Original Article

Relationship between Thickness of Early Oral Tongue Carcinoma (T$_1$, T$_2$) with Cervical Lymph Node Metastasis

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Abstract:

Background: Carcinoma of oral tongue is the most common oral cancer and because of its structure and function is prone for early local and regional spread of cancer. The final outcome of a primary tongue carcinoma patient depends upon various prognostic factors like thickness of tumor, depth of invasion, size of lesion and neck node 67metastasis. Risk of metastasis and spread to neck nodes increases with increase in tumor thickness

Methods: This prospective observational study was carried out in the Department of Otolayngology-Head & Neck Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for 18 months. Thirty patients with early oral tongue carcinoma i.e.T1 & T$_2$ as per UICC and AJC criteria were included in this study by purposive non-randomized sampling technique. Result of the study were expressed as mean, standard deviation (+SD), frequency and percentages. Unpaired Student's t-test and Pearson's correlation co-efficient (r) test were performed.

Results: Result of the study showed the mean (+SD) thickness of the tumor was 3.62 (+1.46) mm. Minimum thickness 1.1mm and maximum thickness 7.8mm. Only 21 (70%) subjects neck node were metastasized from tongue and mean (+SD) tumor thickness of the positive neck node metastasis was 5.54 (+1.07) mm and negative neck node metastasis was 2.87 (+0.75) mm. This indicated a significant difference between the groups. Pearson's correlation co-efficient r (+0.981) which indicated tumor thickness was positively correlated with neck node metastasis.

Conclusion: Tumor thickness of the early oral carcinoma positively correlated with neck node metastasis. Correlation between thickness and metastatic lymph node can help planning the treatment regimen and indicate the disease prognosis.

Key words: Relationship, thickness, early oral tongue carcinoma (T1, T2), cervical lymph node metastastasis.

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Introduction:

Carcinoma of oral tongue is the most common oral cancer in the world with a reported incidence of 17.8–52% and the second commonest cancer of oral cavity in India[1]. Tongue, because of its structure and function is prone for early local and regional spread of cancer. Prognosis of primary tongue carcinoma depends upon stages of the disease. But 81% have one year survival rate whereas the five year survival rates are reported to be 48% to 56%[2-4].

Mortality and morbidity of primary tongue carcinoma remain unraveled despite all the advancement in the field of oncology and surgery. The final outcome of a primary tongue carcinoma patient depends upon various prognostic factors like depth of invasion, size of lesion and neck node metastasis & its extra capsular spread and many other predictive indicators[5].

Tumor thickness is the distance measured from the surface of the tumor including the keratin to the point of maximum invasion in the underlying connective tissue stroma. In cases of ulcerated tumors, base of the ulcer serves as the reference point. Depth of invasion is considered as a synonym for tumor thickness[2]. Many studies have used the terms "depth of invasion" and "tumor thickness" synonymously whereas, few studies like Moore et al (1986) defined tumor thickness and depth of invasion as two different entities. According to them, depth of invasion means the extent of cancer growth into the tissue beneath an epithelial surface. He defined tumor thickness as the entire tumor mass[6].

The mean tumor thickness for patients with neck node metastasis came out to be 9.9 mm. However, it has been found that most of these cases have a cut off value of 5 mm. This value of 5 mm was found significant to predict the cervical lymph node metastasis as no case with lesser thickness had nodal metastasis[2]. A study conducted by O-Charoenrat et al (2003) in London showed that patients with tumors exceeding 5 mm thickness had a metastatic rate of 64%. Whereas, those tumors less than 5 mm, the incidence of cervical nodal metastasis was only 16%[7].

The primary tongue carcinoma is characterized by high potential for local invasiveness and distal metastasis. The metastasis is first to sentinel and then to other cervical lymph nodes which has an impact on patient's survival rate. Studies have been carried out worldwide to show the important prognostic factors of survival among which correlation between the increasing tumor thickness and an increased risk of cervical metastasis is important[5,8].

An accurate, noninvasive method capable of detecting and measuring tumor thickness is yet to be established. To obtain such information preoperatively, digital palpation, USG of tongue, magnetic resonance imaging (MRI) and postoperatively histopathological examination are performed. The tongue carcinoma patients are treated surgically by excision of the primary tumor with neck dissection depending upon the stage of the tumor alone[9]. Optical micrometer is a modern tool to measure the thickness.

Tumor thickness is yet to be uniformly measured. Some authors measured the distance from the deepest point of tumor invasion to the most protruding part of the tumor (tip of the papilla) in exophytic lesions and to the ulcer base in ulcerated lesions, whereas others measured from the deepest point of the tumor to an imaginary line that reconstructed the healthy mucosa. Furthermore, some authors ignored the keratin layer and inflammatory infiltrate, while

others provided no data on this issue. Assuming that healthy tissue presents greater resistance to the vertical than to the superficial growth of the tumor, it is reasonable to think that the most aggressive tumors are those with the greatest capacity to grow downwards vertically[10,11].

Risk of metastasis and spread to neck nodes increases with increase in tumor thickness. Previously this relation of tumor thickness and the metastasis to neck nodes was studied by many authors of different countries[12-15]. Fawzy et al. (2017) demonstrate that conservative elective neck dissection is indicated in patients with stage I/II oral tongue carcinoma whose tumors are >4 mm in thickness as they mostly have latent metastasis[16]. The tongue has characteristic structural features including a high content of muscle bundles and a rich lymphatic network that may influence the properties of tumor spread in it.

The depth of invasion (DOI) indicates the spread of tumor growth to the tissues underlying the epithelium. The tumor thickness (TT) is related to the thickness of the total tumor mass. It is better to consider the DOI rather than thickness of the mass[17,18]. This study is designed to see the relationship of DOI of early oral tongue carcinoma (T$_1$, T$_2$) with neck node metastasis.

Methods:

Study design: Prospective observational study,

Study place: Department of Otolaryngology-Head & Neck Surgery at, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Study period: July' 2017- January' 2019.

Sample Size and calculation : Thirty patients with early oral tongue carcinoma

i.e.T$_1$ & T$_2$ as per UICC – AJC criteria were included in the study by purposive non-randomized sampling technique. Sample size for the study was determinedby $= \dfrac{(u + v)^2\, \sigma^2}{(\mu - \mu_\circ)^2}$

Exclusion criteria:(a) Tumor involving base of the tongue or grossly invading floor of mouth, (b) Recurrent cases, (c) Cases with a second primary carcinoma in oral cavity.

Procedure: The study was conducted with proper clearance from university IRB (BSMMU).Patients with T$_1$& T$_2$ Oral Tongue carcinoma admitted in the department of Otolaryngology & Head-Neck Surgery, BSMMU. Patients were selected as per inclusion, exclusion criteria and taking informed consent. Digital palpation was carried out to get idea about tumor size and apparent thickness. MRI was done to measure tumour thickness and extension. Neck was assessed by clinical examination and MRI. Just after surgery Tongue and Neck dissection specimens were checked visually to see the excision margin and lympthnodes (if any visible or palpable lymph node and their level & number), were sent for histo-pathological examination. Histo-pathological size, thickness & neck node metastasis were considered for TNM staging (p TNM). Tumor was cut in a bread loafing pattern and the section showing maximum tumor involvement was taken in the cassette. All the obtained lymph nodes and sections were dissected and fixed. Pathological size greatest diameter>4cm & thickness > 10 mm (DOI) was excluded from the study.

Statistical analysis: Data were entered in statistical package SPSS-24 (trial version) in order to analyze all quantitative analysis (mean and standard deviation) and qualitative variables (frequency and percentages). All the data were compiled and sorted properly and the numerical data were analyzed statistically by using SPSS-24, trail version.

Photograph of Carcinoma tongue at right lateral margin.

The results were expressed as frequency, percentage and mean ± SD. Unpaired Student's t test was performed to compare all the quantitative parameters between both groups (with neck node metastasis and without neck node metastasis). Pearson's correlation co-efficient (r) test was performed to explore the relationship (positive or negative relationship) between thicknesses of early oral tongue carcinoma (T_1, T_2) with neck node metastasis. p value < 0.05 was accepted as significant.
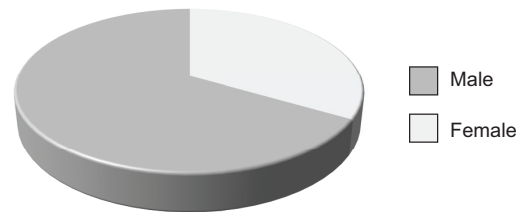
Results:

The youngest patient in our series was 25 years age and the oldest one was 75 years. (Figure-1).
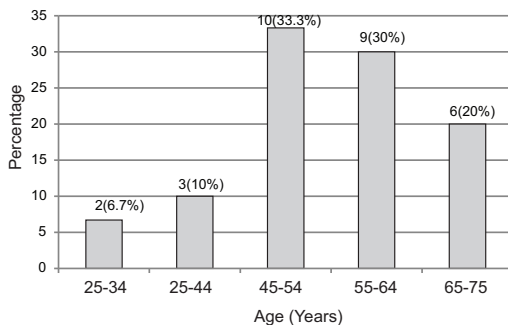
Fig.-1: *Distribution of study population according to age (n=30)*

Majority (66.7%) of the study population were male and 33.30 % were female.(Figure-2)

Fig.-2: *Distribution of study population according to sex (n=30)*

Among thirty(30) cases majority were illiterate (40%) and equal number have attended the primary level of education (40%). Secondary school were attended by 13.3% and higher secondary level by 6.7% patients. All female (33.3%) patients were House wife.

Among the male subjects, 14 (46.6%) were from low socio economic strata, and 04 (13.3%) were from middle class. Only 2 (6.7%) cases came from high socioeconomic condition.

Out of 30 patients 18 (60%) were smokers, 23 (76.7%) were taking betel leaf, 16 (53.3%) were chewing betel nut and 6 (20%) were alcoholic in their habit. Among them, tip of the tongue involved in 2 (6.7%) cases, lateral border involved in 20 (66.7%) cases, ventral

surface in 4 (13.3%) and dorsum of tongue involved in 4 (13.3%) cases.

Clinically primary tongue tumors was categorized as T_1 and T_2. Among 30 patients, majority 18 (60%) were T_2 and 40% were T_1.

But after obtaining the histopathological report the stages of tumor were categorized as T_1N_0, T_1N_1 T_2N_0 and T_2N_1.(Figure-3)
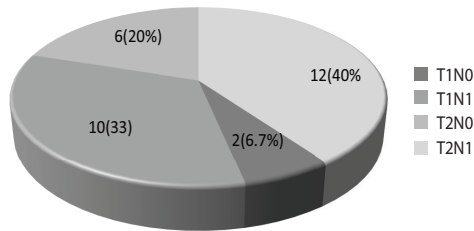
Fig.-3: *Tumor stages according to histo-pathology*

Among 30 subjects, majority 21 (70%) of the study subjects neck node were involved and only 9 (30%) subjects neck node were not metastasized from tongue.

In this study, tumor thickness < 2 mm of positive neck node metastasis was 0 (0%) and negative neck node metastasis was 7

(23.3%), thickness 2-4 mm of positive neck node metastasis was 2 (50%) and negative neck node metastasis was 2 (50%) and thickness > 4-7.8 mm of positive neck node metastasis was 17 (89.47%) (Table-I).

The mean (± SD) thickness of tumor was 3.63 (±1.47) mm. Minimum thicknesses was 1.1 mm and maximum thickness was 7.8 mm (Table I). In tumor thickness $\leq$4 mm group, 7 (23.3%) were smokers, 7 (23.3%) were taking betel leaf, 7 (23.3%) were chewing betel nut and 3 (10%) were alcoholic in their habit. In tumor thickness > 4-7.8 mm group, 11 (36.7%) were smokers, 16 (53.3%) were taking betel leaf, 9 (30%) were chewing betel nut and 3 (10%) were alcoholic in their habit.

In tumor thickness $\leq$4 mm group, lateral border involved in 7 (23.3%) cases only. In tumor thickness > 4-7.8 mm group, tip of the tongue involved in 2 (6.7%) cases, lateral border involved in 13 (43.3%) cases, ventral surface in 4 (13.3%) and dorsum of tongue involved in 4 (13.3%) case.

The mean (± SD) tumor thickness of positive neck node metastasis was 5.55 (±1.07) mm and negative neck node metastasis was 2.88 (±0.75) mm. This indicated a significant difference between the groups (Table-II).

Table I :

Distribution of study subjects according to histopathological findings (N=30)

Thickness of tumor in mm	Number after histopathological assessment	Number of patients with positive lymph node in neck	Percentage (%)
<2	O7	0	0%
2-4	04	2	50%
>4-7.8	19	17	89.47%

Table II :

Relation between tumor thickness and neck node metastasis among study subjects (N=30)

Tumor thickness (mm)	Neck node metastasis		t-test	pvalue
	Positive (n=19)	Negative(n=11)		
Mean ± SD	5.55±1.07	2.88±0.75	9.22	0.001[***]
Range	4.3 - 7.8	1.10 - 4.0		

Data were expressed as mean ± SD. Unpaired Student's 't' test was performed to compare neck node metastasis. Level of significance was calculated at $p<0.05$. N= Study subjects.

In this study, mean (± SD) tumor thickness of positive neck node metastasis was 5.55 (±1.07) mm and negative neck node metastasis was 2.88 (±0.75) mm. This indicated a significant difference between the groups.

In this study, tumor thickness has positively strong correlation with neck node metastasis. This correlation was statistically significant (Table-III).

Table-III :
Correlation of tumor thickness with neck node metastasis (N=30)

	Thickness of tumor (mm)	
	r	*p* value
With neck node metastasis	+ 0.981	<0.001

Pearson correlation coefficient test was performed to observed correlation of tumor thickness with neck node metastasis. Level of significance was calculated at p<0.05. N= Study subjects. In this study, tumor thickness was positively correlated with neck node metastasis. This correlation was statistically significant.

Discussion:
The present study was undertaken to observe relationship between thicknesses of early oral tongue carcinoma (T_1, T_2) with neck node metastasis. For this study, a total number of 30 cases of early oral tongue carcinoma (T_1, T_2) that has the inclusion criteria were enrolled as a study sample.

In, this study clinically stage of tumor was categorized as T_1 and T_2. Majority of the incidence were reported 60% in T_2 stage. Clinically staging done according to length (according to AJCC, 2016)[19]. As far we know tongue have rich lymphatic supply, crisscross

manner of intrinsic muscle and as a mobile organ so with the duration it spread aggressively. Most of our study population are illiterate, came from low socioeconomic stage, lack of knowledge of risk factor and lack of consciousness about aggressiveness of the tumor. So, earlier tongue lesion they neglected it, as a result it spread with greater length.

Pathologically stage or tumor was categorized (according to AJCC, 2016) as T_1N_0, T_1N_1, T_2N_0 and T_2N_1[19]. Tumor staging according to thickness or depth of invention crucial for the management prognosis of early oral carcinoma. Many studies have used the terms depth of invention and tumor thickness synonymously[2].

Our study shows majority subject in T_2N_1 (40%) stage and T_1N_1 (33.3%). Previous studies have shown the tumor thickness is the important prognostic factor in treatment of patients of early oral tongue carcinoma (T_1, T_2)[20].

In this study, tumor thickness <2 mm of positive neck node metastasis was 0 (0%) and negative neck node metastasis was 7(23.3%), thickness 2-4 mm of positive neck node metastasis was 2(50%) and negative neck node metastasis was 2(50%) and thickness >4-7.8 mm of positive neck node metastasis was 17(89.47%). We thought the thickness of attack and micro vascular proliferation caused by neoplastic growth might determine proximity to the blood vessels and lymphitic channels, thus facilitating the metastatic process in this study. Almost similar to finding observed at Fawzy et al; 2017[16].

Positive neck node metastasis was more in subjects whose tumor thickness > 4-7.8 mm and negative neck node metastasis was more in subjects whose tumor thickness <2 mm. Available literature states that, chances of

occult neck metastasis are almost nil if depth of tumor is up to 2 mm and similar results were observed in present study Various researchers of different countries reported that, occult neck metastasis in tumors with depth > 4 mm were 62.2%, 64.70% and 70.3% respectively. Authors observed that, tumors with depth > 4 mm had 60% neck metastasis in present study. They utilized ultrasonography to know pre-operative depth of tumor. They suggested that it was quickly available and low cost effective[17,21,22].

In present study, relatively older population was affected more by oral tongue cancer than younger. The youngest and the oldest patients were 25 and 75 years respectively in present study. This may be due to longer use of tobacco, alcohol, betel nut and exposure of other risk factor. Almost similar to the findings observed by the various investigators from different countries[16,23, 24].

This study shows 66.7% of the study subjects were male and only 33.3% were female. This may be due to male subjects are use more tobacco, alcohol, betel nut, betel leaf than female. Almost similar to the findings observed by the various investigators from different countries[16,23, 24].

In present study, majority were illiterate (40%) and primary level (40%) of education. They have not proper knowledge about the risk factor of tongue cancer, disease process and prognosis of tongue cancer. So they were suffered more. Only 13.3% and 6.7% study subjects had secondary and higher secondary level of education. This finding were agreement with Fawzy et al; 2017[16].

In this study, majority of study population came from low (60%) socioeconomic condition. They had no proper knowledge about the risk factor of tongue cancer and disease process. So they suffered more. This finding was in agreement with Fawzy et al. (2017) and Zia et al.(2017)[16,24].

In present study, out of 30 patients 23 (76.7%) were taking betel leaf, 18 (60%) were smokers, 16 (53.3%) were chewing betel nut and only 6 (20%) were alcoholic in their habit. As far we know smoking is one of the highest risk factor to produce tongue cancer, but female were included in this study who were not smokers. So betel leaf is the major risk factor in present series. Gupta and Mehta (2000), Balaram et al. (2002) and Jetley et al. (2017) found similar results in their studies[23,25,26]. Jetley et al. (2017) observed the favored smoking method was bidi and cigarette[23]. All the smokers were males. The preferred form of smokeless tobacco was gutka, and khaini/surti. They also observed a larger number of male smokeless tobacco users in their study. In contrast a large population based study among tobacco users in Mumbai by Balaram et al. (2002) noted that smokeless tobacco users were mostly women[26]. A study based in Southern India provided strong evidence that smoking bidi is more hazardous than cigarette smoking. Low educational attainment, occupation as a farmer or manual worker and various indicators of poor oral hygiene were associated with significantly increased risk. The study found that among men, 35% of oral cancer was attributable to the combination of smoking and alcohol drinking and 49% to pan-tobacco chewing, whereas among women, chewing and poor oral hygiene explained 95% of oral cancer[25].

On the other hand, study did by Fukano et al. (1997) showed that tongue tumors exceeding 5 mm carried a risk of 65% for neck metastases, whereas those infiltrating 5 mm or less had a risk of only 6%[27]. Yuen et al. (2002) showed in their study that tumor thickness is prognostic for both nodal and local recurrence in oral carcinomas. They showed the variation in the tumor thickness and its effect on the neck metastasis. A tumor

thickness less than 3 mm, had 0% local recurrences and had 8% nodal metastases; tumor thickness of more than 3 mm and up to 9 mm had 44% subclinical nodal metastasis and 7% local recurrence; tumor thickness of more than 9 mm had 53% subclinical nodal metastasis and 24% local recurrence. Local recurrence occurred significantly more in the group with tumor thickness of more than 8 mm[28].

Mücke et al. (2016) highlight the importance of tumor thickness as a predictive variable in tongue cancer. Specifically, a cut-off point of 8 mm allowed for a more accurate and statistically precise prediction of lymph node metastasis[29]. Hu et al. (2015)found that the tumor thickness is a more reliable method for neck node metastasis than tumor volume[30].

In present study, tip of the tongue involved in only 2 (6.7%) cases, lateral border of tongue were involved in most (66.7%) of the cases, ventral surface (13.3%) and dorsum of the tongue (13.3%) also involved. Commonly we know lateral aspect is mostly involved followed by ventral aspect. This finding was agreement with the study of Aslam et al. (2012)[2].

This study shows, the mean (± SD) thickness of tumor was 3.63 (±1.47) mm. Minimum thicknesses was 1.1 mm and maximum thickness was 7.8 mm. Among the study subjects 21 (70%) neck node were metastasized from tongue and the mean (± SD) tumor thickness of positive neck node metastasis was 5.55 (±1.07) mm and negative neck node metastasis was 2.88 (±0.75) mm. This indicated a significant difference between positive nodal metastasis subjects and negative neck node metastasis subjects. Tumor thickness was positively correlated with neck node metastasis. Tumor thickness is thought to involve the multiple proteolytic

enzymes, among which are the matrix metalloproteinases (MMPs). MMPs are a family of proteases commonly expressed in invasive tumors and the adjacent stroma and it are thought to play an important role in tumor invasion, increase thickness and metastasis[31]. This correlation was statistically significant. This finding was agreement with Fawzy et al. (2017)[16].

There is also controversy regarding the thickness values that differentiate patients according to their survival. Ghazi et al. (2019) found that patients with tumors of 4.3 mm thickness have a significantly higher. Their multivariate analysis showed that the thickness of the tumor had the greatest influence on neck node metastasis of their patients[32]. Brown et al. (1989) also described the cut-off point as being 3 mm, whereas Spiro et al. (1986) concluded that patients showed a significant neck node metastasis rate above a tumor thickness of 2 mm [20,33]. Moore et al. (1986) differentiated five groups of patients according to their tumor thickness and found that the neck node metastasis rate significantly increased with increasing tumor thickness, without identifying a cut-off point[6].

Conclusion:

- After analyzing the results of present study it can be concluded that tumor thickness of the early oral carcinoma positively correlated with neck node metastasis. Correlation between thickness and metastatic lymph node can help planning the treatment regimen and indicate the disease prognosis.

- It clearly demonstrate that conservative elective neck dissection is indicated in patients with Stage I/II oral tongue carcinoma whose tumours are > 4 mm in thickness as they mostly have latent metastasis.

References:

1. Niranjan VR, Ranpise SG. Evaluating the epidemiology and needs of oral cancer patients from Aurangabad district, Maharashtra, India. Int. J Res Med Sci. 2017 Jul; 5(7):2905.

2. Aslam F, Atique M, Aslam M, Sarfraz T, Ayaz BA, Alamgir W. Relation of tumour thickness with lymph node metastasis in oral squamous cell carcinoma. Pakistan Armed Forces Medical Journal. 2012 Dec 31;62(4):529-33.

3. Chammas MC, Macedo TA, Moyses RA, Gerhard R, Durazzo MD, Cernea CR, Cerri GG. Relationship between the appearance of tongue carcinoma on intraoral ultrasonography and neck metastasis. Oral Radiology. 2011 Jun 1;27(1):1-7.

4. Warburton G, Nikitakis NG, Roberson P, Marinos NJ, Wu T, Sauk Jr JJ, Ord RA, Wahl SM. Histopathological and lymphangiogenic parameters in relation to lymph node metastasis in early stage oral squamous cell carcinoma. Journal of oral and maxillofacial surgery. 2007 Mar 1;65(3):475-84.

5. Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontology. 2006 Jul 1;102 (1):67-76.

6. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. Archives of Surgery. 1986 Dec 1;121(12):1410-4.

7. O'Brien CJ, Lauer CS, Fredricks S, Clifford AR, McNeil EB, Bagia JS, Koulmandas C. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness?. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2003 Nov;25(11):937-45.

8. ÖNerci M, Yilmaz T, Gedikoðlu G. Tumor thickness as a predictor of cervical lymph node metastasis in squamous cell carcinoma of the lower lip. Otolaryngology—Head and Neck Surgery. 2000 Jan;122(1):139-42.

9. Madana J, Laliberté F, Morand GB, Yolmo D, Black MJ, Mlynarek AM, Hier MP. Computerized tomography based tumor-thickness measurement is useful to predict postoperative pathological tumor thickness in oral tongue squamous cell carcinoma. Journal of Otolaryngology-Head & Neck Surgery. 2015 Dec;44(1):1-4.

10. Gonzalez-Moles MA, Esteban F, Rodriguez-Archilla A, Ruiz-Avila I, Gonzalez-Moles S. Importance of tumour thickness measurement in prognosis of tongue cancer. Oral Oncology. 2002 Jun 1;38(4):394-7.

11. Bashir U, Manzoor MU, Majeed Y, Khan RU, Hassan U, Murtaza A, Aftab K, Hussain SR, Jamshed A, Uddin N, Faruqui ZS. Reliability of MRI in measuring tongue tumour thickness: a 1.5 T study. Journal of Ayub Medical College Abbottabad. 2011 Sep 1;23(3):101-4.

12. Warburton G, Nikitakis NG, Roberson P, Marinos NJ, Wu T, Sauk Jr JJ, Ord RA, Wahl SM. Histopathological and lymphangiogenic parameters in relation to lymph node metastasis in early stage oral squamous cell carcinoma. Journal of oral and maxillofacial surgery. 2007 Mar 1;65(3):475-84.

13. O'Brien CJ, Lauer CS, Fredricks S, Clifford AR, McNeil EB, Bagia JS, Koulmandas C. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness?. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2003 Nov;25(11):937-45.

14. Kane SV, Gupta M, Kakade AC, D'Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. European Journal of Surgical Oncology (EJSO). 2006 Sep 1;32(7):795-803.

15. Wallwork BD, Anderson SR, Coman WB. Squamous cell carcinoma of the floor of the mouth: tumour thickness and the rate of cervical metastasis. ANZ journal of surgery. 2007 Sep;77(9):761-4.

16. Fawzy A, Sabry M, Sabry A, El Fol H, El Kased A. The relationship between primary tumour thicknesses in cancers of the oral cavity to subsequent lymph node metastasis. International Surgery Journal. 2017 Aug 24;4(9):2957-66.

17. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2005 Dec;27(12):1080-91.

18. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph node involvement in squamous cell carcinoma of the oral cavity: a meta analysis of reported studies. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2009 Apr 1;115(7):1489-97.

19. AJCC, 2016.AJCC Cancer staging manual, 8th edition.p.2-4.

20. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. The American journal of surgery. 1986 Oct 1;152(4):345-50.

21. Ganly I, Patel S, Shah J. Early stage squamous cell cancer of the oral tongue—clinicopathologic features affecting outcome. Cancer. 2012 Jan 1;118(1):101-11.

22. Haksever M, Inancli HM, Tunçel Ü, Kürkçüoðlu[a]S, Uyar M, GençÖ, IrkkanÇ. The effects of tumor size, degree of differentiation, and depth of invasion on the risk of neck node metastasis in squamous cell carcinoma of the oral cavity. Ear, Nose & Throat Journal. 2012 Mar;91(3):130-5.

23. Jetley, S., Jairajpuri, ZS.,SamaRizvi. S. Risk factors in oral carcinoma and the relationship between tumor thickness and regional nodal involvement: a pilot study in a semi urban population in New Delhi, India. 2017 J Res Med Sci; 5(3):1021-26.

24. Zia S, Naqvi SU, Adel H, Adil SO, Hussain M. Relationship of Oral Tumor Thickness with the rate of lymph node metastasis in Neck based on CT Scan. Pakistan journal of medical sciences. 2017 Mar;33(2):353.

25. Gupta PC, Mehta HC. Cohort study of all-cause mortality among tobacco users in Mumbai, India. Bulletin of the World Health Organization. 2000;78:877-83.

26. Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, Ravichandran K, Ramdas K, Sankaranarayanan R, Gajalakshmi V, Munoz N. Oral cancer in southern India: The influence of smoking, drinking, paan chewing and oral hygiene. International journal of cancer. 2002 Mar 20;98(3):440-5.

27. Fukano H, Matsuura H, Hasegawa Y, Nakamura S. Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 1997 May;19(3):205-10.

28. Po Wing Yuen A, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, Yuen WF, Wei WI. Prognostic factors of clinically stage I and II oral tongue carcinoma—a comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez Gimeno score, and pathologic features. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2002 Jun; 24(6):513-20.

29. Mücke T, Kanatas A, Ritschl LM, Koerdt S, Tannapfel A, Wolff KD, Loeffelbein D, Kesting M. Tumor thickness and risk of lymph node metastasis in patients with squamous cell carcinoma of the tongue. Oral oncology. 2016 Feb 1;53:80-4.

30. Hu H, Cheng KL, Xu XQ, Wu FY, Tyan YS, Tsai CH, Shen CY. Predicting the prognosis of oral tongue carcinoma using a simple quantitative measurement based on preoperative MR imaging: tumor thickness versus tumor volume. American Journal of Neuro-radiology. 2015 Jul 1;36(7):1338-42.

31. De Vicente JC, Fresno MF, Villalain L, Vega JA, Vallejo GH. Expression and clinical significance of matrix metalloproteinase-2 and matrix metalloproteinase-9 in oral squamous cell carcinoma. Oral oncology. 2005 Mar 1;41(3):283-93.

32. Ghazi N, Ghazi A, Shafiee S, Fayyazi M. Importance of depth of invasion in patients with oral squamous cell carcinoma: A review article. Journal of Orofacial Sciences. 2018 Jan 1;10(1):3.

33. Brown B, Barnes L, Mazariegos J, Taylor F, Johnson J, Wagner RL. Prognostic factors in mobile tongue and floor of mouth carcinoma. Cancer. 1989 Sep 15;64(6):1195-202.