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ORIGINAL RESEARCH

Tumor thickness and its correlation with nodal disease in early squamous cell carcinomas of tongue

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ABSTRACT
Squamous cell carcinomas of tongue is one the most malignancies seen in the South-East Asian region. It is related to chewing a combination of tobacco mixed with betel leaves, areca nut, and lime shell called quid. As it is most commonly due to substance abuse and affects younger population, it has tremendous economical and social consequences. Surgery is the most successful modality of management in these patients when presented early. Many of the patients present with partial to complete ankyloglossia with superadded trismus making the assessment and treatment difficult. The surgery involves wide excision of the diseased tongue and neck dissection, unilateral or bilateral based on the location of the tumor. Tumors of midline or those crossing the midline are dealt with bilateral nodal dissection. Neck dissection is associated with certain morbidities, but is routinely practiced in some centers like ours. We have attempted to evaluate the occurrence of the nodal disease in relation to the thickness of the tumor in cases of early cancers of tongue mostly lateral border disease (stage I and II). We have used ultrasound of the lesion as our modality to assess the tumor thickness preoperatively. AJCC 7th edition was used to assess the clinical and pathological stage of the disease. We have studied 72 patients of early tongue squamous cell carcinoma, and we observed that tumors thicker than 7mm (p-0.05) had highest co-relation with nodal metastases. This study also recommends that neck dissection should be prophylactically performed for tumors thicker than 4mm. Tumor characteristics such as grade, perineural invasion, and lymphatic invasion should be considered as predictors for early nodal involvement.

Key words: Tumor thickness, nodal metastasis, tongue squamous cell carcinoma, neck dissection, early-stage oral cancer

INTRODUCTION

Squamous cell carcinoma of the tongue accounts for 5-8% of all cancers of the oral cavity in North America and Western Europe. It occurs more often in men, with a male:female ratio of 3-4:1, and most commonly in the 7th or 8th decade of life. The incidence of carcinoma of tongue is much higher in Asia. In Southeast Asia, the disease is the second most common form of oral cavity cancer. In India, carcinoma of tongue is the second most common cancer in men and the number is increasing in women. The higher rate of tongue carcinoma in Asia is likely related to the widespread practice of betel nut chewing. Betel nut, composed mainly of the fruit of the Areca Palm and often mixed with tobacco (guthka), is placed along the floor of the mouth to induce a feeling of euphoria. Tongue cancers related to tobacco chewing tends to develop at an earlier age, with most cases occurring between the ages of 40-50 or even earlier. Trauma due to sharp teeth/dentures is second most common cause. Betel nut chewing results in sharp teeth and eventually can cause traumatic tongue ulcers and cancer. Early lesions are usually discrete and exophytic or ulcerative. As they enlarge, they penetrate the underlying muscles of the tongue and eventually extend to the base of the tongue or floor of the mouth. Peripheral growth occurs into the floor of the mouth and eventually onto the gingiva and into bone. The lymphatic spread is first to the level I and level II nodes. The incidence of positive nodes on

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admission is 9% to 31%, and the risk of occult disease is 16%. Small lesions produce the sensation of a lump that is felt on the tongue and inability to consume spicy food. Pain is an early symptom and increases when there is posterior extension to involve the nerves mainly painful swallowing and ear pain(referred pain). Extension inferiorly and posteriorly, when it involves the muscles of the voluntary muscles of the tongue genioglossus and myoglossus causes ankyloglossia resulting in difficulty in swallowing and salivary pooling. Small lesions (≤1 cm) may be excised with or without primary closure sometimes may be treated with radical Radiothearpy. Brachytherapy can also be done. Lesions 2 to 3 cm in size can be treated with surgery followed by radiotherapy depending on the depth of the tumor and nodal status. Larger lesions are usually treated with surgery, and postoperative adjuvant radiotherapy or chemoradiation. Myocutaneous flaps or free pedicled flaps or composite flaps are used when larger reconstruction are required. Tracheostomy and long-term tube feeds are generally required when we do composite resections and reconstructions. Speech therapy is mostly required based on disability.

AIMS AND OBJECTIVES:

This is a descriptive study with an aim:

- To evaluate the co-relation between the tumor thickness and incidence of cervical lymph nodal metastases in operated cases of early squamous cell carcinomas of tongue.
- To explore the utility of ultrasonography to assess the tumor thickness preoperatively.
- To describe the tumor characteristics and its influence over the nodal metastases.

MATERIALS AND METHOD

Seventy two consequent patients of early squamous cell carcinomas of tongue were considered for this study, which were proven by biopsy. Both male and female patients of T stage: cT1, cT2, cT3 and N stage: cN1, cN2a, cN2b were operated subsequently with pathological evaluation of T and N stage according to the AJCC 7th edition (fig: -1) [1]. Patients who had in-situ cancers and those who had received neo-adjuvant chemotherapy or radiotherapy to neck and the tumor or had previous neck surgeries were excluded from the study.

Fig 1: Squamous cell carcinoma of tongue lateral margin

Patients were assessed clinically at admission, clinical stage was assigned. Exclusion and inclusion criteria were applied. Preoperatively Trans-cutaneous high frequency probe ultrasound was used to elucidate the maximal tumor thickness in millimeters using a 10MHz superficial probe. Ultrasound examination of the neck was also done.

All patients were subjected to comprehensive neck dissection or functional neck dissection in the form of supra-omohyoid neck dissection.

Specimen was taken for grossing and pathological assessment was done to assess the tumor and its characteristics. Every attempt was made to include the entire tumor thickness in one slide. A microscope with mounted scale was used to measure thickness correct to 1mm. In those cases in which the tumor was **exophytic**, the most perpendicular section was measured from the surface to the deepest part (fig:2a - A to B). The keratin, parakeratin was not excluded. In **endophytic** lesions the tumor thickness is takenperpendicular from surface of invasive squamous cell carcinoma (A) to the deepest area of involvement(B) (fig:2b).The measurement was not done in tangential sections or in lesions. In **ulcerated** lesions measurements are taken from most lateral extent of invasive carcinoma(C) to the deepest area (fig:2c). Lymph nodes were assessed by routine histopathological examination. Size, number, presence of extra capsular spread was noted.

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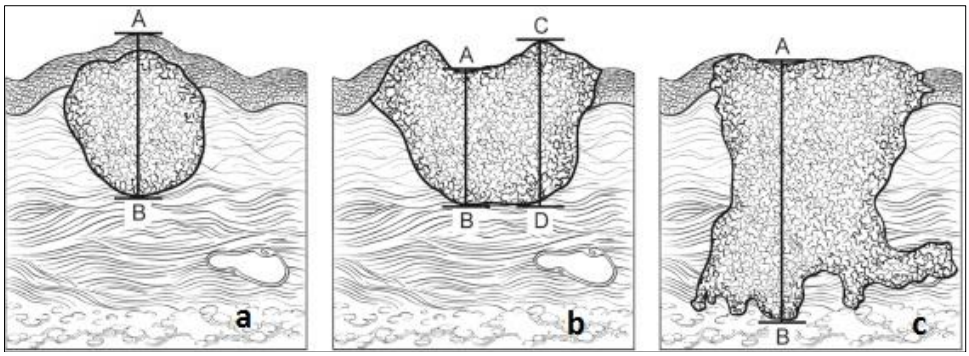

Fig 2: Methods for measurement of depth in different types of tumors

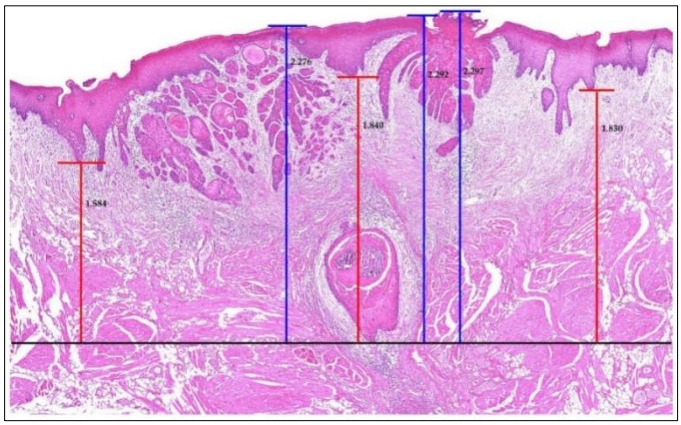

Fig 3:Depth of invasion and tumor thickness on histology of Squamous cell carcinoma of tongue
Blue Line: Tumor thickness.
Redline: Depth of invasion.

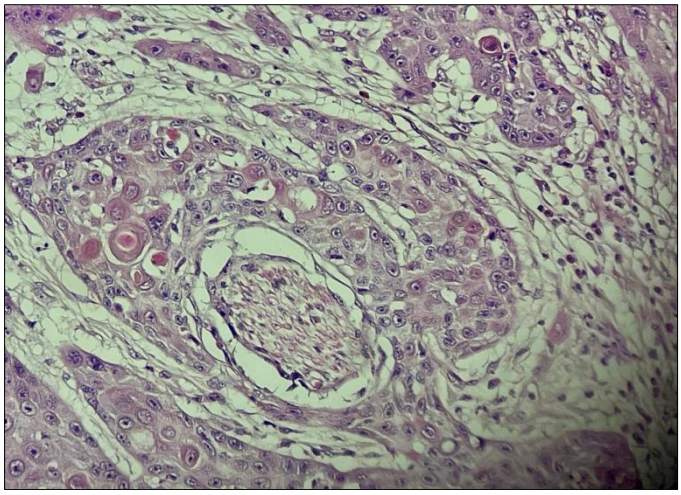

Fig 4: Histology of Squamous cell carcinoma of tongue demonstrating keratin pearls

OBSERVATIONS

We with the help of sonologists we got the preoperative ultrasound of the tongue lesion and the neck for these patients. Wide excision and comprehensive neck dissection was done for all the patients included in this study. Experienced onco-pathologists were involved to report the tumor thickness and the nodal involvement. They also reported about the additional characteristics of the tumor such as, grade, peri-neural invasion (PNI) and lympho-vascular invasion (LVSI) and types of muscle (smooth or skeletal) in the tumor bed. Features of the involved nodes such as number, size and perinodal spread was mentioned.

We observed that clinical T stage correlated quite well with pathologic T stage as it was seen that 6/72 patients were over-staged because of adjacent leukoplakia and 5/72 were under-staged as there was involvement of tongue muscles. While staging the N disease most correlated but for 8/72 were over-staged and 4/72 were under-staged. Ultra-sound of the lesion almost always revealed thicker tumor compared to

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histopathological thickness except in 4/72 patients where final histopathology showed thicker lesions.

When we correlated thickness of the tumor and its association with the nodal disease, we noticed thicker tumors had higher propensity for nodal disease. Other factors which influenced the nodal disease were grade of the lesion, PNI and LVSI and posterior tumors.

Using Student's T-test we found that the tumor thickness of 7mm correlated most closely with nodal disease ($p > 0.005$). We found nodal disease in lesions of thickness of 4-6mm in seven patients where the tumor was poorly differentiated.

CONCLUSION

We should be extremely careful before planning surgery for the patients with carcinoma of tongue. Pre-operative biopsy should always be performed as the surgery is mutilative and also pathologists should report about the grade and other high risk features of the tumor. Proper staging of the disease is extremely important. We recommend that patients who have tumors thicker than 4mm should undergo comprehensive neck dissection. Patients having thinner tumors and those who are not fit for surgery should undergo wide excision under local anesthesia andcan be strictly observed for local and nodal recurrencewhen they have low risk features. Patients who have tumors thick than 7mm and those having high risk features should be recommended for adjuvant radiotherapy.

DISCUSSION

Most authors substantially agree that tumor thickness is a significant parameter for predicting nodal metastasis development and for survival, the cut-off thickness is really quite variable, ranging from 1.5mm to 10 mm. Different measurement techniques and methods are adopted subject to availability form simple scale mounted microscope to calipers and optical micrometers. Woolgar and Scottreported different cutoff values for tumor thickness as related to the tumor site [2]. They found a higher incidence of nodal metastases in tumors that were 7.6-mm thick versus those that were 3.8-mm thick in the floor of the mouth, and 15.1-mm thick versus 9.6-mm thick in the tongue. A possible explanation might be related to the difference in the depth and caliber of the lymphatics at the two sites. Conversely, O'Brien found no differences among 145 cancers from different oral cavity sites, with a median tumor thickness that was similar for the tongue (6.4 mm), the floor of the mouth (6.6 mm), and other sites (5.7 mm)[3]. Mohit-Tabatabai and Spiro were the first authors to apply Breslow's hypothesis to link nodal involvement and tumor thickness and evaluated three thickness ranges <1.5 mm, from 1.6 to 3.5 mm, and >3.6 mm and found a metastases incidence of 2%, 35%, and 60%, respectively [4]. Statistical analysis revealed a significant link between thickness and metastasis in tumors >1.5-mm thick. As a consequence, they suggested performing modified neck dissection in cases of tumor thickness >1.5 mm and with no clinical nodal evidence. Spiro recommended neck dissection for tumors thicker than 2 mm for decreasing loco-regional recurrences and improving survival. Woolgar found a significant increase in nodal metastases and a worsening of survival for thickness of T2 lesions exceeding 8 mm. Among the articles we reviewed, very few authors used multivariate analysis to substantiate the importance of tumor thickness in patients with stage I-II carcinoma who had been surgically treated for the primary tumor alone. Asakage carried out a longitudinal, retrospective of stage I-II cancer of the tongue, who underwent hemiglossectomy, with no treatment for regional nodes. Tumor thickness was measured according to the technique described by Breslow[5]. Univariate and multivariate statistical analysis were applied. They found that a 4-mm cutoff was significant with regard to the development of nodal metastasis-free and disease-free survival. Thus, they suggested planning radical neck dissection on patients with stage I or II lesions thicker than 4 mm and having a G2-G3 Broder's grading. Kurokawa studied carcinoma of the tongue and found a significant increase in regional recurrences and a worsening of overall survival for tumor thickness exceeding 4 mm [6]. Moreover, only prospective studies can avoid the problems related to the lack of strict guidelines for processing the samples and measuring tumor thickness. Morton reviewed the data of 26 patients treated for early-stage tongue carcinoma. None had nodal clinical evidence, and the maximum diameter of the tumor was 30 mm (T1 and T2). All patients only underwent primary tumor surgical therapy, with a follow-up range of 12 to 60 months. They analyzed several parameters, such as grading, thickness, vascular invasion, perineural invasion, inflammatory reaction, and resection border involvement, and related them to the development of nodal metastases. Measurements were made from the base of the overlying epithelium or from the base of the ulcer to the deepest extent of the tumor. They found no relationship between tumor thickness and nodal metastasis or survival in patients whose tumors of the tongue were less than 30 mm in diameter. They believed that tumor thickness became more important when larger (T2-T4) tumors were taken into consideration. Conversely, they found perineural invasion to be a significant parameter. Giacomarra studied patients with tumors of any stage from various sites of the oral cavity and oropharynx, who underwent surgery on tumor and nodes. They found a link between thickness (7 mm) and nodal metastases, regardless of N status (N+ and N0) but not with occult metastases in the N0 neck. It must be pointed out that in this study the term "thickness" is considered a synonym for "depth of invasion",which indicates the part of the tumor below the line of the basal membrane[7]. Po Wing tried to apply the Martinez-Gimeno score to stage I-II carcinoma of the tongue.

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This was based on data from mixed groups of tumors of different stages from both the oral cavity and the oropharynx 8. Multivariate analysis revealed that when both the Martinez-Gimeno score and tumor thickness were included, only tumor thickness was an independent factor for predicting regional involvement. Repeating univariate analysis of the Martinez-Gimeno score with tumor thickness taken out demonstrated that there was no longer a significant link. This suggests that the predictive value of that scoring system in early-stage carcinoma of the tongue was mainly related to tumor thickness. Tumor thickness now seems to be acknowledged as a prognostic parameter in Oral Squamous Cell Carcinomas. Tumuluri studied the proliferating cell density (as expressed by the Ki-67 antigen) at the invasive tumor front and compared it with some known prognostic factors, including tumor thickness. They found a higher Ki-67 labeling index in tumors with an infiltrating depth of invasion greater than 5 mm [9]. Rahima tested the prognostic significance of perineural invasion (PNI) in oral and oropharyngeal carcinoma [10]. The depth of invasion was found to be linked to PNI, local recurrence, and survival, whereas it was not significant for regional recurrence or development of distant metastases. Studies of prognostic factors in patients with head and neck cancers almost invariably seem to recommend that the staging system should be changed or that a prospective, randomized trial is needed to clarify the issue once and for all. Howaldt proposed a modified pTNM staging in which three cutoffs of tumor thickness (5 mm, 10 mm, and 20 mm) were combined with the greatest tumor dimension to obtain the pT classification.

Shintani studied 24 patients, found a strong correlation between tumor thickness measured with US and histology [11]. They found that tumors thicker than 20 mm showed discordant results, possibly caused by tissue constriction during fixation with formalin. Lesions smaller than 10 mm showed significantly better correlation. Shintani also compared the accuracy of US and MRI in assessing tumor thickness. They found that US and MRI correlated well with histopathology. However, MRI could not identify most of the tumors less than 5.0-mm thick. Preda showed a significant direct correlation between the measured histological and measured MRI tumor thickness [12]. In a large clinical review by Pentenero, tumor thickness was shown to be an important parameter for predicting nodal metastases and for survival. They showed that in the literature the cut-off thickness predicting neck metastasis and survival varied from 1.5 mm to 10mm [13]. Thus, it remains difficult to choose a reliable cut-off point for elective neck treatment and/or adjuvant radiotherapy. The indication for elective neck treatment is mainly based on the expected risk of occult metastases. With respect to this risk assessment,retrospectively analyzed tumor thickness in 92 patients treated with surgery for tongue and floor of mouth carcinomas. They concluded that for clinically N0 oral cancer, elective neck dissection was indicated in patients with depth invasion of more than 2 mm because in these tumors the risk of metastases reached 40%. A meta-analysis by Huang showed an association between tumor thickness and cervical lymph node involvement and they stated that the optimal cut-off point for tumor thickness is 4 mm [14]. For oral cavity tumors thicker than 4 mm, prophylactic neck management should generally be recommended according to this study. At present, little is known about the correlation between tumor thickness and local recurrences of oral cavity carcinomas. In our study, there was no significant difference in local recurrences using the cut-off point for tumor thickness of more or less than 7 mm. Yuen showed that tumor thickness is prognostic for both nodal and local recurrence in oral carcinomas [15]. With a tumor thickness less than 3 mm, 0% had local recurrences and 8% had 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. In our series, not enough patients with tumor thickness of 10 mm or more were included to compare these results. Extracting the results from Spiro, local recurrence occurred in 5% of the group of tumors with thickness <2 mm (2/40), 9% (3/35) within the group 3-8mm thick and 25% (4/17) for the group with thickness >9 mm. Local recurrence occurred significantly more in the group with tumor thickness of more than 8 mm [16]. Yet more factors like perineural invasion, radical operation, postoperative treatment and N-staging should also be considered in relation to local recurrence.

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