



## ON THE EDGE: EVALUATING CLINICOPATHOLOGICAL OUTCOMES OF PATIENTS WITH CLOSE AND INVOLVED SURGICAL RESECTION MARGINS IN EARLY-STAGE TONGUE SQUAMOUS CELL CARCINOMA

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### ABSTRACT

**Background:** Early-stage oral tongue cancers, predominantly squamous cell carcinomas, originate in the anterior two-thirds of the tongue. Surgical resection remains the cornerstone of treatment, aiming to excise the tumour along with a margin of healthy tissue. Ensuring clear surgical margins is essential, as it substantially influences prognosis by minimizing the likelihood of local recurrence and enhancing overall survival rates.

**Objectives:** This study examines the outcomes of early-stage squamous cell carcinoma of the oral tongue with close and involved surgical resection margins, focusing on recurrence rates, survival outcomes, and the necessity for adjuvant treatment.

**Materials and Methods:** This retrospective cohort study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre in Lahore, Pakistan from January 1, 2011, to December 30, 2021. A total of 158 patients, aged 18 to 75 years, diagnosed with early-stage oral tongue cancer (stages I and II) were included through consecutive sampling. Patients with metastatic disease, prior head and neck cancers, concurrent malignancies, or significant comorbidities that could affect treatment or prognosis were excluded. Data analysis was performed using SPSS Statistics 27, and Kaplan-Meier analysis was employed to evaluate overall and recurrence-free survival.

**Results:** Among the n=158 patients, n=123 (77.8%) had close margins, n=35 (22.2%) had involved margins. Males were the majority in both groups (p=0.846). The estimated mean survival time was  $110.04 \pm 9.92$  months for patients with close margins and  $69.94 \pm 2.03$  months for those with involved margins. Patients with involved margins exhibited a lower mean survival time (p=0.394). The overall 5-year survival rates were approximately 89.20% (95% CI: 79.60%-99.90%) for close margins and 96.9% (95% CI: 91.00%-100%) for involved margins. The estimated recurrence-free mean survival time was  $93.33 \pm 10.36$  months for close margins and  $54.97 \pm 4.65$  months for involved margins (p=0.549). The 5-year recurrence-free survival rate was 73.90% (95% CI: 91.90%-89.30%) for close

margins and 58.9% (95% CI: 38.30%-90.60%) for involved margins.

**Conclusion:** This study evaluated the outcomes of early-stage oral tongue squamous cell carcinoma (SCC) with close and involved surgical resection margins. The results indicate that patients with involved margins experienced lower mean survival times and higher recurrence rates, although these differences were not statistically significant. The study underscores the critical importance of precise margin assessment during surgery, as margin status can significantly impact survival and recurrence rates. The high overall and recurrence-free survival rates observed reflect effective management strategies, highlighting the potential role of adjuvant treatment decisions based on margin status. These findings contribute to refining treatment approaches and optimizing outcomes for patients with early-stage oral tongue SCC.

**Keywords:** Tongue tumours, Head and neck cancer, Early tumours, Close and involved margins, Early-stage tongue squamous cell carcinoma, Oral tongue cancer, Surgical resection margins, Close margins

### Introduction

Lip and oral cancers globally constitute 9.7% of all cancer cases [1] Developing countries, particularly in Southeast Asia, experience higher oral cancer rates due to the prevalence of chewing tobacco [2,3]. In India, oral cancer is one of the most common cancers and continues to be a major public health problem. Oral tongue squamous cell carcinomas (OTSCC) have been reported to be among the top two most common sub-sites among oral cavity cancers across many studies in India. Tongue cancer is prevalent among users of chewable tobacco and alcohol. Among various forms of tobacco use, such as smoking and smokeless tobacco, the habit of using chewable tobacco is particularly common in this region.[4] The tongue remains the most common intraoral site for oral cancer worldwide and in several countries, it is a serious public health problem with significant morbidity and mortality. While the incidence of tongue cancer appears to be stable or falling in some regions of the world, in other areas it is rising, particularly among younger people [5] Globally, oral cancers are more common in regions where tobacco use, particularly chewing tobacco, is prevalent. This includes parts of Southeast Asia (e.g., India, Pakistan) and parts of Africa. Developed countries also see cases, often linked to alcohol and tobacco use, although there has been a shift towards HPV-related oral cancers in some regions [6] The incidence of OTSCC although showing a slightly decreasing trend in India, is clearly showing an increasing trend in Chennai over the past 25 years as per the data of the National Cancer Control Program. A majority of the oral cavity cancers (85%) in our cancer centre present in advanced stages (Stages III and IV), on the contrary, early tongue cancers (Stages I and II) constitute nearly 45% of all OTSCCs [7.]. The prognosis of oral cancer depends on the TNM classification system, which categorizes patients based on the size of the primary tumour, involvement of nearby lymph nodes, and presence of distant metastases. Additional histopathological factors influencing prognosis include tumour depth, grade, surgical margin status, pattern of invasion (cohesiveness), and the presence of perineural or lymphovascular invasion.[8]. The majority of the epidemiological studies have focused on oral cancers as a whole, and there have been very few studies in the literature which has specifically looked into OTSCC For squamous cell carcinoma of the oral tongue, the standard treatment involves surgically removing the primary tumour with clear margins, ensuring complete cancer cell eradication. Positive surgical margins at a microscopic level led to elevated risks of local recurrence and poor clinical outcomes [5-8].

In 1998, the Royal College of Pathologists introduced guidelines defining margins as involved (< 1 mm), close (1–5 mm), or clear (> 5 mm) [9]. According to National Cancer Comprehension Network (NCCN) guidelines (as of February 2021) for head and neck cancers, a surgical margin is clear if it extends  $\geq 5$  mm from the tumour's invasion front [10]. Notably, mucosal surgical margins tend to shrink during preparation, with buccal mucosal margins shrinking by over 45% and tongue mucosal margins by 30%, making a 7 mm in situ resection margin often appear close (less than 5 mm). Therefore, to ensure adequate pathological margins, tumour resections should encompass 1–1.5 cm

of normal mucosa, accounting for expected shrinkage [11].

Tumour margin involvement substantially increases the risk of local recurrence post-glossectomy, with reported rates ranging from 18% to 23.5%, predominantly occurring within the first year after surgery [12]. The primary factor influencing prognosis significantly is thorough surgical removal, as incomplete removal of the primary tumour remains the leading cause of mortality among patients [13]. While the histopathological condition of resection margins has traditionally been considered an important predictor of local recurrence and survival, many aspects surrounding resection margins, such as their terminology, definition, and the impact of anatomical and histological factors, remain uncertain. [14]

While most epidemiological studies have centred on oral cancers broadly, there is a limited body of literature specifically examining oral tongue squamous cell carcinoma (OTSCC) with both clear and involved margins. Utilizing margin status to assess the necessity for adjuvant therapies and to evaluate outcomes such as survival and recurrence is crucial in guiding effective treatment strategies for oral tongue squamous cell carcinoma (OTSCC). A clear understanding of margin status can guide surgeons in determining the extent of surgical resection needed to achieve clear margins, thereby reducing the risk of local recurrence. Patients with involved margins may benefit from adjuvant therapies such as radiation or chemotherapy to improve outcomes and reduce the likelihood of recurrence. Hence, the study aimed to see the clinicopathological outcome of patients with early SCC of the oral tongue with close and involved margins in terms of overall, recurrence-free and metastasis-free survival.

### **Materials and Methods:**

A retrospective cohort study was conducted at Shaukat Khanum Memorial Hospital, Lahore from January 1, 2011, to December 31, 2021. A total 158 patients of aged 18 to 75 years diagnosed with early-stage oral tongue cancer, specifically stages I and II were included through consecutive sampling. Patients with a confirmed diagnosis of squamous cell carcinoma located in the anterior two-thirds of the tongue, respectable tumours, and no prior treatment for oral cancer were also included. The patients with metastatic disease, previous head and neck cancers, other concurrent malignancies, or significant comorbidities that could interfere with treatment or prognosis were excluded.

### **Data Analysis:**

Data was entered and analyzed in SPSS 27. Frequency and percentages were calculated for the categorical variables and Mean $\pm$ SD was obtained for continuous variables. Kaplan Meier Survival was employed for Overall and recurrence-free survival analysis. Survival comparison between close and involved margins was done by log-rank test. The 5-year survival rates were also calculated with their respective confidence interval. P-value  $\leq 0.05$  was considered significant.

### **Results:**

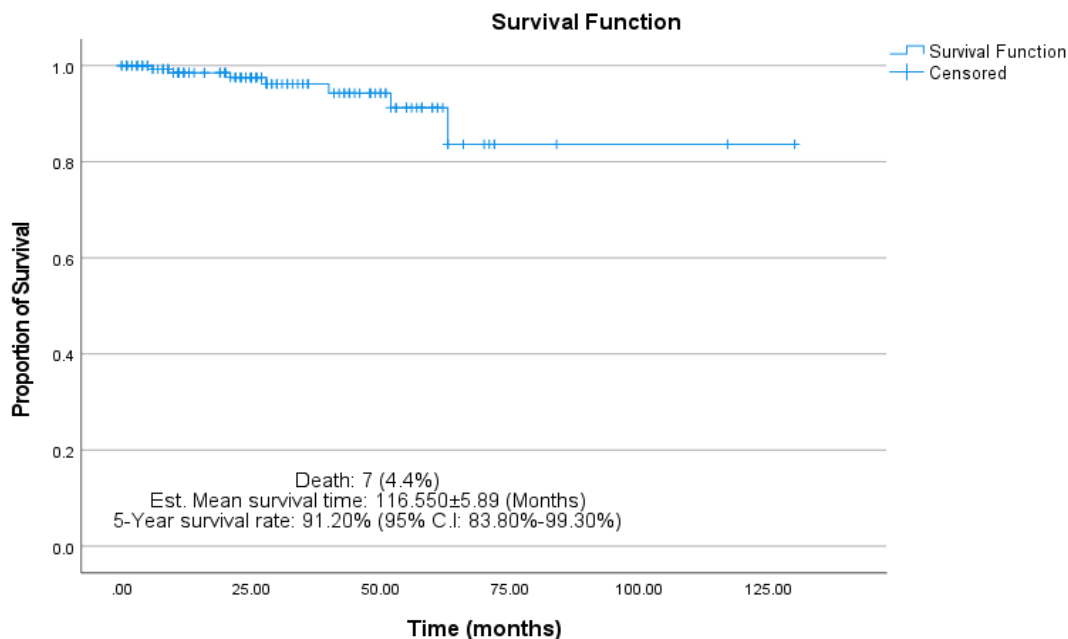
A total of n=158 patients with T1-T2N0 disease who underwent surgery to the primary site in the form of partial glossectomy and ipsilateral or bilateral neck dissection were enrolled in our study. Among them, n=123(77.8%) had close margin and n=35(22.2%) had involved margin. Males were dominant in number with both close and involved margins, but there was no significant difference in the gender distribution among different margins (p=0.846). A total of n=65 (41.1%) were exposed to risk factors, with n=48(39.0%) in close and n=17(48.57%) in involved margins (p=0.311). The final histopathology report showed n=76 (48.1%) cases of moderately differentiated SCC, n=11 (7.0%) cases of poorly differentiated SCC and n=71 (44.9%) cases of well-differentiated SCC, with no significant difference in distribution among close and involved margin group (p=0.677). (**Table 1**) Among n=158 cases examined, n=7(4.4%) patients had locoregional recurrences and died. The estimated mean overall survival time was 116.550 $\pm$ 5.89 months. The overall 5-year survival rate was 91.20% (95% C.I: 83.80%-99.30%) indicating that by years, a small proportion of the patients died and the survival rate was notably high. (**Figure 1**) The estimated mean survival time for patients with

close margins was  $110.04 \pm 9.92$  months and for the patients with involved margins was  $69.94 \pm 2.03$  months. Patients with involved margins exhibit a lower mean survival time compared to those with close margins however, no statistically significant difference was observed ( $p=0.394$ ). The overall 5-year survival rate for close margin was 89.20% (95% C.I: 79.60%-99.90%). There was only one death in the involved margin group so the survival rate was very high: 96.9% (95% C.I: 91.00%-100%). **(Figure 2)**. When the different widths of margin involvement were compared, the analysis revealed that patients with a 3mm margin exhibit a significantly lower estimated mean survival time of  $67.70 \pm 7.73$  months compared to others, indicating a potential subgroup with poorer prognosis however, no statistically significant difference in estimated mean survival time was observed ( $p=0.350$ ). The 5-year survival rates among patients with 2mm-4mm margin involvement were observed to be 87.40% (95% C.I: 71.40%-100%), 89.90% (95% C.I: 77.60%-100%) and 90.90% (95% C.I: 74%-100%), respectively. **(Figure 3)**

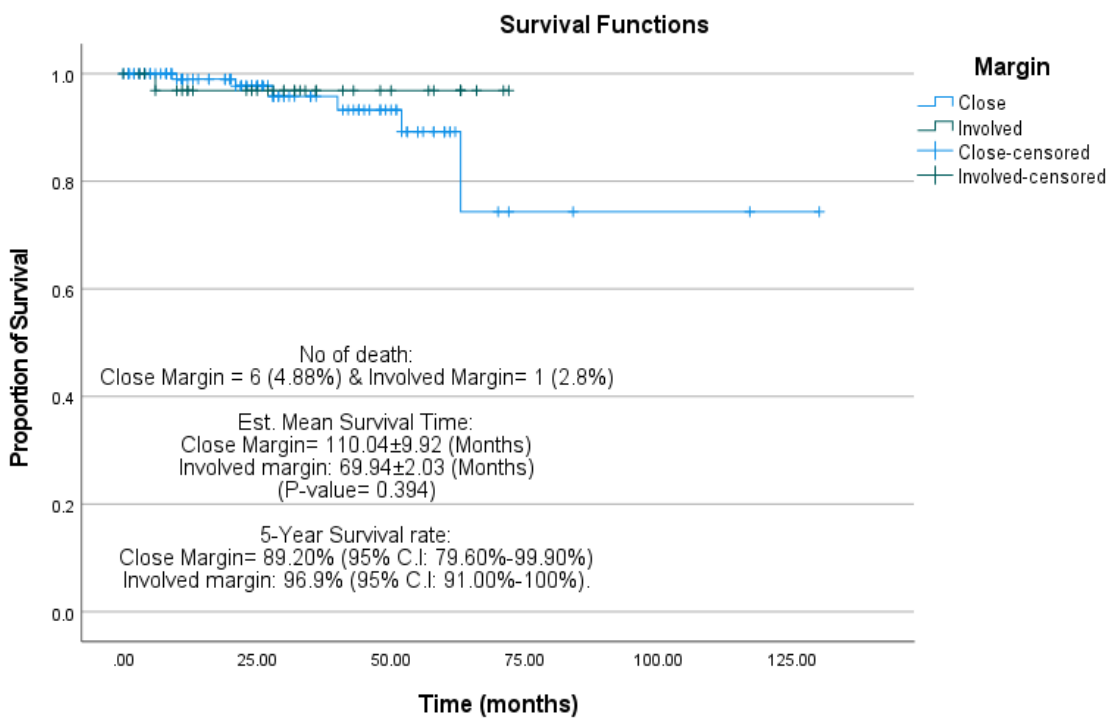
Among  $n=158$  cases,  $n=26$  (16.46%) of the patients had recurrence. The estimated recurrence-free mean survival time was  $94.60 \pm 7.124$  months. The 5-year recurrence-free survival rate was 70.10% (95% C.I 59.30%-82.90%). **(Figure 4)** The estimated recurrence-free mean survival time for patients with close and involved margins was  $93.33 \pm 10.36$  months and  $54.97 \pm 4.65$  months, respectively with no significant difference ( $p=0.549$ ). The 5-year recurrence-free survival rate for the close margin was 73.90% (95% C.I: 61.90%-85.90%) and for the involved margin, it was 58.9% (95% C.I: 48.30%-68.60%). **(Figure 5)**. Patients with a 2mm margin exhibit a significantly better recurrence-free mean survival time:  $98.67 \pm 10.67$  months compared to other margin widths however, no statistically significant difference among different widths of margin involvement was observed ( $p=0.734$ ). The 5-year recurrence-free survival rate among patients with 1mm to 4mm margin was 58.90% (95% C.I: 48.30%-68.60%), 67.20% (95% C.I: 56.70%-76.50%), 77.10% (95% C.I: 67.14%-87.20%) and 77.20% (95% C.I: 67.10%-87.00%), respectively. **(Figure 6)**.

**Table 1: Comparison of Characteristics of patients with close and involved margin**

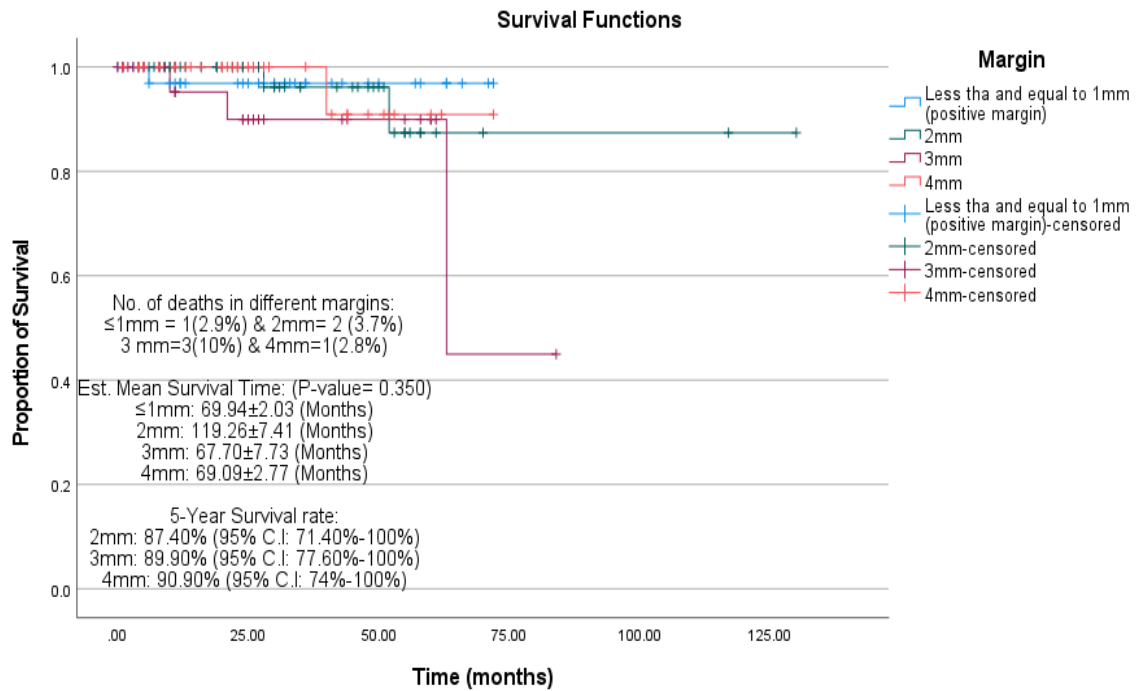
Variables		Margin		Total 158(100)	P-value <sup>1</sup>
		Close 123(77.8)	Involved 35(22.2)		
Gender	Female	49(39.8)	13(37.1)	62(39.2)	0.846
	Male	74(60.2)	22(62.9)	96(60.8)	
Risk Factors	Yes	48(39.0)	17(48.57)	65(41.1)	0.311
	No	75(61.0)	18(51.43)	93(58.9)	
Risk Factor Type	Pan	22(45.8)	6(35.3)	28(43.1)	0.430
	Smoking	32(66.7)	10(58.8)	42(64.6)	0.550
	Naswar	12(25)	6(35.3)	18(27.7)	0.430
	Alcohol	0(0.0)	1(5.88)	1(1.54)	0.087
Histopathology differentiation	Well	53(43.1)	18(51.4)	71(44.9)	0.677
	Moderate	61(49.6)	15(42.9)	76(48.1)	
	Poor	9(7.3)	2(5.7)	11(7.0)	



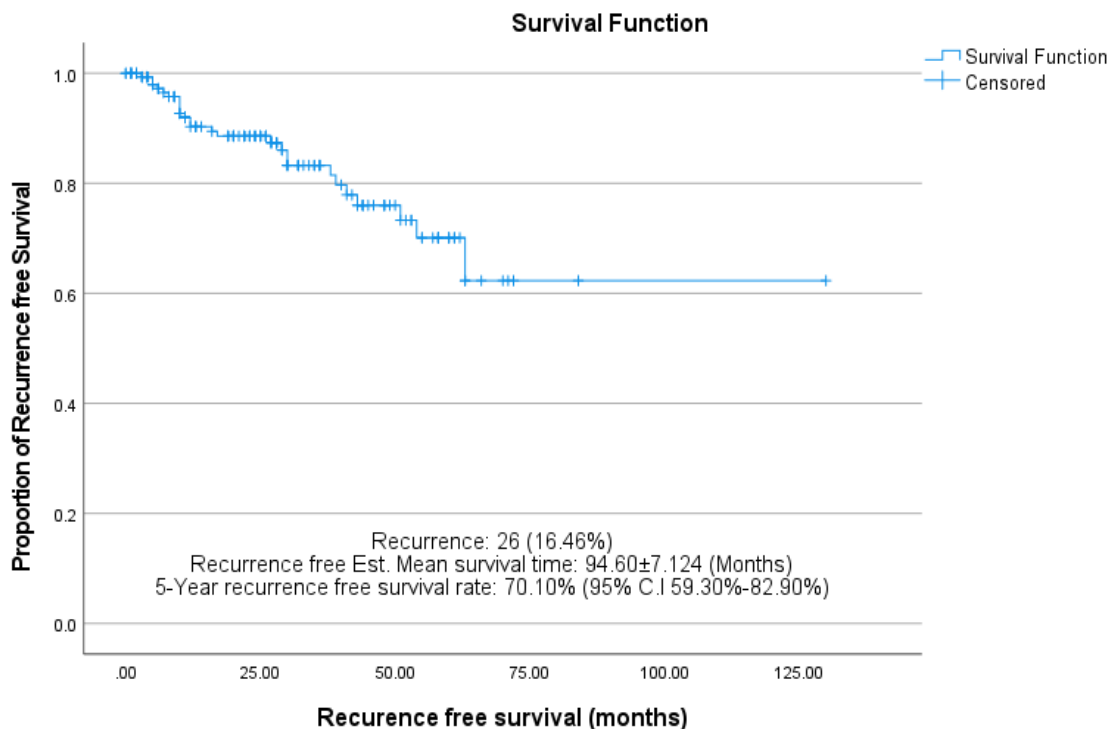
**Figure 1: Overall survival of patients with early SCC of oral tongue**



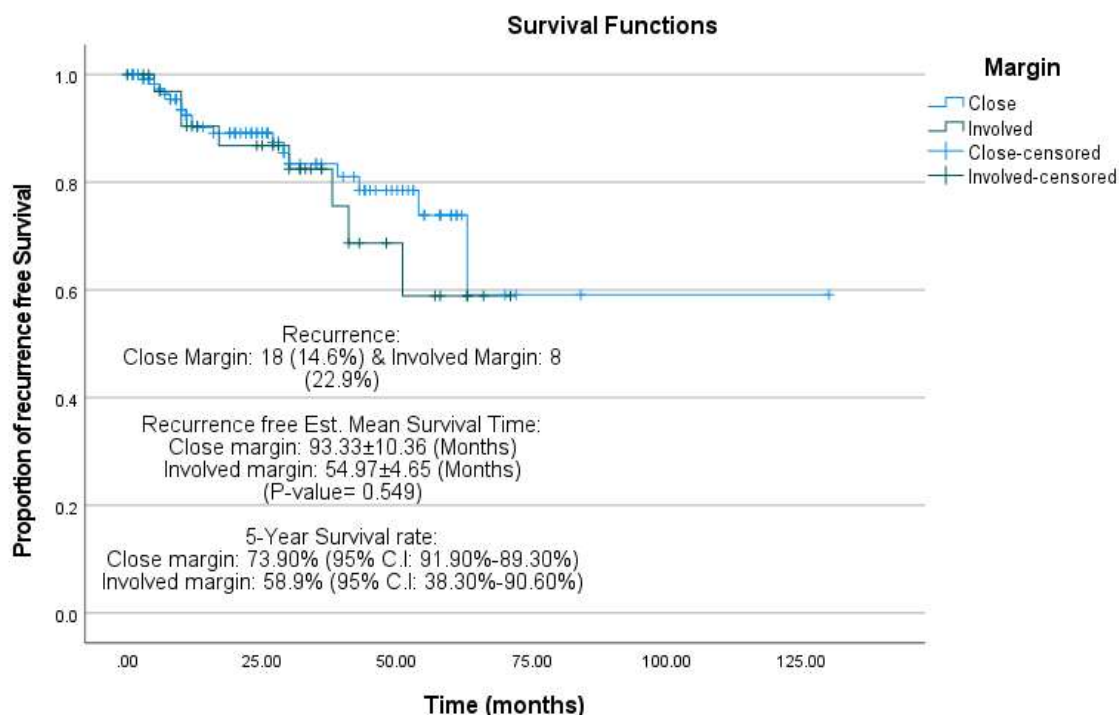
**Figure 2: Survival of early SCC of oral tongue patients with close and involved margins**



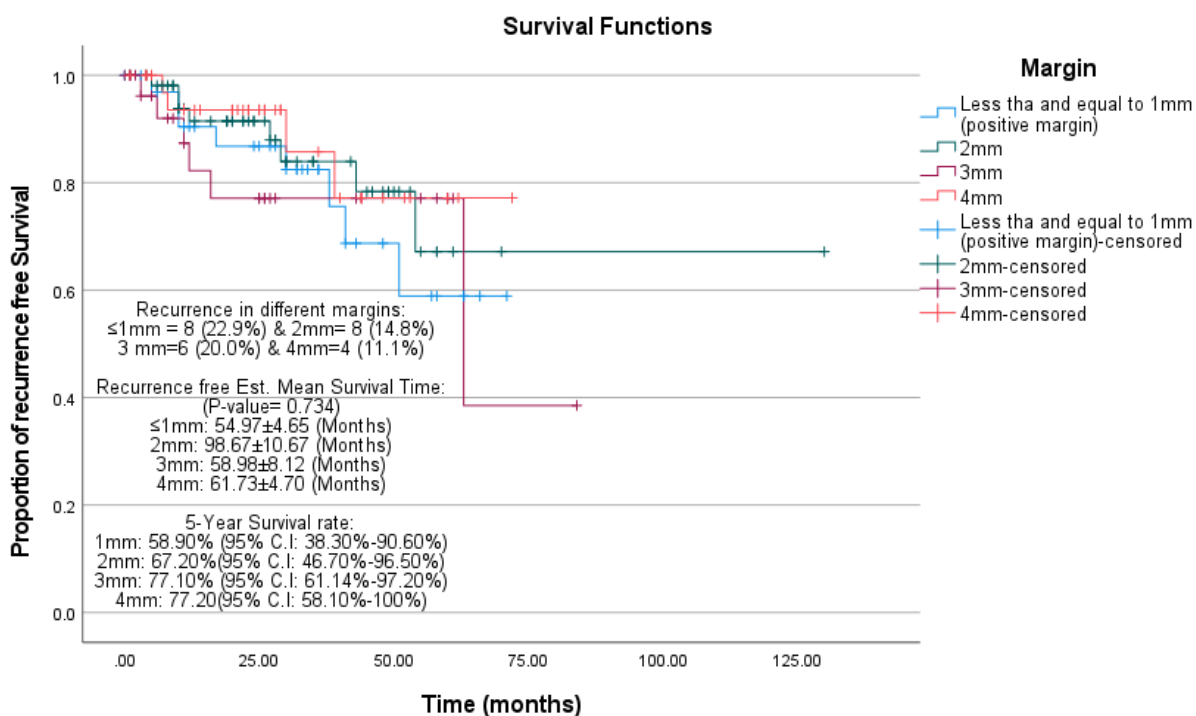
**Figure 3: Overall Survival of early SCC of oral tongue patients with individual margins**



**Figure 4: Recurrence-free survival of patients with early SCC of oral tongue**



**Figure 5: Recurrence-free survival (months) in close and involved margins**



**Figure 6: Recurrence-free survival (months) in individual margins**

### Discussion

The primary goal of surgical oncology is the complete removal of the tumour while preserving a margin of normal tissue surrounding the neoplasm. However, even after apparent tumour removal, recurrences and cancer-related deaths still occur. This raises the question of whether examining resection edges under a microscope can provide prognostic information regarding the likelihood of recurrence and survival. Studies of these questions, particularly in the context of head and neck carcinomas, have been extensive. Articles by Landmark et al have found that microscopic margins

correlate with recurrence and survival, suggesting that obtaining and analyzing intraoperative frozen sections can increase the chances of obtaining a negative margin [12-15]. Some studies support these conclusions [16-18]. Other studies present contradictory evidence, indicating that a positive margin is just one of several indicators of aggressive tumour biology and is not independently sufficient for determining prognosis [19-26]. A commonality among these studies is that they all assessed margins based on the main specimen but used different definitions of "involved." Our study also focuses on specimen sampling for intraoperative margin evaluation, which is in alignment with the typical approach used in prior studies.

Our study included n=158 patients with T1-T2N0 disease who underwent surgery to the primary site in the form of partial glossectomy and ipsilateral or bilateral neck dissection. The patients were divided into two groups based on their margin status: close (n=123) and involved (n=35).

Our analysis demonstrated an overall survival probability of 83.6% at 63 months, highlighting the encouraging prognosis for this patient population. However, the mean survival time varied significantly based on margin status, with patients with involved margins experiencing notably lower survival rates compared to those with close margins. While the difference did not reach statistical significance, the trend is clinically significant.

Recurrence-free survival estimates revealed a similar trend, with an overall proportion of 62.3% at 63 months. Notably, patients with a 2 mm margin exhibited significantly better recurrence-free survival, suggesting the importance of margin width in predicting disease recurrence.

In addition to our findings, Solomon et al, Chen et al and Park et al found that patients with close surgical margins had better recurrence-free survival compared to those with involved margins, emphasizing the importance of clear margins in improving patient outcomes [27] [28][29]. This finding aligns with our study, reinforcing the critical role of margin status in determining prognosis.

These findings have important implications for clinical practice. While overall survival rates are promising, the significance of margin status cannot be overstated. Close monitoring and tailored interventions may be warranted for patients with involved margins to mitigate the risk of disease recurrence. Additionally, the association between smoking addiction and SCC underscores the importance of smoking cessation interventions in reducing disease burden.

Being conducted at a single institution limits the generalizability of findings, as patient demographics, treatment protocols, and outcomes may not be representative of broader populations. Retrospective studies are susceptible to inherent biases and limitations in data collection, potentially impacting the reliability and interpretation of results. Factors such as variations in surgical technique, adjunctive therapies, and patient characteristics are not fully accounted for in the analysis and could influence outcomes and conclusions drawn from the study. Overall, while highlighting the critical need for close monitoring of patients with involved margins, the study's findings should be considered within the context of its methodological constraints, particularly its single-centre, retrospective design.

## Conclusion

The main lessons learned from this study are that achieving clear surgical margins in early-stage oral tongue cancer significantly improves both overall survival and recurrence-free survival. Patients with close surgical margins had better survival outcomes compared to those with involved margins. The 5-year overall survival and recurrence-free survival probabilities were notably higher in the close margin group. The statistically significant differences in survival metrics underscore the importance of precise surgical techniques to ensure optimal patient outcomes.

Margin status significantly influences outcomes in early-stage oral tongue cancer, with involved margins correlating strongly with lower overall survival rates. Achieving clear margins through precise surgical techniques is crucial for improving patient prognosis and reducing the risk of disease recurrence. This study emphasizes the importance of closely monitoring high-risk patients with involved margins, highlighting the need for vigilant post-operative care and potentially adjuvant therapies. Utilization of robust outcome measures such as overall survival and recurrence-free survival provides meaningful insights into treatment efficacy and patient outcomes. By concentrating



on a specific cohort (early-stage oral tongue cancer patients with involved margins), the study provides targeted recommendations for clinical management.

### Author contributions

All authors contributed to the study's conception and design. Material preparation and data collection were performed by Muhammad Faisal and Raza Tasawar Hussain, and the data analysis and results write-up was done by Muhammad Awais Kanwal. The first draft of the manuscript was written by Hanif Ullah and Saqib Aziz, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Data availability** All data generated or analyzed during this study are included in the article.

**Conflict of interest** the authors declare no conflicts of interest.

### Ethics approval and consent to participate

Ethical approval was given by the Institutional Review Board, Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan.

**Consent for publication** All authors consent to the publication of this work

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