Ukrani *et al.*
The Egyptian Journal of Otolaryngology (2023) 39:70
https://doi.org/10.1186/s43163-023-00435-x

The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Survival of oral tongue cancer in low middle-income country: a cohort study

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Abstract

Introduction The incidence of oral tongue squamous cell carcinoma (OTSCC) is increasing. OTSCC is comparatively higher in our region owing to the consumption of tobacco, beetle nut, alcohol, and poor oral hygiene. There is paucity of survival data for OTSCC from our high-burden region.

Background There is paucity of survival data for OTSCC from our high-burden region, we aimed to determine 5-year overall and disease-free survival of patients with OTSCC.

Methods A retrospective chart review was conducted for all the patients treated for oral tongue squamous cell carcinoma from January 2000 and December 2013. The data on overall survival and disease-free survival was collected via telephonic interviews up till 2018. Kaplan Meier curves were plotted to graphically represent survival.

Results A total of 131 patients were included. The mean age of the patients was 49.4 ± 12.98 years, with most patients being male (65.9%). The most common tumor stage was T2 (55.1%) and the most common nodal stage was N0 (57.7%). Five-year disease-free survival was 59.2%, and overall survival was 60.7%. Overall survival dropped steeply from 84.4 to 7.5% in patients who developed recurrence in our cohort.

Conclusion The most significant factor influencing the survival of patients with OTSCC is tumor recurrence. 5-year recurrence-free survival was 84.4% which is greater than reported in literature. This could be due to the low incidence of perineural and perivascular invasion in our population. Further research on factors leading to recurrence should be done.

Keywords Mouth neoplasms, Disease-free survival, Head and neck neoplasm, Tongue neoplasms

Background

Oral cavity cancer is the eleventh most common cancer worldwide and is the second most common cancer in Pakistan [1, 2]. The most frequently affected sub-site is the oral tongue [3]. More than 95% of oral tongue cancers are squamous cell carcinomas [3]. Oral tongue squamous cell carcinoma (OTSCC) is more common among males [2]. In recent years, the incidence of OTSCC has increased greatly, with significant geographic variations [3, 4]. The incidence of OTSCC is also rising among younger patients, i.e., fifth decade and lower [5]. In 2018, there were approximately 354,864 cases worldwide, with 18,881 in Pakistan alone [6, 7]. This high incidence of OTSCC is contributed to the consumption of tobacco, beetle nut,

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alcohol, and poor oral hygiene [1]. There is an ever-growing need for awareness of the risk factors and early symptoms of OTSCC among the high-risk groups [1].

Various operative and non-operative treatment modalities are available for OTSCC, the choice of treatment modality is based on prognostic factors such as the clinical and radiological staging which includes the presence or absence of ipsilateral and contralateral nodal metastases [4, 8]. The main stay of treatment for OTSCC is surgical resection of the tumor with wide margins with dissection of cervical lymph nodes which is followed by adjuvant radiotherapy and chemotherapy in case of high-risk features on histopathology [8–12]. Neck dissection is considered an integral part of the treatment plan as approximately 25% of the cases of OTSCC have occult neck nodal metastases [13]. Although surgery is known for its better survival outcome, it also has its own share of potential complications, which include wound infection, orocutaneous fistula formation, and flap necrosis [14, 15]. Late-stage OTSCC (Stage IVb) patients are offered non-curative, palliative treatment options which include radiotherapy and chemotherapy, these can prolong as well as improve quality of life [16, 17].

There is paucity of survival data for OTSCC from our region, the aim of our study was to determine the survival as well as associated factors for OTSCC patients presenting to our tertiary care center which caters to a high disease burden population.

Methods

A retrospective chart review was conducted at a tertiary care referral center on OTSCC patients. Data was collected after prior approval from Aga Khan University Hospital Institutional Ethical Review Committee (ERC Approval Number: 5150-CHS-ERC-17). Data was retrieved for patients operated on between January 2000 and December 2013 at an academic private tertiary care hospital. Survival was assessed till May 2018. The data on overall survival and disease-free survival was collected via telephonic interview.

All the patients with OTSCC treated in the designated time bracket were included. Patients with a history of initial treatment before January 2000 or those treated outside our center (to maintain homogeneity) were excluded. Patients who underwent palliative treatment or those with missing records were also excluded. Data was collected on demographics, disease-related variables, treatment, and survival of patients. Margins of primary tumor resection if more than 5 mm were reported as clear, ≤ 5 mm but >1 mm were reported as close, and ≤ 1 mm or with gross tumor present at margin bed was reported as involved.

Mean and standard deviation were reported for continuous normally distributed variables, and frequency and percentages were reported for categorical variables. Kaplan–Meier curve was plotted to graphically represent survival. Survival was reported months from the date of surgery. Analysis was performed on Stata version 12 (StataCorp LLC, College Station, TX, USA).

The work has been reported in line with the STROCSS criteria [18].

Results

A total of 131 patients fulfilling the eligibility criteria were included in our study. The mean age of the patients was 49.4 ± 12.98 years, with most patients being male (65.9%). The mean depth of tumor invasion was 0.97 ± 0.64 mm. While 52.7% of the patients had right-sided oral tongue cancer, 47.3% of the patients had left-sided oral tongue cancer. The most common ipsilateral neck dissection was modified radical neck dissection (69.2%), whereas the most common contralateral neck dissection was selective neck dissection (43.6%).

On histopathology, majority of the patients had moderately differentiated tumor (61.5%) and poorly differentiated tumor was the least common (3.8%). Moreover, on histopathology, most of the patients had clear surgical margins (58.3%) whereas 32.3% had close surgical margins and in only 9.4% of the cases, surgical margins were involved. On pathologic review, we found that peri-neural invasion (PNI) was present in 3 cases (2.3%) and peri-vascular invasion (PVI) was present in 5 cases (3.9%). Patients had T stage ranging from T1 to T4a with T2 (55.1%) being the most common and N stage ranging from N0 to N2c with N0 (57.7%) being the most common. Majority of the patients had stage II oral tongue cancer. The results for patient and tumor characteristics are further illustrated in Table 1.

Radiation was part of the treatment in 59.5% of the patients whereas chemotherapy was part of the treatment in 26% of the patients. Recurrence was seen in 42.7% of the patients. The mean disease-free survival was 45.6 ± 1.8 months, overall 5-year survival was 60.7% and time of mortality was 46.60 ± 19.81 months. The results for treatment and survival are shown in Table 2. When stratified on recurrence overall survival of 84.4% was seen in patients who did not develop recurrence at 5 years whereas, survival dropped exponentially (7.5%) in patients who did develop recurrence. Kaplan-Miere curve of disease-free survival (5 years) and overall survival (5 years) of oral tongue squamous cell carcinoma are shown in Figs. 1, 2, and 3.

Table 1 Patient and tumor characteristics of patients with tongue squamous cell carcinoma

Variable	Frequency (percentage) ($n=131$)
Age (years)[a]	49.41 ± 12.98
Gender	
Male	85 (65.9)
Female	44 (33.6)
Depth[a]	0.97 ± 0.64
Side	
Right	69 (52.7)
Left	62 (47.3)
Neck dissection	
Radical	18 (15.0)
Modified radical	83 (69.2)
Supraomohyoid	9 (7.5)
Selective	9 (7.5)
Functional	1 (0.8)
Contralateral neck dissection	
Radical	1 (1.8)
Modified radical	12 (21.8)
Supraomohyoid	18 (32.7)
Selective	24 (43.6)
Tumor grade	
Well differentiated	45 (34.6)
Moderately differentiated	80 (61.5)
Poorly differentiated	5 (3.8)
Surgical argins	
Clear	74 (58.3)
Close	41 (32.3)
Involved	12 (9.4)
Perineural invasion	
Yes	3 (2.3)
No	94 (72.3)
Not mentioned	33 (25.4)
Perivascular invasion	
Yes	5 (3.9)
No	119 (93.7)
Not mentioned	2 (1.6)
T stage	
T1	43 (33.9)
T2	70 (55.1)
T3	11 (8.7)
T4a	3 (2.4)
N stage	
Nx	0 (0.0)
N0	75 (57.7)
N1	20 (15.3)
N2a	1 (0.8)
N2b	26 (19.8)
N2c	8(6.2)
Stage	
I	34 (26.8)
II	38 (29.9)
III	21 (16.5)
IVa	34 (26.8)

[a] Mean and standard deviation

Table 2 Adjuvant treatment and survival of patients with tongue squamous cell carcinoma

Radiation	
Yes	78 (59.5)
No	53 (40.5)
Chemotherapy	
Yes	34 (26.0)
No	97 (74.0)
Recurrence	
Yes	56 (42.7)
No	75 (57.3)
Disease-free survival (months)*	45.6 ± 1.83
Overall survival (months)*	46.5 ± 1.73

[*] 5-year disease-free and overall survival

Discussion

OTSCC is a sinister disease and can result in a significant decline in the quality of life and survival of patients. The number of OTSCC cases are on the rise, especially in young adults. The goal of this retrospective analysis was to review the patients who were treated at a tertiary care referral center in a low middle-income country with a high disease burden. The primary focus was on the survival of patients as well as the treatment modalities used.

Most individuals in our study were males (65.9%), which is similar to other studies that have reported 63.2% and 65% male patients in the Indian and Australian populations, respectively [19, 20]. Smoking, alcohol, and betel nuts, risk factors for OTSCC, are generally more common among the male population, probably leading to the increased incidence of OTSCC in males [1]. The mean age of patients in our study was 49.4 ± 12.98 years, which is higher than reported in most studies, although

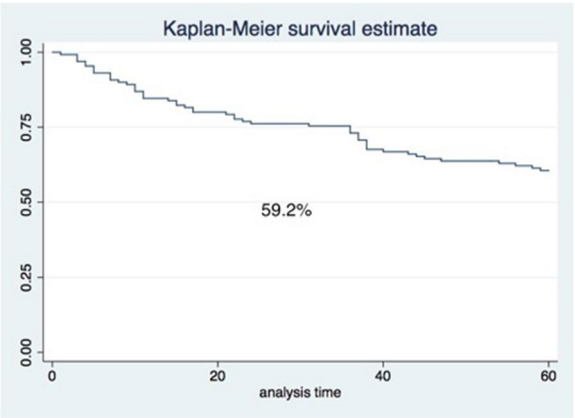

Fig. 1 Kaplan-Miere curve of disease-free survival (5 years) of oral tongue squamous cell carcinoma. Disease-free survival of 59.2% at 5 years

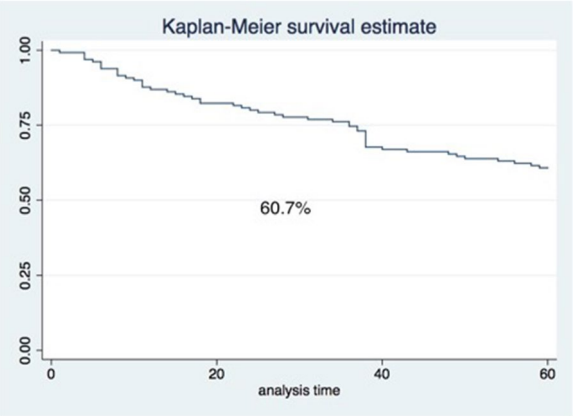

Fig. 2 Kaplan-Miere curve of overall survival (5 years) of oral tongue squamous cell carcinoma. Overall survival of 60.7% at 5 years

a study conducted at our center previously in 2007 by Akhtar et al. showed a mean age of 55 years [21]. One study conducted in India showed that OTSCC in older patients was associated to smoking, alcohol, or chewing tobacco whereas in younger patients it is not related to these addictions [2, 22]. In these younger patients, the increasing incidence might be due to viral etiology such as HPV [1]. Increasing age is associated with a worse disease-specific survival [15].

In our study, the most common histological grade was moderately differentiated carcinoma seen in 61.5% patients, similar to a previous study that reported moderately differentiated carcinoma in 68.9% [2]. Moderately differentiated tumors tend to have a poor prognosis as compared to well differentiated cancers [19].

The management of OTSCC is challenging as it depends on several disease-related and patient-related factors. In our study, every case was discussed in the

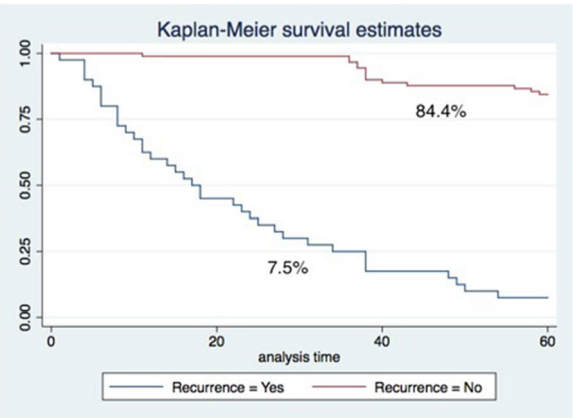

Fig. 3 Kaplan-Miere curve of overall survival (5 years) of oral tongue squamous cell carcinoma stratified on recurrence

head and neck MDT before the treatment was instituted. All resectable cases stage I to stage IVa were offered surgical resection (wide local excision) with or without neck dissection depending on the stage of disease. Majority of the patients had presented with early-stage OTSCC and underwent elective neck dissection. This was followed by adjuvant therapy in the form of radiotherapy + / − chemotherapy. Some physicians advocate that negative neck nodes, in the case of T1 and T2 stages, should be treated with elective neck dissection while others believe that the "wait and watch policy" is best suited [8, 9]. In recent years, however, elective neck dissection is considered as the optimal treatment, as there is always a risk for occult metastasis, which occurs in up to 30% of the cases [8, 9]. In comparison to radiological investigations, elective neck dissection is more accurate for the staging of the neck and can better guide the subsequent use of postoperative radiotherapy for a pathologically node-positive neck [21]. Elective neck dissection helps lower the risk of local and regional recurrences and increases the long-term survival rate [9]. In the experience of the authors of this article, performing an elective neck dissection only adds 45 to 60 min to the operative time and does not add significantly to the surgery-related morbidity. Therefore, we recommend elective neck dissection in every case of biopsy-proven OTSCC who is undergoing surgical resection.

Following surgery, the postoperative management consists of adjuvant radiotherapy or chemoradiotherapy depending on tumor grade, depth of invasion, size of the primary tumor, status of surgical margins, perineural, and lymphovascular invasion [4, 11]. The purpose of adjuvant therapy after surgery is to decrease the chance of loco-regional recurrence [17]. Concurrent chemotherapy and radiotherapy have been suggested for patients with positive resection margins, multiple metastatic lymph nodes, and lymph nodes with extracapsular growth [8, 9, 17, 23]. Although radiotherapy and chemotherapy are considered as options in the management of OTSCC (higher disease-free survival rate and improved locoregional control), they are not very effective and have various adverse effects [8, 9, 24]. Radiation can lead to complications such as poor wound healing, osteoradionecrosis of the mandible, xerostomia, etc. [8, 24].

In our study, the Kaplan Meier curve revealed an overall survival (OS) at 5 years to be 60.7%, which is nearly identical to the 5-year OS reported in a retrospective study by Miller et al., which looked at outcomes in oral tongue squamous cell carcinoma in young adults [25]. However, a study from Kerala (India), which is a high-burden region, observed better 5-year overall survival

[26]. This could be due to better public health awareness and access to the health care system [26]. Moreover, overall survival observed in our study was marginally less as compared to other studies. According to American Joint Committee on Cancer, tumor stage and depth of invasion are predictors of overall survival and hence the outcomes [10].

We also reported disease-free survival of 59.2%. Similarly, a study conducted by Manuel et al. reported disease-free survival of 57.4% [19]. Previously published literature suggests that several significant factors influence the survival rates such as tumor stage, pathological nodes, resection margins, sequence of treatment, and type of primary and neck surgery [19]. While the early stage OTSCC has a favorable prognosis with high cure rates, late-stage OTSCC is associated with poor OS and higher disease recurrence rates [16].

The 5-year recurrence-free survival (RFS) in our study was reported as 84.4%. In contrast, a study by Miller et al. reported 5-year recurrence-free survival as 62% [25]. Perineural invasion is associated with worse RFS, however, only 2.3% of patients in our study population had perineural invasion due to which we had a higher overall RFS [25]. Furthermore, tumors with perineural invasion have a poor prognosis, greater risk of recurrence, and shorter disease-specific survival [12].

The study had several limitations that should be acknowledged. Owing to the retrospective nature of the study design important prognostic factors such as depth of invasion which were previously not reported were not assessed. In our study, data regarding important socioeconomic factors was not available in medical records and hence could not be collected. The data was from a single private tertiary care referral center, which caters to the whole region and treats patients from all social backgrounds which increases the external generalizability of our study.

We feel that our study not only adds to the scarce amount of survival data on OTSCC available for this region, but also highlights the clinical characteristics of patients who consume smokeless tobacco.

Conclusion

The overall survival after treatment for OTSCC was 60.7% in our study which is comparable to what is reported in other parts of the world. The factor with the most negative influence on the survival of patients is tumor recurrence. The 5-year recurrence-free survival was 84.4% which is greater than what is reported, probably due to lower incidence of PNI positivity in our population. Multicenter studies with greater sample sizes are recommended so that stage-specific survival data can be better assessed.

Abbreviations

OTSCC	Oral tongue squamous cell carcinoma
PNI	Peri-neural invasion
PVI	Peri-vascular invasion
OS	Overall survival
RFS	Recurrence-free survival

Acknowledgements

Not applicable.

Authors' contributions

RDU, study design and concept, statistical analysis, manuscript writing; MHD, study design and concept, data collection, authoring and editing manuscript; MI, study design and concept, authoring and editing manuscript; KRN, study design and concept, authoring and editing manuscript; SS, data collection, authoring and editing manuscript; AYM, data collection, authoring and editing manuscript; SR, study design and concept, authoring and editing manuscript, statistical analysis; NZ, study design and concept, statistical analysis; HI, study design and concept, manuscript writing, statistical analysis. The final manuscript was revised and approved by all authors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

Data was collected after prior approval from Aga Khan University Hospital Institutional Ethical Review Committee (ERC Approval Number: 5150-CHS-ERC-17). The ERC exempted the consent from participants as data was collected retrospectively from charts, and human subjects were not directly involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no competing interests.

Received: 29 December 2022 Accepted: 31 March 2023
Published online: 21 April 2023

References

1. Ghantous Y, Abu El (2017) GLOBAL INCIDENCE AND RISK FACTORS OF ORAL CANCER. Harefuah 156(10):645–649
2. Adeel M, Suhail A (2016) Squamous cell carcinoma of oral tongue in young patients - A 10 years tertiary care experience. J Pak Med Assoc 66(2):155–158
3. Moore SR, Johnson NW, Pierce AM, Wilson DF (2000) The epidemiology of tongue cancer: a review of global incidence. Oral Dis 6(2):75–84
4. Omura K (2014) Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. Int J Clin Oncol 19(3):423–430
5. Vered M, Dayan D (2013) Tongue cancer: an ongoing problem which needs new therapeutic approaches. Harefuah 152(6):352–367
6. Globcan 2018. https://gco.iarc.fr/today/data/factsheets/populations/586-pakistan-fact-sheets.pdf (last assessed on 02-08-2020)
7. Globcan 2018. https://gco.iarc.fr/today/data/factsheets/cancers/1-Lip-oral-cavity-fact-sheet.pdf (last assessed on 02-08-2020)
8. H ain R, Jamshed A, Iqbal H, Usman S, Irfan M, Hafeez Bhatti AB. Long term survival and impact of various prognostic factors in T1, T2 oral

tongue cancer in Pakistan. JPMA The Journal of the Pakistan Medical Association. 2016;66(2):187–93.uss
9. Gad ZS, El-Malt OA, El-Sakkary MAT, Abdal Aziz MM (2018) Elective Neck Dissection for Management of Early- Stage Oral Tongue Cancer. Asian Pac J Cancer Prev 19(7):1797–1803
10. Mannelli G, Arcuri F, Agostini T, Innocenti M, Raffaini M, Spinelli G (2018) Classification of tongue cancer resection and treatment algorithm. J Surg Oncol 117(5):1092–1099
11. Rajappa SK, Ram D, Bhakuni YS, Jain A, Kumar R, Dewan AK (2018) Survival benefits of adjuvant radiation in the management of early tongue cancer with depth of invasion as the indication. Head Neck 40(10):2263–2270
12. Cracchiolo JR, Xu B, Migliacci JC, Katabi N, Pfister DG, Lee NY et al (2018) Patterns of recurrence in oral tongue cancer with perineural invasion. Head Neck 40(6):1287–1295
13. Makinen LK, Hagstrom J, Makitie A, Atula T (2016) Cancer of the tongue - early detection improves the prognosis. Duodecim 132(22):2063–2070
14. Sharma RG, Bang B, Verma H, Mehta JM (2012) Profile of oral squamous cell cancer in a tertiary level medical college hospital: a 10 yr study. Indian J Surg Oncol 3(3):250–254
15. Nair D, Singhvi H, Mair M, Qayyumi B, Deshmukh A, Pantvaidya G et al (2017) Outcomes of surgically treated oral cancer patients at a tertiary cancer center in India. Indian J Cancer 54(4):616–620
16. Mroueh R, Haapaniemi A, Saarto T, Grönholm L, Grenman R, Salo T, Mäkitie AA (2019) Non-curative treatment of patients with oral tongue squamous-cell carcinoma. Eur Arch Otorhinolaryngol 276(7):2039–2045
17. Huang SH, O'Sullivan B (2013) Oral cancer: Current role of radiotherapy and chemotherapy. Medicina oral, patologia oral y cirugia bucal 18(2):e233–e240
18. Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C and Mathew G, for the STROCSS Group. The STROCSS (2019) Guideline: Strengthening the Reporting of Cohort Studies in Surgery. Int J Surg 2019(72):156–165
19. Manuel S, Raghavan SKN, Pandey M, Sebastian P (2003) Survival in patients under 45 years with squamous cell carcinoma of the oral tongue. Int J Oral Maxillofac Surg 32(2):167–173
20. Hyam DM, Conway RC, Sathiyaseelan Y, Gebski V, Morgan GJ, Walker DM et al (2003) Tongue cancer: do patients younger than 40 do worse? Aust Dent J 48(1):50–54
21. Akhtar S, Ikram M, Ghaffar S. Neck involvement in early carcinoma of tongue. Is elective neck dissection warranted? JPMA The Journal of the Pakistan Medical Association. 2007;57(6):305–7.
22. Mathew Iype E, Pandey M, Mathew A, Thomas G, Sebastian P, Krishnan NM (2001) Squamous cell carcinoma of the tongue among young Indian adults. Neoplasia 3(4):273–277
23. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL (2016) Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer 139(3):574–583
24. Foster CC, Melotek JM, Brisson RJ, Seiwert TY, Cohen EEW, Stenson KM et al (2018) Definitive chemoradiation for locally-advanced oral cavity cancer: A 20-year experience. Oral Oncol 80:16–22
25. Miller C, Shay A, Tajudeen B, Sen N, Fidler M, Stenson K et al (2019) Clinical features and outcomes in young adults with oral tongue cancer. Am J Otolaryngol 40(1):93–96
26. Thavarool SB, Muttath G, Nayanar S, Duraisamy K, Bhat P, Shringarpure K et al (2019) Improved survival among oral cancer patients: findings from a retrospective study at a tertiary care cancer centre in rural Kerala, India. World J Surg Oncol 17(1):15

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