Journal of Oral Biology and Craniofacial Research 15 (2025) 718–723

Contents lists available at ScienceDirect

Journal of Oral Biology and Craniofacial Research

journal homepage: www.elsevier.com/locate/jobcr

Reduction in tongue space/tongue volume ratio as a risk factor for oral tongue squamous cell carcinoma-an exploratory study

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ARTICLE INFO

Keywords:
Oral tongue squamous cell carcinoma (OTSCC)
Tongue cancer
Tongue space
Tongue volume
Tongue space tongue volume ratio
Magnetic resonance imaging (MRI)

ABSTRACT

Background: The occurrence of tongue cancers in young adults with no associated habitual risk factors is emerging as a major health concern. The objective of the study was to investigate the role of low tongue space-tongue volume ratio as a risk factor for oral tongue squamous cell carcinoma.

Methods: A case control study was conducted among histopathologically confirmed cases of squamous cell carcinoma of lateral border of the tongue who underwent treatment at the Department of Head & Neck Surgery (case group, n = 50). The patients with normal tongue referred for the evaluation of Magnetic Resonance Imaging of head region for other ailments formed the control group (n = 50). The space available for the tongue and the tongue volume of the study population were measured from the Magnetic Resonance Images (MRI), using in built software, and the mean Tongue space/Tongue volume ratio (TS/TV) of both the case group and the control group were calculated. A comparison of the TS/TV ratio was made between the test group and the control group using independent two sample *t*-test. The cut off value for TS/TV ratio between the groups was determined using Receiver Operating Characteristic (ROC) Curve method and Odds ratio was calculated by grouping the study population as low or high TS/TV ratio group using the cut off value obtained.

Results: A statistically significant variation was observed in the TS/TV ratio between tongue cancer patients and the normal controls with the mean value in normal controls higher than tongue cancer patients (p value = 0.009). The cut off value for TS/TV ratio for the development of tongue cancer was determined as 1.259 using ROC curve and the Odds ratio for malignant transformation in patients with low TS-TV ratio was calculated as 2.6.

Conclusion: A significant difference in TS/TV ratio between cases & normal controls observed in our study indicated that a lack of available space for the tongue either due to increase in tongue volume or decrease in tongue space may predispose an individual for the development of tongue cancer.

1. Introduction

Oral squamous cell carcinoma (OSCC) represents 2–5 % of all cancers and presently ranked 8th among the common cancers affecting the humans.[1,2] In India with an age standardized incidence rate of 12.6 per one lakh population,[3] OSCC tops the list among common cancers. Tobacco use is the prime etiological factor for oral cancer in Indian population. However, recently an increase in the incidence of cancers of oral mucosa is noticed among young men and women who do not use tobacco. Most common site of occurrence of oral cancer among non-tobacco users is the lateral border of tongue.[4] The incidence of oral cancer at this site is twice more common in patients without tobacco habit when compared to those with the habit.[4] Identification of etiological factor being the basis for primary prevention, attempts are being made to recognize the causative factor responsible for the development of oral cancers in patients without any known risk factors. Being one of

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https://doi.org/10.1016/j.jobcr.2025.04.002
Received 28 September 2024; Received in revised form 2 April 2025; Accepted 3 April 2025

most common sites to be subjected to dental trauma, the site predilection for the lateral border of tongue suggests the possibility of a constant trauma from the adjacent teeth as a possible predisposing factor in the development of cancer at this site.

Chronic mechanical irritation from teeth is now being accepted as a major etiological factor in the development of oral cancers.[4–6] But the studies done in this regard are mostly retrospective analysis based on the available medical records which considered factors like sharp teeth, less than ideal fillings, badly fitting dentures and unsuitable denture-bearing tissue. Apart from these sources, constant mechanical irritation to tongue from parafunctional habits also had been recently identified as a risk factor for oral tongue squamous cell carcinoma (OTSCC).[7] Hence functional factors also need to be considered where a specific cause for dental trauma is not discernible. The occurrence of cancer on the lateral border of the tongue in relation to lingually placed posterior teeth[8] and the presence of crenations due to teeth, observed on the tongue in close proximity to the lesional areas in OTSCC patients (Fig. 1), indicate that encroachment of tongue space by teeth may also place an individual at a higher risk for tongue cancer. In this background we hypothesized that a discrepancy in the space available for the tongue (tongue space) and the size of the tongue (tongue volume) which favours trauma of the lateral border may act as predisposing factor for the development of tongue cancers. This paper is aimed to evaluate the association between tongue space/tongue volume ratio and the cancer involving the lateral border of tongue.

2. Materials & methods

This case control study was conducted at a tertiary care centre at Ernakulam, Kerala, India from January 2018 to March 2021. Since there were no similar studies in literature, this was designed as an exploratory study. Hence a convenience sampling of 50 cases and controls were chosen considering the availability of eligible population during the study period.

The cases consisted of 50 histopathologically confirmed cases of squamous cell carcinoma of lateral border of the oral tongue who underwent treatment at the Department of Head & Neck Surgery and controls of 50 patients with normal tongue referred from other Departments of our hospital for the evaluation of magnetic resonance image of the brain for various ailments. Low TS/TV ratio was considered as the exposure. The cut-off values for TS/TV ratio categorization was based on the Receiver Operating Characteristic curve.

The participants were selected based on following inclusion and exclusion criteria.

Fig. 1. Crenation due to tooth related trauma observed associated with lesional area of tongue cancer.

Inclusion criteria.

1 Patients with tongue cancer involving the lateral border of tongue.
2 Patients with early tongue lesions (white or red patch or ulcer).
3 Patients with dentulous arch where full complement of posterior teeth was present.

Exclusion criteria.

1 Patients with exophytic lesions of the tongue where exact volume of tongue could not be assessed.
2 Patients with cranio-facial developmental defects.
3 Patients who had already undergone treatment for tongue cancers were excluded from the study.

Demographic details and baseline risk factor variables for oral cancer like tobacco habit, alcohol, trauma from teeth or ill-fitting dentures and history of oral cancer in the family of both study group and the control group were recorded. TS/TV ratio was calculated from magnetic resonance images of both the groups. For the assessment of TS/TV ratio, each subject was imaged with 3 T GE discovery 850W MRI system (General Electric medical systems, Milwaukee, WI, VSA) using the standard protocol for imaging of oral cavity. The imaging was acquired with mouth closed and tongue resting against palate. Patients were instructed not to swallow or move and to keep the lip closed, lightly opposed to each other during the scan. Imaging sections were carried out in axial direction from upper border of hard palate to lower end of mandible including the soft tissue component. Volume acquisition of the area of interest was done using T1 weighted gradient sequences (3D SPGR-spoiled gradient recalled acquisition in steady state) (Fig. 2). Imaging parameters were as follows: TR-19 msec, TE-3.20 msec, Flip angle-12, Matrix size- 288 X288, F0V- 24 X,21.6 cm, NEX -1, Total scan time - 4 min. Images thus acquired were transferred to GE AW server 2.0 work station (GE healthcare, Milwaukee, WI, USA) for evaluation of volume. Volume was estimated in the axial sections but was correlated in coronal and sagittal sections also using multiplanar reformation. All analysis were carried out by a single radiologist with experience of more than 10 years. Margins of tongue was defined according to its anatomical

Fig. 2. T1 weighted magnetic resonance image showing gradient sequences in sagittal plane for volume acquisition of area of interest.

contour and manual tracing of all slices was done where upper border was the superior margin of the dorsum of tongue and lower border was the separation between genioglossus and geniohyoid (Fig. 3),(Fig. 4). The tongue space was defined by inferior surface of palate as the superior margin, the separation between genioglossus & geniohyoid border as the inferior margin, the vertical plane along the posterior margin of base of tongue forming the posterior margin and the lateral margins following the dental arches. The sublingual space was included for the evaluation of tongue space. From the data obtained the tongue space and tongue volume were measured using in built software and the mean TS/TV ratio of both test group and control group was calculated.

2.1. Statistical analysis

Statistical analyses were conducted using SPSS Version 20.0 for Windows (IBM Corporation ARMONK, NY, USA). The TS/TV ratio between the cases & controls were compared using independent sample *t*-test and the categorical risk factors were compared with outcome using Chi-square test. The cut off value for TS/TV ratio between the groups was determined using Receiver Operating Characteristic (ROC) Curve method and Odds ratio was calculated by grouping the study population as low or high TS/TV ratio group using the cut off value obtained. Binary logistic regression analysis was used to estimate the effect of predictor variables on OTSCC.

3. Results

The characteristics of the study population and the distribution of the baseline risk factors for oral cancer among the two groups are provided in Table 1 & Diagram 1. The mean age of the study population was 50.4 years. About 75 % of the subjects among the test group and 54 % of the subjects among the control group were males. The mean value of TS/TV ratio in tongue cancer patients and the control group were 1.297 & 1.368 respectively and this difference was statistically significant with a p value = 0.009 (Table 2). The cut off value for TS:TV for the development of tongue cancer was determined as 1.259 using ROC curve (Fig. 5). Area under curve was 0.64 indicating discriminating ability of TS/TV ratio to diagnose patients with and without tongue cancer. Sensitivity and specificity were 78 % and 42 % respectively while the false positivity was 58 %. Based on the cut off value the study group was further divided into low and high TS: TV group and the Odds ratio was calculated as 2.6 (Table .2) which means that the chances of cancer development at the lateral border of tongue in those with low TS/TV ratio is 2.6 times more than those with high TS/TV ratio. A bivariate analysis of the risk factors between the study group and the control group is presented in Table 3. Among the various risk factors considered, patients with a history of trauma were 7.66 times more likely to have oral cancer compared to those without trauma (OR: 7.66 95 % CI: 2.60 to 22.54; $p < 0.001$) suggesting that trauma from teeth may play a major role in the causation of tongue cancers. A logistic regression was performed to ascertain the effects of age, gender, TS/TV ratio, tobacco, alcohol and trauma on the likelihood that patients had tongue cancer. The model explained 35.9 % (Nagelkerke R^2) of the variance in tongue cancers and correctly classified 74.0 % of cases. Increasing age, was associated with an increased likelihood of exhibiting tongue cancer. Patients with trauma were 4.69 times more likely to exhibit tongue cancer than those without trauma (Table 4).

Fig. 3. MRI showing the diagrammatic representation of the margins used for estimation of tongue volume.

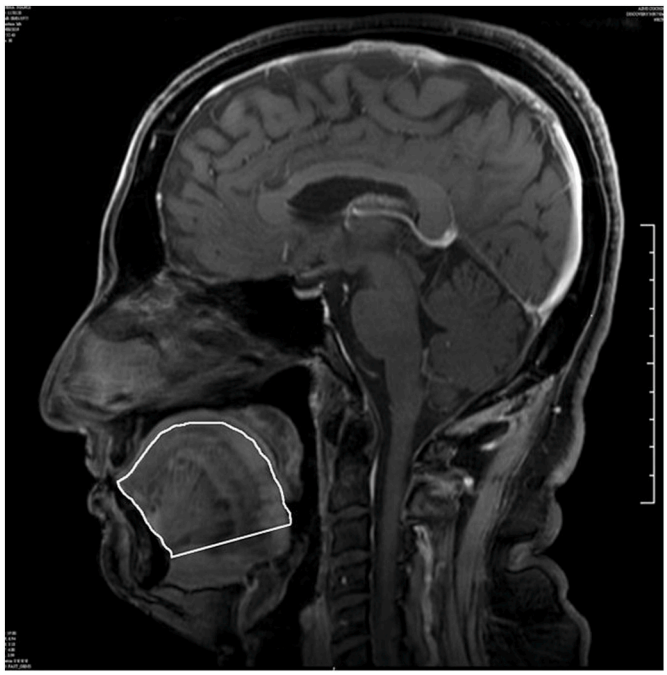

Fig. 4. MRI showing the diagrammatic representation of the margins used for estimation of tongue volume.

Table 1
Characteristics of study population.

Factor	Variable	n (%)
Gender	Female	62 (62 %)
	Male	38 (38 %)
Age	Mean ± SD	50.4 ± 15.2
Tobacco use	Yes	69 (69 %)
	No	31 (31 %)
Alcohol use	Yes	84 (84 %)
	No	16 (16 %)
Trauma from teeth	Yes	72 (72 %)
	No	28 (28 %)
Family history of cancer	Yes	2 (2 %)
	No	98 (98 %)

4. Discussion

Increased incidence of tongue cancer is being observed in non-tobacco users. There is growing evidence that chronic trauma from

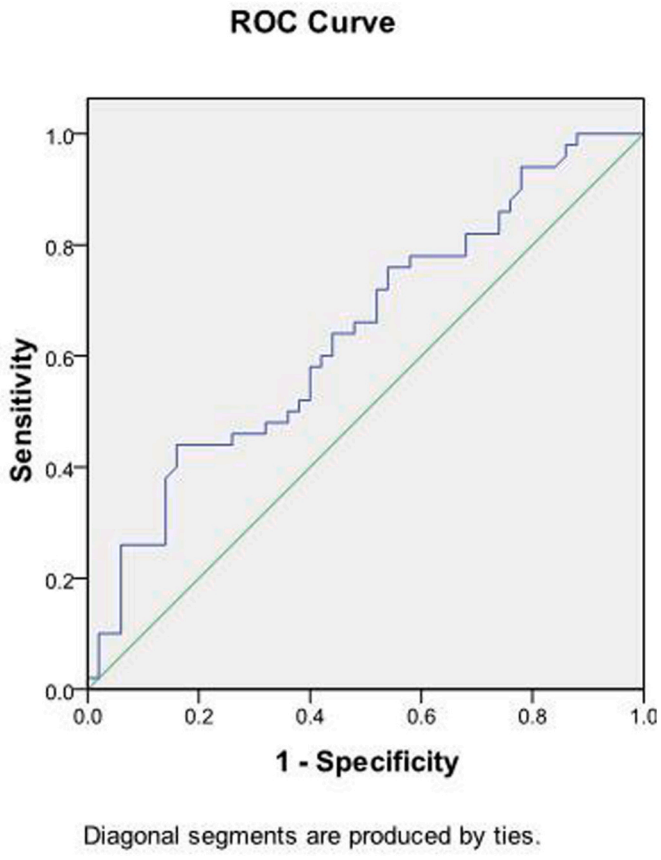

Fig. 5. ROC curve.

Table 2
Association of TS/TV ratio and categories between cases and controls.

Factor	Variable	Cases	Controls	OR (95 % CI)	p value
TS/TV Ratio	Mean ± SD	1.297 ± 0.120	1.368 ± 0.144	–	0.009*
TS/TV Ratio	<1.26	21 (42 %)	11 (22 %)	2.56 (1.07–3.15)	0.032*
	≥1.26	29 (58 %)	39 (78 %)		

Table 3
Association of other risk factors between cases and controls.

Factor	Variable	Cases	Controls	OR (95 % CI)	p value
Age	Mean ± SD	56.0 ± 10.8	44.8 ± 16.9	–	<0.001*
Gender	Male	35 (70 %)	27 (54 %)	1.98 (0.87–4.52)	0.099
	Female	15 (30 %)	23 (46 %)		
Tobacco use	Yes	18 (36 %)	13 (26 %)	1.60 (0.68–3.76)	0.280
	No	32 (64 %)	37 (74 %)		
Alcohol use	Yes	7 (14 %)	9 (18 %)	0.74 (0.25–2.17)	0.585
	No	43 (86 %)	41 (82 %)		
Trauma from teeth	Yes	23 (46 %)	5 (10 %)	7.66 (2.60–22.54)	<0.001*
	No	27 (54 %)	45 (90 %)		
Family history of cancer	Yes	2 (4 %)	0 (0 %)	–	1.000
	No	48 (96 %)	50 (100 %)		

teeth plays a significant role in oral carcinogenesis and one of the possible etiological factors suggested for the development of tongue cancer in people who do not use tobacco is chronic trauma of the oral mucosa (CTOM). In a retrospective study of 406 patients, Piemonte ED et al.[5] analyzed the relationship between chronic trauma of oral mucosa, oral potentially malignant disorder and oral cancer and observed a significant association between oral cancer and chronic trauma of oral mucosa. Kivanc Bektas-Kayhan et al.[6] in a case control study conducted in 47 patients observed 44.7 % of their patients with tongue cancer had chronic trauma and a significant association was noted between chronic dental trauma and tongue cancer. Brendan J. Perry et al.[4] in a retrospective analysis of 390 oral cancer cases noticed that most mouth cancers occurred on the edge of the tongue and non-smokers had a significantly higher proportion occurring on the edge of the tongue when compared smokers. Our study also revealed a significant association between chronic dental trauma and cancer involving the lateral border of the tongue. These observations along with our clinical experiences suggested that apart from the established risk factors such as tobacco and alcohol, dental factors also need to be considered in assessing the risk factors involved in the development of oral cancers. CTOM results from the repeated mechanical intraoral injuries caused by dental factors like defective, sharp, broken or malpositioned teeth, prosthetic factors like sharp dentures or functional factors like bruxism. In the background of lack of enough supportive evidences in this regard, the causality criteria set out by Bradford Hill was recommended to be applied in assessing the association between chronic trauma and oral cancer.[9] The association of these factors with the occurrence of oral cancer has been observed, but their cause-and-effect role is yet to be established. However, the role of inflammation in carcinogenesis is well established and the immune suppression and immune evasion mediated by the inflammatory cells in the tumour micro environment is at present considered as hall marks of cancer. The mucosa which is subjected to constant irritation apart from inducing immune response also stimulates the cells in the proliferative compartment to divide continuously making those cells more prone for DNA damage by other agents. The genetic and epigenetic changes responsible for malignant transformation may also be induced by the chronic inflammation at the site through chemical mediators or oxidative stress.[5]

Discrepancy in the size of the tongue and the space available for the tongue as a causative factor for tongue cancers was not evaluated earlier to the best of our knowledge. However, a previous study which assessed the association of tongue space determined using coronal and axial CT images with tongue cancer observed a significant difference in the tongue space area in young OTSCC patients and normal control suggesting that the narrow tongue space may be a potential factor influencing OTSCC development in young patients.[8] It has also been observed that tongue interposition which causes continuous mechanical irritation was strongly associated with tongue cancers.[10]

Tongue volume and oral cavity volume had been evaluated earlier using various methods like fluid displacement method,[11] lateral cephalograms,[12–14] alginate impressions,[15,16] computed tomography (CT)[17] magnetic resonance imaging (MRI)[18] and CBCT.[19] A previous study has documented a mean tongue volume of 71.20 ± 11.04 and a mean oral cavity volume of 86.48 ± 14.59 estimated by CBCT (Cone beam tomography) in normal human adults (TS:TV = 1.215).[20] But a similar study using MRI has shown a mean value of 138.84 ± 16.92 for tongue volume & a mean value of 159.7 ± 20.24 for oral cavity volume (TS:TV = 1.1150).[18] The variations in the values observed in the studies may be attributed to inconsistencies in the anatomic definition of the area measured, variations in the techniques employed or variations in actual dimensions, between the individuals. Several previous studies discussed the tongue and oral cavity volumes in participants with obstructive sleep apnea and most of them has included pharynx and airways for measuring tongue volume and oral cavity volume respectively.[21–23] Hence a standardized approach needs to developed for an accurate comparative evaluation of these two parameters, if we are to apply a cut

Table 4
Multivariate analysis with established risk factor and likelihood of tongue cancer

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.045	.018	6.558	1	.010	1.046	1.011	1.083
	Gender(1)	.412	.536	.590	1	.442	1.510	.528	4.317
	TS_TV_ratio	−3.437	2.086	2.715	1	.099	.032	.001	1.918
	Tobacco(1)	.364	.615	.351	1	.553	1.440	.431	4.807
	Alcohol(1)	−.790	.754	1.098	1	.295	.454	.104	1.989
	Trauma(1)	1.547	.590	6.878	1	.009	4.696	1.478	14.919
	Constant	1.595	2.936	.295	1	.587	4.930		

[a] Variable(s) entered on step 1: Age, Gender, TS_TV_ratio, Tobacco, Alcohol, Trauma.

off value for TS/TV ratio for the risk assessment of tongue cancers in a population. In our study based on MRI evaluation, we observed a statistically significant variation in the TS/TV ratio between tongue cancer patients and normal controls with the value in normal controls slightly higher that OTSCC patients. The cut off value was determined as 1.29 and the risk for malignant transformation in patients with low TS-TV ratio was found to be 2.6 times higher than those with high TS-TV ratio. The limitation of our study is that trauma from teeth and family history were recorded based on patient's self-reported history, hence there is a possibility of recall bias. Chronic trauma could have been due to reasons other than occluding teeth, like defective restoration, foreign body trauma etc., which could not be verified. The tracing of tongue borders on MRI was done manually, by a single examiner followed by measurement of TS and TV digitally. Chances of measurement bias was minimal as tongue borders were clearly defined and tracings were carried on images with sufficient contrast. However, we recommend the use of automated segmental tools for the tracing of tongue borders to reduce manual measurement bias in future studies.

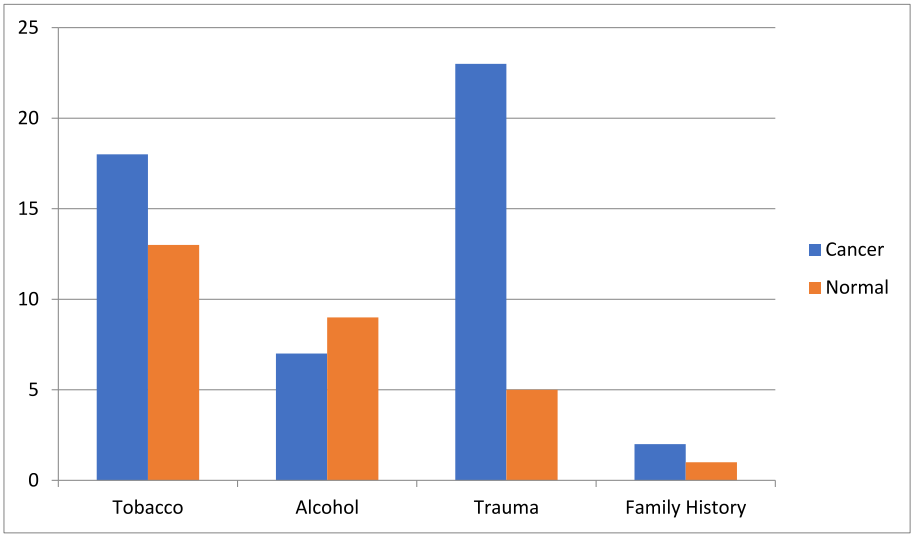

Diagram 1. Distribution of risk factors among study groups.

4.1. Conclusion

The present study suggests a possible association between TS/TV ratio and OTSCC. However, future studies in this direction with objective assessment of risk factors to reduce recall and self-reported bias in larger population from multiple centre settings may be required to ascertain the causative role of reduced TS/TV ratio in the development of OTSCC.

Ethics statement

The study was approved by the Institutional Ethics Committee of Amrita Institute of Medical Sciences (IEC-AIMS-2017-DENT-091 dated 06-03-2017). Voluntary informed consent was obtained from all participants.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

All the authors associated with present manuscript declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgement

Nil(Apart from the authors we have not taken help from anyone for providing language help, writing assistance or proof reading the article, etc.).

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