

# Sex Differences in Presentation, Management, and Prognosis of Surgically Treated Oral Tongue Carcinoma: A Retrospective Cohort Study

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**AIM:** Tongue carcinoma is an aggressive subtype of oral cavity cancer. Sex-related differences in disease presentation and prognosis remain incompletely understood.

**METHODS:** This retrospective cohort study included patients with histologically confirmed oral tongue squamous cell carcinoma treated at Oncology Center Mansoura University (OCMU) in Egypt between 2007 and 2025. Baseline clinicopathological characteristics, recurrence, and overall survival were analyzed by sex. Survival was assessed using Kaplan–Meier analysis, log-rank testing, and Cox proportional hazards regression.

**RESULTS:** Of 151 patients identified, 41 were excluded because of missing or indeterminate vital status, leaving 110 patients in the final analytic cohort (52 males and 58 females). Males had a significantly higher smoking prevalence than females (13/49 [26.5%] vs 2/55 [3.6%];  $p = 0.001$ ), but age, body mass index (BMI), T stage, nodal status, depth of invasion, histologic grade, and other adverse pathological features were broadly similar between sexes. Overall survival did not differ significantly by sex (log-rank  $p = 0.785$ ). In univariate Cox analysis, advanced T stage, nodal positivity, and perineural invasion were associated with worse survival, but in a parsimonious multivariable model, only nodal positivity and advanced T stage remained significant.

**CONCLUSIONS:** In this Egyptian cohort of oral tongue squamous cell carcinoma (SCC) patients, sex differences in presentation and outcome were minimal. Smoking exposure was substantially higher in men, but sex itself was not associated with survival after adjustment. Tumor burden, particularly nodal involvement and advanced T stage, was the main determinant of prognosis.

**Keywords:** oral tongue squamous cell carcinoma; sex differences; overall survival; nodal metastasis; depth of invasion

## Introduction

Oral tongue squamous cell carcinoma (SCC) is among the most aggressive malignancies of the oral cavity, with prognosis that depends primarily on local tumor extent, depth of invasion, nodal metastasis, histologic features, and treatment factors. Because these tumor-related characteristics strongly determine outcome, identifying patient- and population-level factors that influence presentation and survival remains critical for risk stratification and treatment planning [1,2,3,4].

Sex has been examined as a potential modifier of head and neck cancer risk and outcome, but findings for oral tongue SCC are mixed. Several studies report that men more often present with classical behavioral risk factors, particularly tobacco and alcohol exposure, while women may de-

velop oral tongue cancer with fewer traditional carcinogenic habits. At the same time, once oral SCC has developed, many analyses find only limited or inconsistent sex differences in clinicopathological features and survival, with stage, nodal disease, and other tumor characteristics typically exerting the dominant prognostic effect [1,4].

The epidemiologic context matters for interpreting these patterns. In Egypt and across the broader Middle East and North Africa (MENA) region, tobacco use is markedly more common among men than women, creating a setting in which behavioral exposures and sex are less collinear than in other populations. This setting provides an opportunity to determine whether sex-related differences reported elsewhere persist in a population where female tobacco exposure is uncommon, and whether such differences influence recurrence or overall survival [5,6].

Accordingly, this study evaluates sex-related differences in presentation, treatment, recurrence, and overall survival among patients with oral tongue squamous cell carcinoma treated at a single tertiary oncology center in Egypt. We also sought to identify the clinicopathological factors most strongly associated with prognosis in this cohort.

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## Methods

### *Study Design, Setting, and Population*

This is a retrospective cohort study conducted at a single tertiary cancer center in Egypt: Oncology Center Mansoura University (OCMU). Data from all patients treated between 2007 and 2025 with histologically confirmed primary SCC of the oral mobile tongue were collected from our center's electronic database. The anatomical site was defined as the oral tongue/anterior two-thirds of the tongue, including lateral, ventral, dorsal, and tip lesions when documented as oral tongue primaries. Tumors arising from the base of tongue or other oropharyngeal subsites were not eligible for inclusion, as these tumors are managed through separate medical oncology/oropharyngeal pathways at our institution and were not part of this surgical oral cavity registry. Eligible patients were required to undergo definitive surgical management with curative intent at our unit. Exclusion criteria were base-of-tongue/oropharyngeal primary tumors, non-squamous histology, recurrent disease at presentation, non-surgical management, and previous surgery, radiotherapy, or chemotherapy for the same tumor. No patients in the screened cohort had recurrent disease at presentation or prior treatment for the same tumor. Patients with carcinoma *in situ* lesions were eligible if managed surgically and confirmed histopathologically as oral tongue squamous cell carcinoma (OTSCC) *in situ* according to American Joint Committee on Cancer (AJCC) staging criteria [7].

Ethical approval from the Mansoura Faculty of Medicine institutional review board (MFM-IRB) was obtained under the code R.26.04.3678. Informed consent for participation is not required due to the retrospective design of the study.

### *Outcomes*

The primary outcome is overall survival (OS). The secondary outcome is recurrence, which was analyzed as a binary variable (any recurrence [local, nodal, distant] vs none).

### *Follow-up*

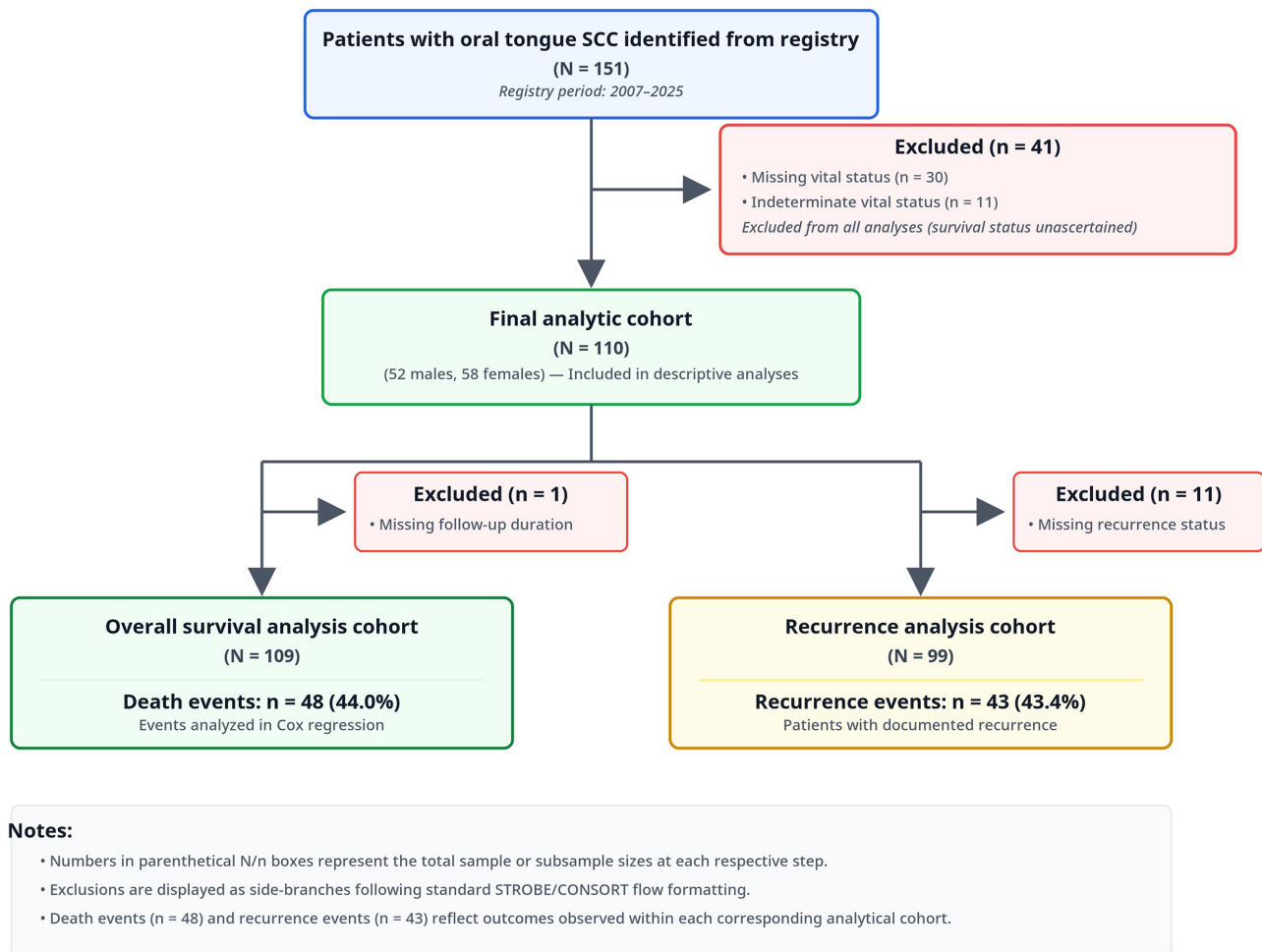
The diagnosis date was defined as the date of first histopathologic confirmation of oral tongue squamous cell carcinoma. The initial treatment date was defined as the date of definitive primary surgery.

Follow-up duration (months) was calculated from the diagnosis date to the date of last follow-up or death. Because enrollment spanned 2007–2025, follow-up duration varied substantially across patients, with more recently treated patients contributing shorter observation time. Survival analyses used time-to-event methods to account for censoring; however, recurrence was analyzed descriptively as a binary endpoint because recurrence-event dates were incomplete for a subset of patients.

### *Statistical Analysis*

Continuous variables (e.g., age, body mass index [BMI], depth of invasion [DOI], follow-up time) were assessed for distribution using visual inspection of histograms and quantile-quantile (Q–Q) plots and the Shapiro–Wilk test, and summarized as mean  $\pm$  standard deviation (SD) or median with interquartile range (IQR), according to distribution. Categorical variables (e.g., smoking, American Society of Anesthesiologists (ASA) score, T and N stage, grade, perineural invasion (PNI)/vascular/lymphatic invasion) were summarized as counts and percentages and compared using the Chi-square test or Fisher's exact test when expected cell counts were small. Because this was a retrospective registry study, missing data varied by variable; therefore, analyses were performed using available cases for each endpoint, and denominators are reported in the tables and figure legends.

OS was estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Exploratory univariate and multivariable survival analyses were performed using Cox proportional hazards regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was assessed using Schoenfeld residuals and visual inspection of log-minus-log survival plots. Age was dichotomized at the cohort median ( $\geq 56$  vs  $< 56$  years) to provide a clinically interpretable comparison with balanced group sizes. DOI was dichotomized at  $> 10$  mm versus  $\leq 10$  mm because this threshold reflects advanced local invasive burden and is aligned with clinically meaningful AJCC staging concepts. T stage was dichotomized as T3–4 versus T1–2/Tis and nodal status as N+ versus N0, to preserve model stability given the limited number of death events. Because of limited event count, a restrained multivariable model was prespecified using clinically relevant covariates with strongest univariate or established prognostic relevance to reduce overfitting. DOI was not included together with T stage because of conceptual overlap between DOI and AJCC T classification. Variables considered in survival modeling included sex, age, smoking, T stage, N stage, DOI, PNI, and grade. Smoking status and tumor grade were evaluated in univariate Cox analysis but were not retained in the final multivariable model. Smoking was excluded because only 15 patients were documented as active/former smokers, including only 2 females, producing an unstable estimate and increasing the risk of sparse-data bias. Tumor grade was not retained because the poorly differentiated subgroup was small and showed only borderline univariate association with overall survival. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant.



**Fig. 1. Study flow diagram.** SCC, squamous cell carcinoma.

## Results

### Cohort Derivation and Patient Characteristics

Of 151 patients with oral tongue SCC in the registry, 41 were excluded due to missing or indeterminate vital status, leaving 110 patients in the final analytic cohort (52 males [47.3%], 58 females [52.7%]) Fig. 1.

The median age at diagnosis was 56 years (range 18–94), with similar distributions between males and females. Median follow-up among patients with available follow-up duration was 29.0 months (IQR 14.0–49.0), and among survivors it was 35.0 months (IQR 15.0–55.0). Given the long enrollment period, follow-up duration was variable, and patients treated closer to the end of the study period contributed to shorter follow-up time. Overall, 49 of 110 patients (44.5%) died during follow-up (25/52 males [48.1%] and 24/58 females [41.4%]). One deceased patient lacked follow-up duration data and was therefore excluded from time-to-event survival analyses, leaving 109 patients and 48 death events for time-to-event survival analysis. Excluded patients may have differed systematically from included patients. Among 99 patients with documented recurrence status, 43 experienced recurrence (43.4%), with rates of 50.0%

in males (23/46) and 37.7% in females (20/53). Baseline demographic and clinicopathological characteristics by sex are summarized in Table 1 and Fig. 2.

Age at diagnosis did not differ significantly between sexes (median 55.5 years in males vs 56.5 years in females,  $p = 0.993$ ). BMI showed no significant difference between males and females (median 29.8 vs 30.4 kg/m<sup>2</sup>,  $p = 0.231$ ). Smoking was significantly more frequent in males (13/49; 26.5%) than in females (2/55; 3.6%,  $p = 0.001$ ). ASA distribution was similar between sexes, with most patients classified as ASA II in both groups (55.8% of males vs 60.8% of females,  $p = 0.366$ ).

T stage distribution was comparable between males and females, with no statistically significant difference ( $p = 0.076$ ). Among males, 34.7% had T1 and 41.3% had T2 disease, compared to 37% and 33.3%, respectively, in females. Advanced T3–T4 tumors were seen in 21.7% of males and 24.1% of females. Nodal status was also similar: pathologic N+ disease was present in 48.9% of males and 40.0% of females ( $p = 0.480$ ). Overall clinical stage (0–IV) did not differ significantly by sex ( $p = 0.381$ ), with early stages (0–II) and advanced stages (III–IV) broadly balanced between the groups. DOI tended to be slightly higher in males

**Table 1. Baseline demographic and clinicopathological characteristics.**

| Variable                                           | Male (n = 52)    | Female (n = 58)  | p-value |
|----------------------------------------------------|------------------|------------------|---------|
| Age at diagnosis (years), median (IQR)             | 55.5 (43.5–64.2) | 56.5 (44.2–62.8) | 0.993   |
| Body mass index (kg/m <sup>2</sup> ), median (IQR) | 29.8 (26.8–31.5) | 30.4 (26.3–38.5) | 0.231   |
| Depth of invasion (mm), median (IQR)               | 7.0 (4.0–10.0)   | 5.0 (3.0–9.0)    | 0.303   |
| Follow-up duration (months), median (IQR)          | 31.0 (14.0–45.3) | 27.0 (15.0–49.0) | 0.702   |
| Smoking status (N = 104)                           |                  |                  | 0.001   |
| Non-smoker                                         | 36 (73.5%)       | 53 (96.4%)       |         |
| Active/Ex-smoker                                   | 13 (26.5%)       | 2 (3.6%)         |         |
| ASA score (N = 94)                                 |                  |                  | 0.366   |
| I                                                  | 14 (32.6%)       | 18 (35.3%)       |         |
| II                                                 | 24 (55.8%)       | 31 (60.8%)       |         |
| III                                                | 5 (11.6%)        | 2 (3.9%)         |         |
| Biopsy grade                                       |                  |                  | 0.279   |
| Well differentiated                                | 18 (35.3%)       | 15 (27.3%)       |         |
| Moderately differentiated                          | 26 (51.0%)       | 36 (65.5%)       |         |
| Poorly differentiated                              | 7 (13.7%)        | 4 (7.3%)         |         |
| Pathology grade                                    |                  |                  | 0.219   |
| Well differentiated                                | 22 (43.1%)       | 16 (27.6%)       |         |
| Moderately differentiated                          | 27 (52.9%)       | 38 (65.5%)       |         |
| Poorly differentiated                              | 2 (3.9%)         | 4 (6.9%)         |         |
| T stage (N = 100)                                  |                  |                  | 0.076   |
| T1                                                 | 16 (34.7%)       | 20 (37%)         |         |
| T2                                                 | 19 (41.3%)       | 18 (33.3%)       |         |
| T3                                                 | 4 (8.7%)         | 12 (22.2%)       |         |
| T4                                                 | 6 (13%)          | 1 (1.9%)         |         |
| Tis                                                | 1 (2.2%)         | 3 (5.6%)         |         |
| N stage                                            |                  |                  | 0.480   |
| N0                                                 | 24 (51.1%)       | 33 (60.0%)       |         |
| N+                                                 | 23 (48.9%)       | 22 (40.0%)       |         |
| Overall stage                                      |                  |                  | 0.381   |
| Stage 0                                            | 1 (2.2%)         | 3 (5.5%)         |         |
| Stage 1                                            | 11 (24.4%)       | 18 (32.7%)       |         |
| Stage 2                                            | 13 (28.9%)       | 10 (18.2%)       |         |
| Stage 3                                            | 8 (17.8%)        | 15 (27.3%)       |         |
| Stage 4                                            | 12 (26.7%)       | 9 (16.4%)        |         |
| Perineural invasion                                | 8 (18.6%)        | 12 (22.6%)       | 0.817   |
| Vascular invasion                                  | 8 (18.6%)        | 12 (22.6%)       | 0.817   |
| Lymphatic invasion                                 | 13 (30.2%)       | 13 (24.5%)       | 0.693   |
| Midline crossing                                   | 3/45 (6.7%)      | 9/48 (18.8%)     | 0.122   |
| Floor of mouth infiltration                        | 7/40 (17.5%)     | 14/46 (30.4%)    | 0.254   |
| Extrinsic muscle infiltration                      | 15/42 (35.7%)    | 15/45 (33.3%)    | 0.994   |
| Suspicious lymph nodes (imaging)                   | 30/46 (65.2%)    | 35/53 (66.0%)    | 1.000   |
| Bony infiltration                                  | 3/45 (6.7%)      | 0/50 (0.0%)      | 0.103   |
| Operation type                                     |                  |                  | 0.824   |
| WLE                                                | 25 (50.0%)       | 27 (49.1%)       |         |
| Partial glossectomy                                | 7 (14.0%)        | 8 (14.5%)        |         |
| Hemiglossectomy                                    | 17 (34.0%)       | 17 (30.9%)       |         |
| Subtotal glossectomy                               | 1 (2.0%)         | 3 (5.5%)         |         |

Table 1. Continued.

| Variable              | Male (n = 52) | Female (n = 58) | p-value |
|-----------------------|---------------|-----------------|---------|
| Compartmental surgery | 15/42 (35.7%) | 11/44 (25.0%)   | 0.397   |
| Adjuvant chemotherapy | 21/40 (52.5%) | 19/46 (41.3%)   | 0.411   |
| Adjuvant radiotherapy | 20/40 (50.0%) | 24/47 (51.1%)   | 1.000   |

IQR, interquartile range; ASA, American Society of Anesthesiologists; Tis, Tumor *in situ*; WLE, Wide Local Excision.

Percentages were calculated using available cases. Continuous variables were compared using the independent-samples *t*-test or Mann–Whitney U test according to distribution. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

Tis denotes carcinoma *in situ* of the oral tongue according to the American Joint Committee on Cancer (AJCC) 8th edition staging system. Tis cases were included because these lesions were surgically treated and histopathologically confirmed within the oral tongue SCC registry.

T-stage data were unavailable for 10 patients (6 males and 4 females); therefore, percentages were calculated using available cases.

Denominators vary across variables because of missing data. Missing observations included smoking status (3 males and 3 females), ASA score (9 males and 7 females), T stage (6 males and 4 females), and other variables as indicated by the reported denominators.

Denominators vary because of missing data. Missing observations were as follows: smoking status N = 6, ASA score N = 16, T stage N = 10, Midline crossing N = 17, Mouth floor infiltration N = 24, Extrinsic muscles infiltration N = 23, Radiologically suspicious L.Ns N = 11, Bony infiltration N = 15, Compartmental surgery N = 24, Adjuvant chemotherapy N = 24. Adjuvant radiotherapy N = 23.

(median 7.0 mm, IQR 4.0–10.0) than in females (5.0 mm, IQR 3.0–9.0), but this was not statistically significant ( $p = 0.303$ ).

Pathologic grade distributions were similar, with well- or moderately differentiated tumors predominating in both sexes (well: 43.1% males vs 27.6% females; moderately differentiated: 52.9% vs 65.5%;  $p = 0.219$ ). Rates of PNI, vascular invasion, and lymphatic invasion showed no significant sex differences (PNI: 18.6% males vs 22.6% females,  $p = 0.817$ ; lymphatic invasion: 30.2% vs 24.5%,  $p = 0.693$ ). Radiologic markers of aggressiveness (midline crossing, floor infiltration, extrinsic muscle involvement, suspicious lymph nodes, and bony infiltration) were also broadly similar between males and females.

#### Treatment Characteristics

Surgical management patterns were comparable between the two groups. Wide Local Excision (WLE) was performed in approximately half of both males and females (50.0% vs 49.1%), while hemiglossectomy was used in about one-third (34.0% vs 30.9%). The proportion undergoing compartmental surgery among those with documented data was 35.7% in males and 25.0% in females ( $p = 0.397$ ).

Use of adjuvant therapy did not differ significantly by sex: adjuvant chemotherapy was given to 52.5% of males and

41.3% of females ( $p = 0.411$ ), and adjuvant radiotherapy to 50.0% and 51.1%, respectively ( $p = 1.000$ ) (Table 1).

#### Overall Survival by Sex

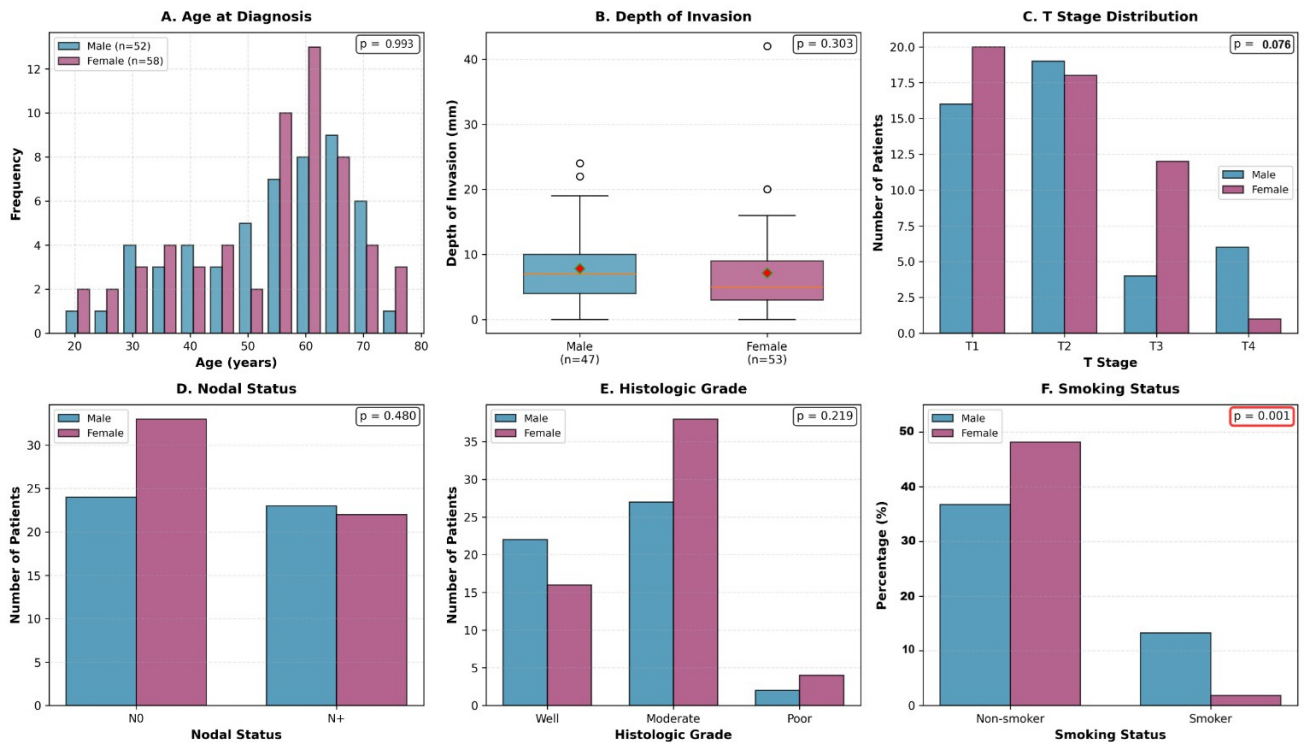
Kaplan–Meier curves showed no significant difference in OS between males and females (log-rank  $p = 0.785$ ; Fig. 3). One-year OS was 91.7% in males and 90.8% in females; two-year OS was 73.8% vs 78.1%, and three-year OS was 63.7% vs 64.3%, respectively. Median OS for the entire cohort was 51.0 months, with 43.0 months in males and 59.0 months in females.

In univariate Cox regression, female sex was not associated with worse survival compared with male sex (HR 0.92, 95% CI 0.52–1.64;  $p = 0.787$ ; Table 2). In a parsimonious multivariable Cox model including sex, age, T stage, nodal status, and PNI, female sex remained non-significant (adjusted hazard ratio [aHR] 1.26, 95% CI 0.68–2.36;  $p = 0.465$ ; Table 3).

#### Prognostic Factors

Exploratory univariate Cox analyses identified several clinicopathological factors associated with OS (Table 2). Advanced T stage (T3–4 vs T1–2/Tis) was associated with worse survival (HR 2.87, 95% CI 1.54–5.33;  $p < 0.001$ ), and nodal involvement (N+ vs N0) also predicted poorer OS (HR 3.00, 95% CI 1.65–5.46;  $p < 0.001$ ). Presence of PNI

### Presentation Characteristics by Sex Oral Tongue Squamous Cell Carcinoma



**Fig. 2. Presentation characteristics by sex in surgically treated oral tongue squamous cell carcinoma.** Selected demographic and clinicopathological variables are shown by sex, including (A) age at diagnosis, (B) depth of invasion, (C) T-stage distribution, (D) nodal status, (E) histologic grade, and (F) smoking status. Only smoking status differed significantly between cohorts ( $p = 0.001$ ).  $p$ -values compare males and females using the appropriate test according to variable type and distribution. Denominators vary because of missing data. Complete numerical values, denominators, and missing-data details are provided in Table 1.

**Table 2. Univariate Cox regression.**

| Variable                         | HR   | 95% CI     | $p$ -value |
|----------------------------------|------|------------|------------|
| Sex (Female vs Male)             | 0.92 | 0.52–1.64  | 0.787      |
| Age ( $\geq 56$ vs $< 56$ years) | 0.86 | 0.48–1.53  | 0.601      |
| Smoking (Yes vs No)              | 0.15 | 0.04–0.63  | 0.01       |
| T stage (T3–4 vs T1–2/Tis)       | 2.87 | 1.54–5.33  | $< 0.001$  |
| N stage (N+ vs N0)               | 3.00 | 1.65–5.46  | $< 0.001$  |
| DOI ( $> 10$ mm vs $\leq 10$ mm) | 1.83 | 0.90–3.70  | 0.095      |
| Perineural invasion (Yes vs No)  | 2.33 | 1.13–4.82  | 0.022      |
| Grade (Poorly vs Well/Moderate)  | 3.14 | 0.96–10.32 | 0.059      |

HR, hazard ratios; CI, confidence interval; DOI, depth of invasion.

The apparent inverse association between smoking and mortality is based on a very small smoker subgroup (15 patients, including only 2 females). It should not be interpreted as evidence of a protective effect. The number of patients included in each Cox regression model varied according to the availability of covariate data.

was associated with worse survival (HR 2.33, 95% CI 1.13–4.82;  $p = 0.022$ ), while poor grade showed a borderline association with worse outcome (HR 3.14, 95% CI 0.96–10.32;  $p = 0.059$ ). DOI  $> 10$  mm showed a non-significant trend toward worse survival (HR 1.83, 95% CI 0.90–3.70;

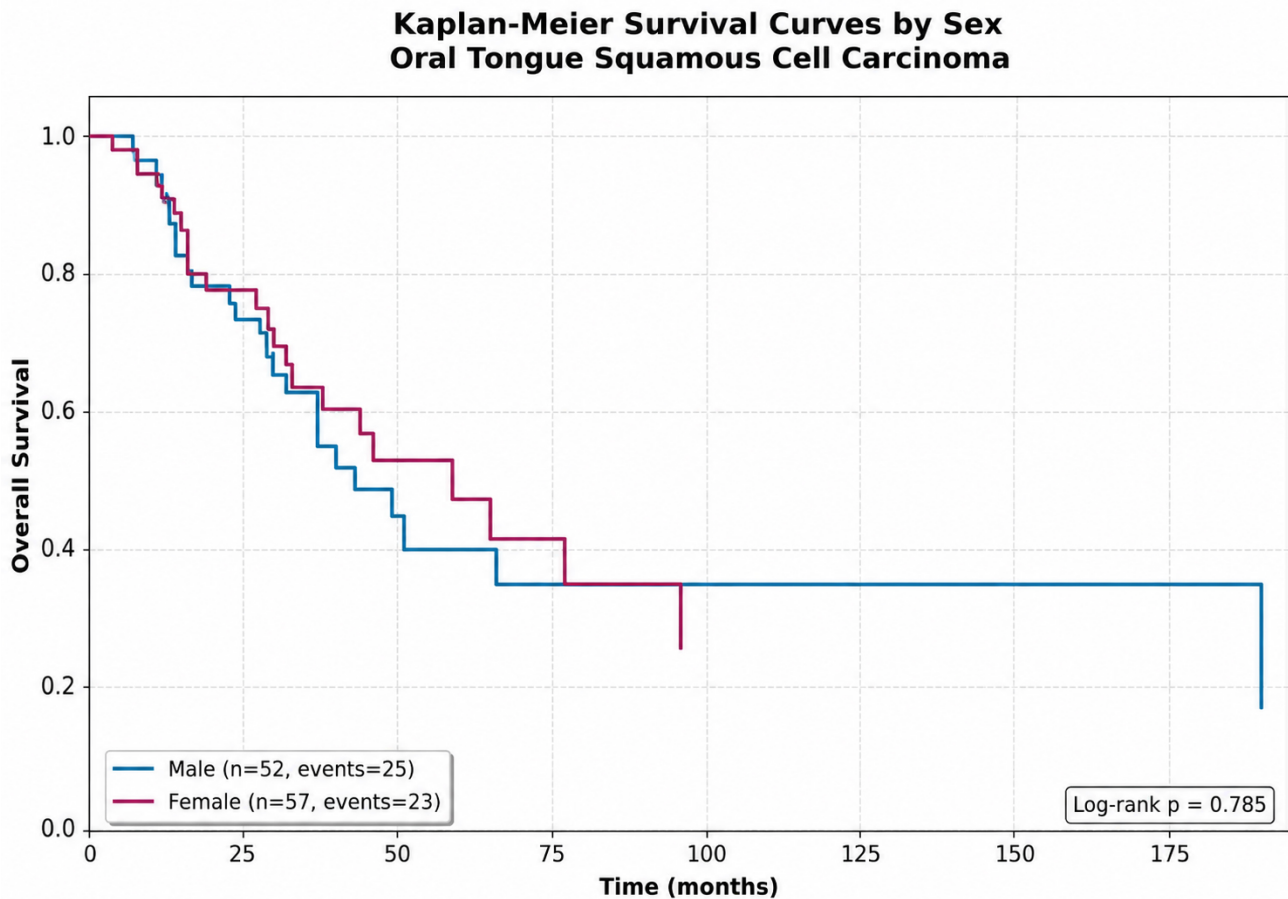
**Table 3. Multivariable Cox regression.**

| Variable                         | aHR  | 95% CI    | $p$ -value |
|----------------------------------|------|-----------|------------|
| Sex (Female vs Male)             | 1.26 | 0.68–2.36 | 0.465      |
| Age ( $\geq 56$ vs $< 56$ years) | 0.87 | 0.48–1.57 | 0.638      |
| T stage (T3–4 vs T1–2/Tis)       | 2.24 | 1.13–4.44 | 0.02       |
| N stage (N+ vs N0)               | 2.76 | 1.43–5.34 | 0.003      |
| Perineural invasion (Yes vs No)  | 1.24 | 0.55–2.79 | 0.61       |

aHR, adjusted hazard ratio. The number of patients included in each Cox regression model varied according to the availability of covariate data.

$p = 0.095$ ). Age was not significantly associated with OS ( $p = 0.601$ ). Smoking showed an apparent inverse association with mortality (HR 0.15, 95% CI 0.04–0.63;  $p = 0.01$ ), but this finding should not be interpreted as causal or protective. Only 15 patients with documented smoking status were active or former smokers, including only 2 female smokers, making this estimate frankly unstable and vulnerable to sparse-data bias, confounding, and imbalance in baseline clinicopathological features.

In the multivariable Cox model, both advanced T stage and nodal positivity remained independently associated with



**Fig. 3. Overall survival by sex.** Kaplan–Meier curves comparing overall survival between males and females with oral tongue squamous cell carcinoma. Survival analysis included patients with no missing follow-up duration; one deceased female patient was excluded from time-to-event analysis because follow-up time was unavailable. The log-rank test showed no significant difference in overall survival between sexes.

worse survival. Advanced T stage was associated with more than a twofold higher hazard of death (adjusted hazard ratio [aHR] 2.24, 95% CI 1.13–4.44;  $p = 0.02$ ), while nodal positivity showed the strongest independent association with survival (aHR 2.76, 95% CI 1.43–5.34;  $p = 0.003$ ). Sex, age, and PNI were not independently significant after adjustment (Table 3).

Taken together, these results indicate that while classical tumor factors, especially nodal status, influence prognosis, sex itself does not appear to be an independent determinant of presentation or overall survival in this cohort.

#### Recurrence

Overall, 43.4% of evaluable patients (43/99) developed recurrence, with a non-significant trend toward higher recurrence in males (50.0%) than females (37.7%;  $p = 0.306$ ; Table 4). Because recurrence was analyzed as a binary outcome and follow-up was shorter for recently treated patients, recurrence rates should be interpreted as descriptive and may underestimate late recurrence.

**Table 4. Oncologic outcomes and overall survival stratified by sex.**

| Characteristic                | Overall    | Male       | Female     |
|-------------------------------|------------|------------|------------|
| Total patients                | 110        | 52         | 58         |
| Deaths                        | 49 (44.5%) | 25 (48.1%) | 24 (41.4%) |
| Patients with recurrence data | 99         | 46         | 53         |
| Recurrence                    | 43 (43.4%) | 23 (50.0%) | 20 (37.7%) |
| 1-year OS                     | 0.912      | 0.917      | 0.908      |
| 2-year OS                     | 0.758      | 0.738      | 0.781      |
| 3-year OS                     | 0.639      | 0.637      | 0.643      |
| Median OS (months)            | 51         | 43         | 59         |

OS, overall survival.

#### Discussion

This retrospective cohort study of 110 patients with histologically confirmed SCC of the oral tongue found no meaningful sex-related differences in the measured presentation variables, including T stage, N stage, histologic grade, depth of invasion, or other pathological markers of aggressiveness. Smoking was more frequent in males than

females, but overall survival was similar between the two groups. In a restrained multivariable Cox model, sex was not associated with overall survival, whereas nodal positivity and advanced T stage remained the main adverse prognostic factors.

#### *Sex and Smoking at Presentation*

The most striking sex difference in our cohort was a significantly higher rate of smoking in males (13/49 [26.5%] vs 2/55 [3.6%];  $p = 0.001$ ). This is well-corroborated in the literature: sex is consistently linked to differential exposure to behavioral risk factors in oral SCC, with males disproportionately represented among tobacco and alcohol users across most studied populations. Saba et al. [6], in a large Surveillance, Epidemiology, and End Results (SEER)-based analysis, identified male sex as strongly associated with greater tobacco exposure and with a higher incidence of oral tongue SCC overall. Similarly, Wolfer et al. [4] demonstrated that men with oral SCC were significantly more likely to engage in smoking and alcohol use, while a substantial proportion of female patients developed oral tongue cancer in the absence of classical risk behaviors. This observation that females appear to develop oral tongue SCC without the traditional tobacco or alcohol exposure has been a recurring theme in the literature and suggests the possible contribution of alternative etiological mechanisms in women, including immune dysregulation, estrogen-related pathways, and possibly human papillomavirus (HPV), though the latter is more strongly associated with oropharyngeal than oral tongue carcinoma [8]. However, these hypotheses could not be evaluated in the present cohort because HPV status, molecular profiling, hormonal markers, and detailed alcohol exposure data were unavailable.

In our Egyptian cohort, the very low prevalence of smoking among female patients (3.6%) reflects the well-known sociocultural pattern of tobacco use in Egypt and the broader MENA region, where smoking among women remains substantially less prevalent than among men. This underscores an important difference between our cohort and Western or Asian cohorts, where female smoking rates are considerably higher, and where the sex gap in smoking-related head and neck cancer is narrowing [4,6,8].

#### *Sex Differences in Tumor Presentation and Staging*

Despite the marked difference in smoking exposure, tumor presentation characteristics were broadly similar in the two groups. Age at diagnosis ( $p = 0.993$ ), BMI ( $p = 0.231$ ), T stage distribution ( $p = 0.076$ ), nodal involvement (N+: 48.9% males vs. 40.0% females;  $p = 0.480$ ), DOI (median 7.0 vs. 5.0 mm;  $p = 0.303$ ), histologic grade ( $p = 0.219$ ), and rates of PNI, vascular invasion, and lymphatic invasion were all comparable between sexes.

These findings are consistent with the literature. Lin et al. [8], in a case-matched analysis of 122 female and 2451 male Oral Squamous Cell Carcinoma (OSCC) patients in Taiwan, found no significant sex differences in clinical characteristics, except for older age of diagnosis, or pathological characteristics other than anatomical tumor site and carcinogenic habits; they concluded that once patients develop Oral Squamous Cell Carcinoma (OSCC), survival conditions are similar regardless of sex. Ko et al. [3], in a 2025 Taiwanese cohort study, similarly found no significant sex differences in OS after multivariate adjustment, while noting that females more frequently presented with tongue cancer and males with buccal mucosa cancer.

A notable trend in our data was a higher proportion of T3 tumors in females (22.2%) compared to males (8.7%), against more T4 disease in males (13.0% vs. 1.9%), although this did not reach statistical significance ( $p = 0.076$ ). Whether this pattern reflects genuinely different pathways of tumor progression by sex warrants evaluation in larger series. Comparable radiologic findings across sexes, including rates of midline crossing, floor infiltration, extrinsic muscle involvement, suspicious lymph nodes, and bony infiltration, further support an absence of systematic sex-driven anatomic aggressiveness at presentation in this population.

#### *Sex and Overall Survival*

Our Kaplan–Meier analysis demonstrated no significant OS difference between males and females (log-rank  $p = 0.785$ ), with 1-, 2-, and 3-year OS rates of 91.7% vs. 90.8%, 73.8% vs. 78.1%, and 63.7% vs. 64.3%, respectively. This aligns with multiple prior studies. Lin et al. [8] concluded that there is no difference in survival between men and women with OSCC once the cancer has developed. Ko et al. [3] confirmed no significant difference in OS by sex in their multivariate model. In a study specifically examining sex differences in prognostic factors for OSCC, no differences in overall survival between males and females were found, with regional metastasis identified as a negative prognostic factor for both sexes equally [9].

Gayà et al. [10], however, in a large retrospective study of 857 oral cavity SCC patients, reported a significantly worse 5-year cancer-specific survival (CSS) in women (52.3%) vs. men (67.0%;  $p < 0.001$ ), with female sex remaining an independent predictor of worse CSS on multivariable analysis (HR 1.55, 95% CI: 1.14–2.10;  $p = 0.005$ ), even though 5-year OS did not differ significantly between sexes (53.4% vs. 45.8%;  $p = 0.238$ ). The authors attributed this discrepancy to underlying biological or hormonal differences influencing cancer behavior in women who had less tobacco and alcohol exposure. In our cohort, a non-significant trend toward longer median OS in females (59 vs. 43 months) and lower recurrence rates (37.7% vs. 50.0%;  $p = 0.306$ ) may reflect the relatively less advanced T4 presentation and near-absence of tobacco exposure in female patients. A

cause-of-death analysis in a larger powered study would be needed to examine this further. These hypotheses could not be evaluated in the present cohort.

#### *Depth of Invasion as a Prognostic Factor*

DOI >10 mm showed a non-significant trend toward worse OS in our cohort (HR 1.83, 95% CI: 0.90–3.70;  $p = 0.095$ ), likely reflecting limited statistical power rather than a true absence of effect. Koh et al. [11], in a Cox regression analysis of early-stage oral cavity SCC patients treated with surgery alone, confirmed DOI as an independent predictor of both recurrence (HR 1.16, 95% CI: 1.01–1.32;  $p = 0.034$ ) and death (HR 1.42, 95% CI: 1.11–1.83;  $p = 0.006$ ). Alman-gush et al. [12], in a study of 233 T1/T2 N0M0 oral tongue SCC patients, demonstrated that DOI  $\geq 4$  mm was independently associated with poor prognosis after multivariate analysis (HR 2.55, 95% CI: 1.25–5.20), alongside tumor budding. The incorporation of DOI into the 8th edition AJCC TNM classification as a T-stage modifier formalizes its biological significance as a surrogate of invasive depth and lymphovascular potential [7]. These data collectively support the routine use of DOI in clinical decision-making for elective neck dissection, and its inclusion in future multivariable models of this cohort is strongly recommended.

#### *Perineural Invasion*

PNI was a significant predictor of worse OS in our univariate analysis (HR 2.33;  $p = 0.022$ ). Li et al. [13], in a systematic review and meta-analysis specifically focused on OTSCC, demonstrated that PNI significantly worsens locoregional recurrence and survival: PNI had an impact on OS, disease-free survival, and CSS in both all-stage and early-stage OTSCC, with sensitivity analyses confirming robust and consistent results. A separate meta-analysis of 56 studies on PNI in oral cancer reported an incidence of 28% (95% CI: 24–31%), a 5-year survival relative risk of 0.67 (95% CI: 0.59–0.75) in PNI-positive patients, and a locoregional recurrence relative risk of 2.09 (95% CI: 1.86–2.35) [14]. These data, consistent with our findings, underscore PNI as a high-risk histopathological feature that should routinely inform adjuvant therapy planning regardless of sex.

#### *T Stage and Nodal Status as Dominant Prognostic Factors*

Advanced T stage (T3–4 vs. T1–2: HR 2.87;  $p < 0.001$ ) and nodal involvement (N+ vs. N0: HR 3.00;  $p < 0.001$ ) were unsurprisingly the strongest prognostic predictors in our univariate analysis. This is well-supported in the literature. Saba et al. [6] identified stage as a critical determinant of survival across all sex and ethnic groups in oral tongue SCC. Gayà et al. [10] confirmed that advanced stage (stage IV vs. I: HR 8.93, 95% CI: 6.04–13.20) and tongue tumor location (HR 3.10, 95% CI: 1.43–6.70) were among the strongest independent predictors of CSS. The convergence of our results with this body of evidence reinforces

that TNM staging retains paramount importance in prognosis, irrespective of patient sex.

#### *Multivariable Prognostic Analysis*

In the restrained multivariable Cox model, sex was not independently associated with overall survival after adjustment for age, T stage, nodal status, and PNI. By contrast, nodal positivity remained the strongest independent prognostic factor, and advanced T stage also retained prognostic significance. This pattern suggests that the apparent sex-related differences in crude outcomes are better explained by tumor burden and nodal disease than by sex itself. The loss of statistical significance for PNI after adjustment likely reflects both sample size limitations and correlation with other adverse pathological features.

#### *The Smoking Paradox*

Our univariate analysis yielded an unexpected finding: smokers appeared to have a lower crude hazard of death (HR 0.15;  $p = 0.01$ ). This paradox must be interpreted with considerable caution. The total number of smokers in the cohort was small (15 patients, predominantly male), severely limiting the precision of the hazard estimate and creating conditions favorable for confounding. It is well-established in the literature that smoking at diagnosis is associated with significantly worse head and neck cancer outcomes: Sharp et al. [15], in a large population-based study from the National Cancer Registry Ireland including 5652 head and neck cancer patients, demonstrated that current smokers at diagnosis had a significantly raised cancer-specific death rate compared with never-smokers (multivariate HR 1.36, 95% CI: 1.21–1.53), with the effect even stronger in surgically treated patients (HR 1.49, 95% CI: 1.25–1.79). Conversely, smoking cessation after diagnosis significantly improves survival: a prospective cohort study of 835 newly diagnosed Head and Neck Squamous Cell Carcinoma (HNSCC) patients followed for 7 years found that patients who quit smoking after diagnosis had a 61% reduction in mortality risk compared to continuing smokers (HR 0.39, 95% CI: 0.22–0.69), with the greatest benefit in oral cavity cancer patients [16]. The apparent protective effect of smoking in our cohort most plausibly reflects residual confounding and the small smoker sample size; multivariable adjustment in a larger cohort is necessary before any interpretation of this finding is warranted.

#### *Strengths and Limitations*

This study presents a granular, single-center dataset from an Egyptian tertiary oncology center spanning nearly two decades (2007–2025), representing one of the few studies to examine sex differences in oral tongue SCC specifically within an Egyptian and MENA-region context. Comprehensive clinicopathological, treatment, and outcome variables were captured, enabling simultaneous assessment of presentation, treatment patterns, and prognosis.

Key limitations include the retrospective design with inherent risks of selection and information bias. The analytic cohort of 110 patients, while representative of institutional experience, limits statistical power for multivariable Cox modeling, particularly for detecting modest effect sizes. A significant proportion of cases (41/151; 27.2%) had indeterminate vital status and were excluded from survival analyses, introducing potential survivorship bias. Cause-specific mortality could not be reliably determined from the available registry data, precluding disease-specific survival analysis, an important limitation given the conflicting CSS vs. OS findings reported elsewhere. The long study period also resulted in heterogeneous follow-up duration. Patients treated in later years had less opportunity to experience death or recurrence events, which may reduce the precision of survival estimates at later time points and may lead to underestimation of recurrence when recurrence is analyzed as a binary endpoint. Accordingly, recurrence findings should be interpreted as exploratory. The small number of smokers among women precludes meaningful smoking-stratified survival analysis and limits generalizability to populations with higher female smoking prevalence. Finally, molecular markers and HPV status were unavailable, precluding evaluation of biological sex-specific pathways that may independently influence prognosis.

## Conclusions

In this Egyptian cohort of surgically treated oral tongue SCC, marked sex differences in smoking exposure did not translate into meaningful differences in tumor presentation, treatment patterns, recurrence, or overall survival. These findings suggest that once oral tongue SCC develops, prognosis was associated more strongly with tumor burden and disease extent, while no significant association between sex and overall survival was observed in this cohort. Clinically, management and risk stratification should remain focused on established prognostic factors, particularly T stage and nodal status, while larger multicenter studies are needed to determine whether sex-specific biological factors contribute to outcome in selected patient populations.

## Availability of Data and Materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

AMS, MELmo and AMF contributed to the study design and data collection. MA and SSE contributed to conception, design of the study and wrote the manuscript. AMS and MELme contributed to data analysis and prepared the tables and figures. AMS, MELme, MELmo and AMF contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the

final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

All procedures complied with the principles outlined in the Declaration of Helsinki. Ethical approval from the Mansoura Faculty of Medicine institutional review board (MFM-IRB) was obtained under the code R.26.04.3678. The requirement to obtain written informed consent was waived due to the retrospective nature of the chart review, absence of additional patient interventions, and full anonymization of all clinical and pathological identifiers to protect participant confidentiality.

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## Conflict of Interest

The authors declare no conflict of interest.

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