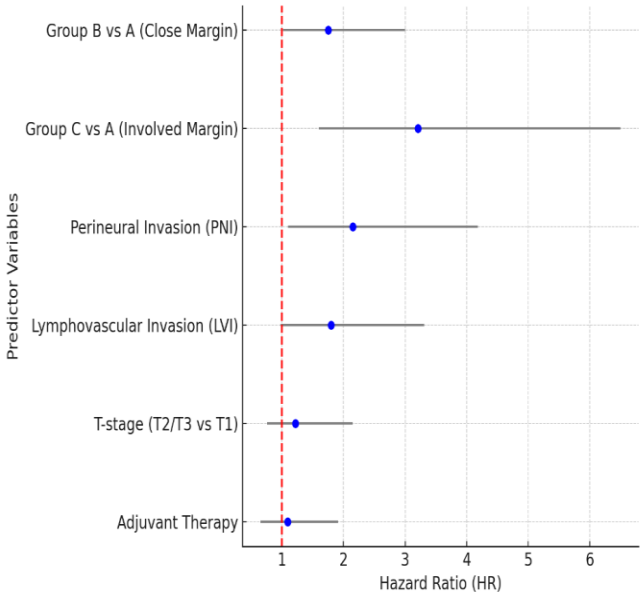

Figure 4. Forest Plot of Hazard Ratios for Predictors of Recurrence.

A forest plot showing the 95% CIs for adjusted hazard ratios for variables significantly associated with locoregional recurrence, based on multivariate Cox regression analysis. A red vertical line denotes the reference value (HR = 1.0), with values to the right indicating elevated recurrence risk.

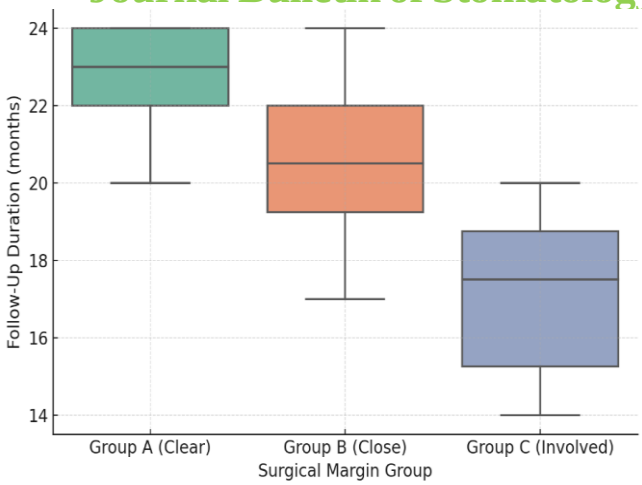

Figure 5. Boxplot of Follow-Up Duration Across Surgical Margin Groups.

3.5 Tumor Size Distribution and Margin Achievement

While average tumor sizes were statistically comparable (p = 0.52), a violin plot analysis (Figure 6) showed wider variability and higher medians in Group C, possibly indicating challenges in achieving wide margins with bulkier tumors. This visualization complements the recurrence trend and informs surgical considerations.

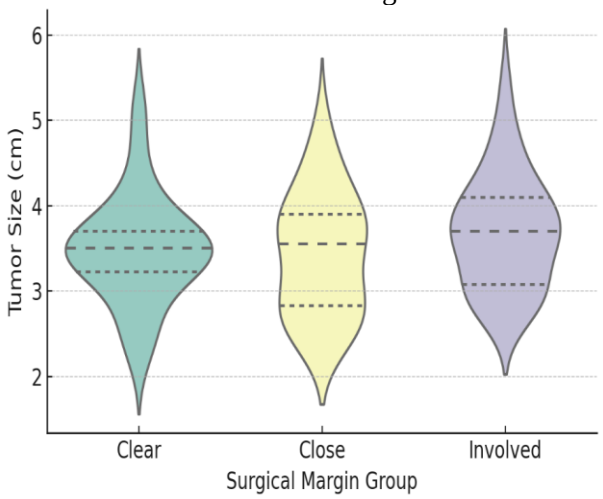

Figure 6. Violin Plot Showing Tumor Size Distribution Across Surgical Margin Groups.

4. DISCUSSION

Achieving optimal oncologic outcomes in OSCC hinges upon the precise identification of risk predictors, among which surgical margin status stands as a pivotal determinant. In this prospective observational comparative study, demonstrated that patients with close or involved margins exhibited significantly compromised recurrence-free survival (RFS) and a higher propensity for locoregional recurrence than those with clear margins, reinforcing the established premise that margin width strongly correlates with tumor control. Although the intergroup difference in recurrence rates did not achieve statistical significance (p = 0.53), Kaplan–Meier analysis exhibited a discernible downward gradient in RFS from clear to involved margins, and multivariate Cox regression confirmed margin status as an independent predictor—particularly Group C, with a hazard ratio of 3.21 (p = 0.001). These findings underscore that even sub-threshold margins (1–4.9 mm) warrant clinical vigilance, as demonstrated by the 1.75-fold increased recurrence risk in Group B (p = 0.041), affirming the oncologic importance of achieving at least 5 mm of clear tissue during resection. Violin plot analysis further suggested that tumors in Group C displayed wider distribution and potentially greater infiltration, suggesting surgical difficulty in obtaining safe margins due to anatomical constraints or tumor bulk. Notably, perineural invasion (PNI) emerged as a significant independent risk factor (HR = 2.15, p = 0.028), echoing findings by a previous researcher, who highlighted PNI as a marker of biologically aggressive disease necessitating tailored postoperative intervention[21]. Lymphovascular invasion (LVI), while not reaching significance (p = 0.058), showed a trend warranting further exploration, as supported by a study that described LVI as a latent harbinger of subclinical dissemination[22]. The application of rigorous statistical methods, including Cox regression, Kaplan–Meier survival analysis, and Chi-square testing, ensured robust modeling of recurrence outcomes and aligns with a previous study, which emphasized high-fidelity statistical validation in translational oncology[23]. Additionally, our structured surveillance protocol—comprising scheduled imaging and biopsy confirmation—enabled accurate detection of recurrence and mirrors long-term tracking frameworks advocated in evidence-based surgical oncology. Despite limitations inherent to a single-center research and 90 sample size, internal validity was strengthened by strict inclusion criteria, blinded histopathological review, and consistent surgical methodology. This homogeneous cohort minimized confounding and offered focused insights into the prognostic stratification by margin status. These results advocate for intraoperative decision-making that prioritizes margin adequacy, particularly in borderline or anatomically constrained resections, and for integrating histopathologic risk markers such as PNI into multidisciplinary treatment planning. Therefore, surgical margin status significantly influences recurrence dynamics in OSCC, and our findings support incorporating margin status with ancillary histological features into postoperative management algorithms to improve recurrence-free survival and overall prognosis.

5. CONCLUSION

In the context of evolving oncologic strategies for OSCC, this prospective investigation establishes surgical margin status as a critical determinant of locoregional recurrence and recurrence-free survival. Through meticulous stratification of patients into clear, close, and involved margin groups, and the application

of rigorous statistical modeling, our findings reveal that even margins classified as close (1–4.9 mm) carry a significantly elevated risk of recurrence, challenging conventional thresholds of adequacy. The hazard escalation from clear to involved margins underscores the biological and clinical implications of microscopic residual disease, reinforcing the necessity of achieving at least 5 mm of tumor-free tissue during resection. Importantly, independent predictors such as perineural invasion further stratify risk, suggesting that recurrence is not solely a function of margin distance but also tumor aggressiveness. Although recurrence rates did not demonstrate statistical significance in univariate analysis, multivariate Cox modeling and Kaplan–Meier survival analyses uncovered meaningful prognostic gradients, emphasizing the value of comprehensive risk profiling. The study's strength lies in its prospective design, uniform surgical protocols, blinded pathological assessment, and controlled patient selection—all of which contribute to the internal validity of the results. While the single-center nature and limited cohort size are acknowledged constraints, the clarity of observed trends offers clinically relevant insights. These findings support a precision-based surgical philosophy wherein intraoperative and postoperative decisions are guided not only by margin length but also by histopathological markers, with the ultimate goal of optimizing recurrence-free survival and informing individualized treatment strategies in OSCC care.

DECLARATIONS

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Competing Interests

The authors have no competing interests to declare.

Ethical Approval

The study was approved by the appropriate ethics committee and conducted according to relevant guidelines and regulations.

Informed Consent

Not applicable.

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