Original Article

Relationship between Thickness of Early Oral Tongue Carcinoma (T₁, T₂) 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 metastasis. 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 Otolaryngology-Head & Neck Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for 18 months. Thirty patients with early oral tongue carcinoma i.e. T₁ & T₂ 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 metastasis.

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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 India¹. 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 indicators⁵.

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 thickness². 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 mass⁶.

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 metastasis². 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 important⁵,⁸.

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 alone⁹. 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.\textsuperscript{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.\textsuperscript{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 \textgreater 4 mm in thickness as they mostly have latent metastasis.\textsuperscript{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.\textsuperscript{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 purposeful non-randomized sampling technique. Sample size for the study was determined by $n = \frac{(u + v)^2 \sigma^2}{(\mu - \mu_0)^2}$.

**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 lymphnodes (if any visible or palpable lymph node and their level & number), were sent for histopathological 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 >4 cm & 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.
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 (T₁, T₂) 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). Majority (66.7%) of the study population were male and 33.30 % were female. (Figure-2)

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)

**Table I**: Distribution of study subjects according to histopathological findings (N=30)

| Thickness of tumor in mm | Number of patients after histopathological assessment | Number of patients with positive lymph node in neck | Percentage (%) |
|--------------------------|------------------------------------------------------|---------------------------------------------------|----------------|
| <2                       | 7                                                   | 0                                                 | 0%             |
| 2-4                      | 4                                                   | 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 | p-value |
|----------------------|----------------------|--------|---------|
| Mean ± SD            | Positive (n=19)      | Negative (n=11) |         |
| 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<sub>1</sub>, T<sub>2</sub>) with neck node metastasis. For this study, a total number of 30 cases of early oral tongue carcinoma (T<sub>1</sub>, T<sub>2</sub>) that has the inclusion criteria were enrolled as a study sample.

In, this study clinically stage of tumor was categorized as T<sub>1</sub> and T<sub>2</sub>. Majority of the incidence were reported 60% in T<sub>2</sub> stage. Clinically staging done according to length (according to AJCC, 2016)<sup>19</sup>. 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<sub>1</sub>N<sub>0</sub>, T<sub>1</sub>N<sub>1</sub>, T<sub>2</sub>N<sub>0</sub> and T<sub>2</sub>N<sub>1</sub><sup>19</sup>. Tumor staging according to thickness or depth of invasion crucial for the management prognosis of early oral carcinoma. Many studies have used the terms thickness or depth of invasion synonymously.<sup>2</sup>

Our study shows majority subject in T<sub>2</sub>N<sub>1</sub> (40%) stage and T<sub>1</sub>N<sub>1</sub> (33.3%). Previous studies have shown the tumor thickness is the important prognostic factor in treatment of patients of early oral tongue carcinoma (T<sub>1</sub>, T<sub>2</sub>)<sup>20</sup>.

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<sup>16</sup>.

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. 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.

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 than female. Almost similar to the findings observed by the various investigators from different countries.

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.

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).

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. Jetley et al. (2017) observed the favored smoking method was bidi and cigarette. 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. 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.

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%. 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.
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.

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. Hu et al. (2015) found that the tumor thickness is a more reliable method for neck node metastasis than tumor volume.

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).

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.

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. 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. 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.

**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.
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