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Original Research Article

Analysis of Histomorphological Features at Invasive Tumour Front in Tongue Squamous Cell Carcinoma

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Abstract

Oral cancer accounts for 3% of all malignant neoplasm's and is the eighth most common cancer in the world, with epidemiologic variations among different geographic regions. It causes substantial mortality and morbidity. Oral squamous cell carcinoma (OSCC) is of significant public health problem in India, and it accounts for approximately 30% of all cancers in the country. The objective of the present study was to compare individual histopathology parameters of malignancy between non-metastatic and metastatic SCC of the tongue to contribute to the identification of morphologic parameters associated with cervical metastasis that could serve as indicators of aggressiveness. We carried out a retrospective analysis of 69 patients with tongue cancer who had undergone wide excision and neck dissection. The histopathological characteristics of the tumour, such as, degree of tumour cell differentiation, depth of invasion, pattern of invasion, perineural invasion, and local host response were studied using standard statistical analysis to determine their association with neck nodal metastasis. The goal is to correlate these parameters with cervical metastasis to determine the optimal treatment for tongue cancer.

Keywords: Oral cancer; Pattern of invasion (POI); Aggressiveness.

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Introduction

Oral cancer accounts for 3% of all malignant neoplasms and is the eighth most common cancer in the world, with epidemiologic variations among different geographic regions. It causes substantial mortality and morbidity.[1-3] Oral squamous cell carcinoma (OSCC) is of significant public health problem in India, and it accounts for approximately 30% of all cancers in the country.[4] New cases are diagnosed each year, and >48,000 patients succumb to the disease yearly.[5] Cervical lymph node metastasis is the most well established prognostic factor in oral squamous cell carcinoma (OSCC). Cases with cervical lymph node metastasis show 50% decrease in survival and higher incidence of distant metastasis. The most important negative prognostic factor for

tongue cancer is the high incidence of neck nodal metastasis. Even in the early stages of tongue cancer, there is a high incidence of subclinical nodal metastasis.[6–8] Although, various published studies favours elective neck dissection in early-stage tongue cancers[7,9,10] there are no established protocol for when to perform radical surgery in these patients. Despite the large number of studies, the use of histological grading systems of malignancy as indicators of aggressiveness in oral SCC is still controversial. Hence, the objective of the present study was to compare individual histopathology parameters of malignancy between non-metastatic and metastatic SCC of the tongue to contribute to the identification of morphologic parameters associated with cervical metastasis that could serve as indicators of aggressiveness. The histopathological characteristics of the tumour, such as, degree of tumour cell differentiation, depth of invasion, pattern of invasion, perineural invasion, lymphovascularinvasionand local host responsewere studied using standard statistical analysis to determine their association with neck nodal metastasis. The goal is to correlate these parameters with cervical metastasis to determine the optimal treatment for tongue cancer.

Materials and Methods

The records of the Department of Pathology, Tertiary care Cancer Hospital, were searched to identify all patients with primary SCC of the tongue, registered for treatment during 2019. Total 69 patients who underwent both primary tumour resection and neck dissection (ND) were included in the analysis. Patients with recurrence of squamous cell carcinoma, those with prior history of chemotherapy and radiation therapy, inadequate tumour material, non-squamous malignancies of tongue, and those having multiple tumours were excluded from study.

Sections (5 μm) cut from paraffin-embedded tumour specimens and stained with hematoxylin and eosin were examined and reported in final histopathology reports for parameters including degree of tumour cell differentiation, depth of invasion (DOI), pattern of invasion (POI), perineural invasion (PNI), lymphovascularinvasion (LVI) and local host response (LHR). POI and LHR were assessed at the tumour-host interface.

According to Brandwein-Gansler et al.[11] there are two entities predominant pattern of invasion (PPOI) and worst pattern of invasion (WPOI). POI was determined by measuring POI at the tumour interface of each slide of the resection specimen. PPOI is the most common POI found; the WPOI is the highest score present, no matter how focal. We evaluated WPOI in our study. WPOI Type 1 was allocated to a tumour with broad pushing borders with smooth outline; WPOI Type 2 to a tumour with broad pushing "fingers"(Fig. 1); POI Type 3 (Fig. 2) was assigned to a tumour with invading islands with more than 15 cells per island; WPOI Type 4 (Fig. 3) to a tumour with invading islands with fewer than 15 cells per island, or single cell invasion; and WPOI Type 5 (Fig. 4) indicated tumour satellites of any size with a 1-mm distance of intervening normal tissue (not fibrosis) at the tumour-host interface including PNI and LVI outside tumour.

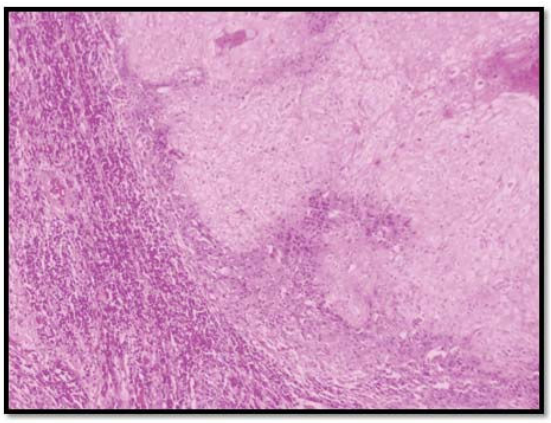


Fig. 1: Tumor With Broad Pushing "Fingers [WPOI II].

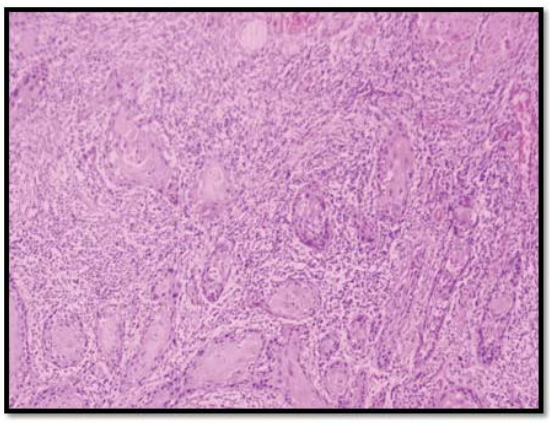


Fig. 2: Tumor With Invading Islands With More Than 15 Cells Per Island; [WPOI III].

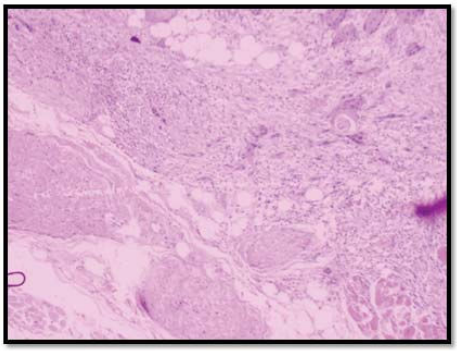


Fig. 3: Tumor With Invading Islands With Fewer Than 15 Cells Per Island, Or Single Cell Invasion [WPOI IV].

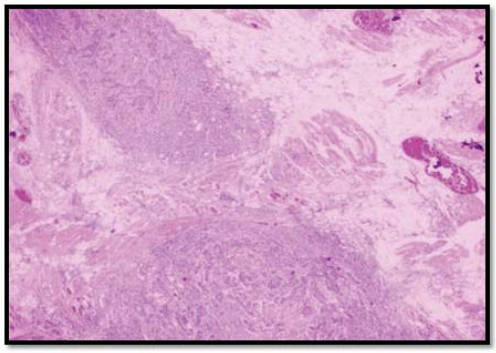


Fig. 4: Tumor Satellites Of Any Size With A 1-Mm Distance Of Intervening Normal Tissue (Not Fibrosis) At The Tumor-Host Interface. [WPOI V].

LHR was classified as Dense (Fig. 5), which was assigned when a continuous and dense rim of lymphoplasmacytic infiltration was present; Moderate when patches of lymphocytic infiltrates were present but discontinuous along the tumour-stromal interface; and Mild to minimal which was assigned for limited or no lymphocytic response.

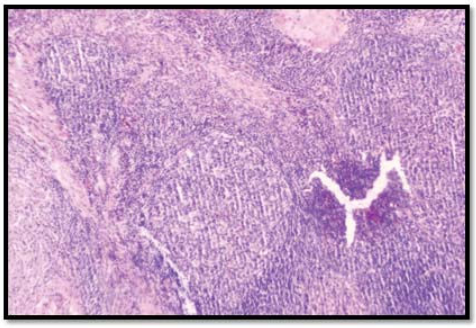


Fig. 5: Dense Local Host Response: Continuous and Dense Rim of Lymphoplasmacytic Infiltration.

According to Batsaki et al.[12] PNI was defined as tumour cell invasion in, around and through the nerves. Liebig et al.[13] in addition to the definition of Batsakis added "tumour in close proximity to nerve and involving at least 33% of its circumference or tumour cells within any of the 3 layers of the nerve sheath." We considered PNI as positive on finding tumour cells in the perineural space or epineurium (Fig. 6).

DOI was measured as the invasive part of the tumour extending below the basement membrane of the adjoining unremarkable mucosa to the pointofdeepest invasion[14].

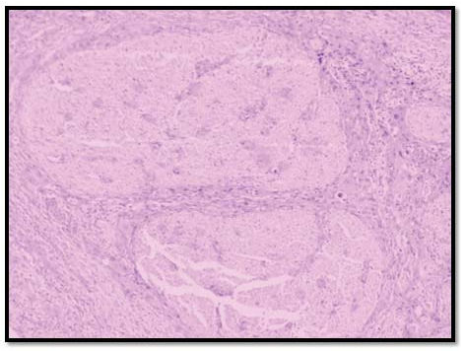
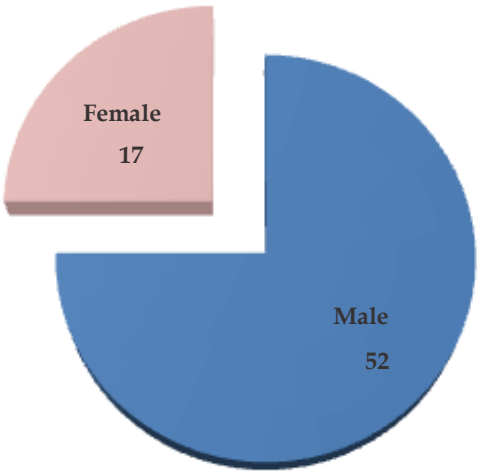


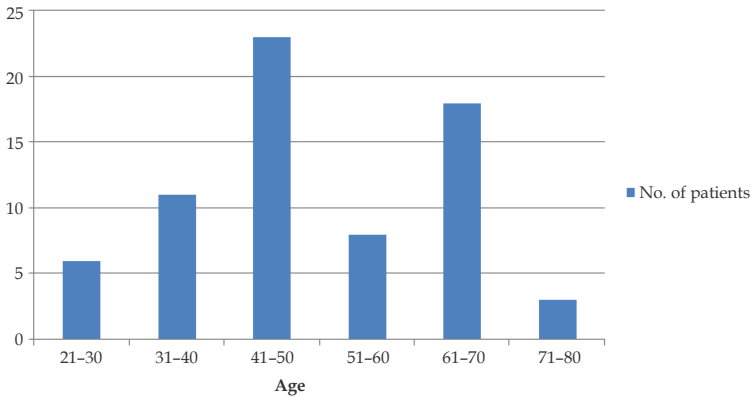
Fig. 6: Perineural Invasion-Complete Encirclement of Nerve.

Statistical analysis

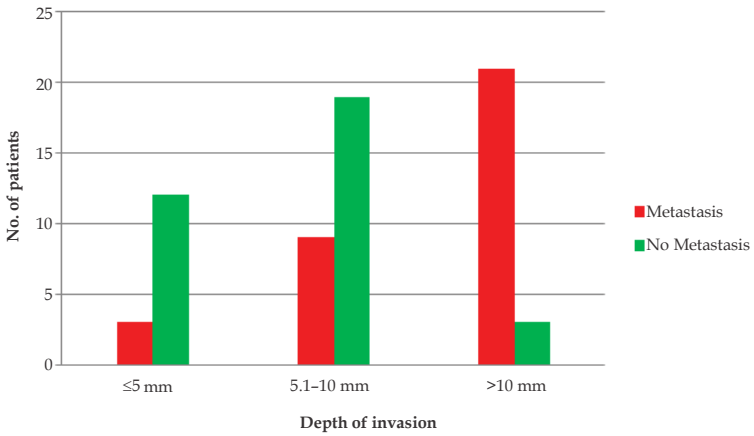
Univariate analysis with Fisher exact test and Chi-square test were used to assess the variables in predicting lymph node metastasis. The factors then entered into multivariate analysis using multiple logistic regression model to detect independent predictors. All tests were two sided with significance considered at $p < 0.05$. Statistical analysis done by using SPSS software (SPSS Inc. Chicago, IL).



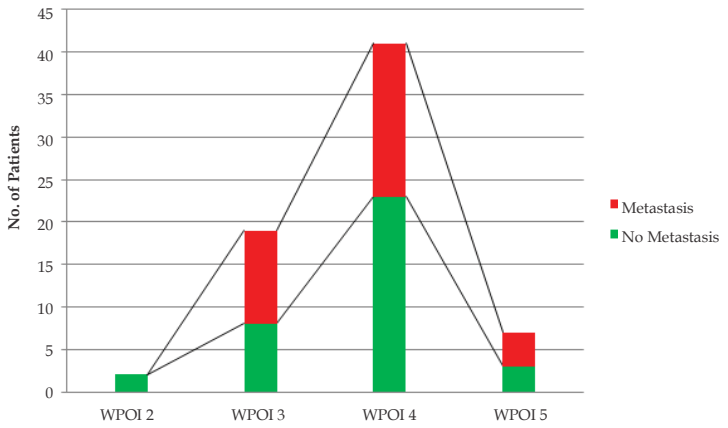
Graph 1: Sex wise distribution of cases.



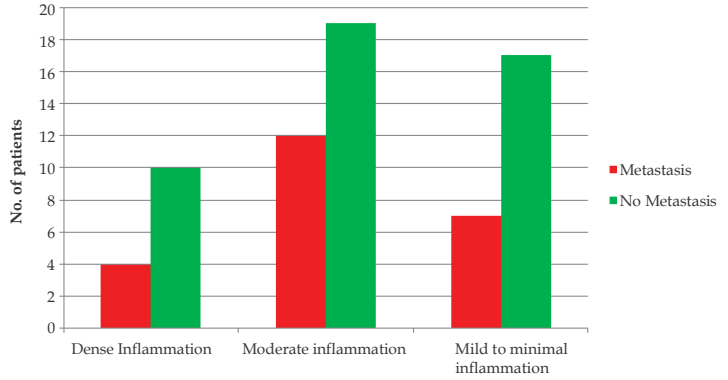
Graph 2: Age wise distribution of cases



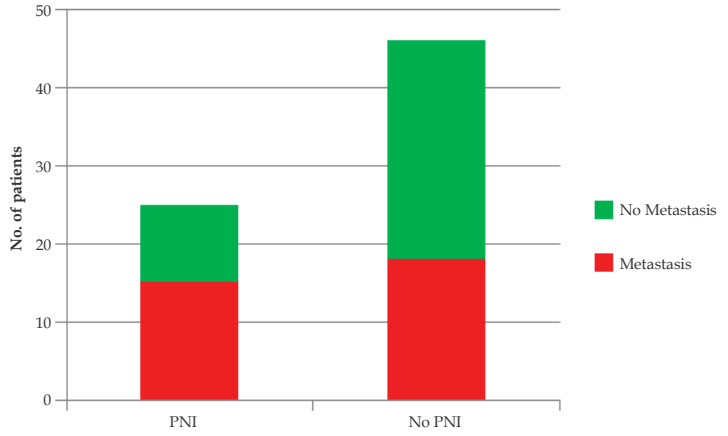
Graph 3: Association of depth of invasion (DOI) with cervical metastasis



Graph 4: Distribution of cases of different WPOI and correlation with cervical metastasis.



Graph 5: distribution of cases of different local host reaction and correlation with cervical metastasis.



Graph 6: distribution of cases of different PNI and correlation with cervical metastasis.

Results

Among total 69 patients 52 were males and 17 were females. Youngest age amongst these patients was 20 years and 77 years was oldest.

Worst pattern of invasion 1 was not seen in any of the patients included in study. Two patients were having worst pattern of invasion 2 i.e. tumour with broad pushing fingers.

Pattern 4 was most common patterns amongst all patterns; 31 patients were having pattern 4; 19 patients were havingworst pattern of invasion 3 and worst pattern of invasion 5 was seen in total 7 cases.

Perineural invasion was seen in 25 patients.

Local host response i.e. lymphoplasmacytic infiltrate at tumour host interface was classified as mild, moderate and dense lymphocytic infiltrate. Moderate lymphoplasmacytic infiltrate was most common followed by mild lymphoplasmacytic infiltrate.

33 out of 69 cases showed cervical metastasis on histopathological examination. Worst pattern of invasion 4 was found to be most commonly associated with lymph node metastasis; this finding was attributed to more number of cases with pattern 4.

Univariate and multivariate analysis

The correlation of nodal metastasis and depth of invasion (DOI), worst pattern of invasion (WPOI), local host response (LHR)and Perineural invasion (PNI) were evaluated using appropriate statistical analysis. Statisticaly significant correlation was found only with DOI ($p < 0.001$). Other parameters did not exhibit a significant correlation with lymph node metastasis.

Multivariate analysis

The correlation of nodal metastasis showed that independent variable for predicting lymph node metastasis is DOI only (odds ratio [OR] = 12.53, 95% CI = 0.006–0.331; $p = 0.002$). All the other parameters did not show statistically significant correlation.

Discussion

Oral SCC accounts for about 40% of total cancer-related deaths in some regions of Asia. In India, it is the commonest cancer in males. It mostly occurs in male individuals after the fifth decade of life. The age at presentation ranges from the fifth to the sixth decade[5,15] concordant with our study with male preponderance and most common decade being fifth decade. Tongue squamous cell carcinoma are most common among oral cancers. We chose to study tongue SCC because it has features like abundantmuscle bundles, lymphatics and rich neural network, which influence tumour spreading. Hence tongue SCC shows more metastasis and less favourable prognosis. Number of studies in literature hypothesized that histomorphological parameters can be used to prognosticate oral SCC. For oral cancer, a histopathological grading system of the ITF was firstly introduced by Bryne et al. in 1992.[16] These parameters seggregate high risk groups and need of Neoadjuvant chemotherapy can be calculated. An appealing feature of ITF assessment is that it is based on the examination of the H&E-stained slides, it can be performed easily as a part of routine histopathological examination, the results are fairly reproducible and without added cost. Later, Brandwein–Gansler 11 proposed multiparametric histologic risk assessment (HRS) model with oral SCC, on the basis of worst POI, lymphocytic host response and PNI. Score predicted local recurrence, overall survival of patients, and differentiated two catagories; 1) High risk casesrequire multimodal and aggressive treatment while 2) Low risk cases havefavourable outcome. Lymph node metastasis is considered as an independent poor prognostic factor for OSCC. Histological examination of the excised cervical LNs is the gold standard to detect the presence of LN metastasis. However, clinical examination and radiological investigations like computed tomography scan is routinely used to search LN metastasis, with variable sensitivity. Many studies has shown that these histomorphological parameters can predict lymph node metastasis in OSCC.

Worst pattern of invasion

Studies on oral SCC by Lundqvist et al.,[17] Kane et al.[18] and Yeun et al.[19] did not find any correlation of POI with lymph node metastasis, similar to our observation. The study by Lundqvist comprised all stages of oral tongue SCC and used only biopsy specimens, whereas the Kane et al. had a small sample size ($n = 48$), which may have influenced their findings. On the contrary Lim et al.[20] reported that Grade 3 or Grade 4 mode of invasion independently predicts late cervical metastasis in Stages I and II of oral SCC. Hiratsuka et al.[21] found that POI was the most significant predictor for occult lymph node metastasis. According to Aditi-Nuzhat et al.[22] cutoff for POI was Type 3, and it predicted lymph node metastasis with a sensitivity and specificity of 87% and 86%, respectively. Spiro et al.[23] and Odell et al.[24] showed that POI 3 or 4 at the tumour host interface were associated with an increased incidence of local and distant metastasis

Perineural Invasion

Kane et al[18]applying stringent selection criteria, and standard pathological evaluation methods, this retrospective study aims to establish histological predictors of subclinical cervical node metastasis in early (T1-T2/N0, Lim et al.[20] and Yeun et al.[19]

did not find correlation of PNI with LN metastasis in patients with early-stage OSCC. Our study also did not elicite significant correlation of LN metastasis with PNI. However, Results of various studies have highlighted that PNI is a significant and independent predictor for local and distant metastasis, and is associated with poor overall survival SCC. Martinez-Gimeno et al.[25] found that a tumour with PNI showed 54.5% rate of metastasis as compared with 32.8% in those without PNI and reported that PNI is a significantly important risk factor for cervical lymph node metastasis in patients with oral SCC. Aditi-Nuzhat et al.[22] found that the presence of PNI independently predicts lymph node metastasis with a sensitivity of 85% and specificity of 83%.

Local Host Response

This study did not find significant correlation between localhost response and LN metastasis, lymph node metastasis was 29% with mild, 38% with moderate and 28% with dense host response. Martinez-Gimeno et al.[26] found no significant correlation with inflammatory cell infiltrates and cervical lymph node metastasis when the degree of inflammatory reaction was divided into light, moderate, and intense, even though lymph node metastasis was 55.8% in specimens with light inflammatory infiltration, 30% in specimens with moderate inflammatory infiltration, and 27.2% in specimens with high inflammatory infiltration. Similarly, Yeun et al.[19] and Kane et al.[18] applying stringent selection criteria, and standard pathological evaluation methods, this retrospective study aims to establish histological predictors of subclinical cervical node metastasis in early (T1-T2/N0 also did not find correlation of lymphoid response with lymph node metastasis. However, in study by Aditi-Nuzhat et al.[22] lymphoid response at the tumour-host interface was found to be an independent factor predicting lymph node metastasis in early-stage OSCC. The chances of lymph node metastasis was found to be 1.56 times higher in pattern 3 than in lower patterns. Similarly, Hiratsuka et al.[21] reported that the degree of lymphocytic infiltration predicts occult lymph node metastasis in oral SCC. In the study by Lundqvist et al.[17] on oral SCC, the authors found that dense lymphocytic host response was associated with complete response to therapy. Brandwein-Gensler et al.[11] reported that lymphocytic response shows significant correlation with local recurrence and poor overall survival.

Conclusion

- These facts point to the immediate need for new diagnostic/prognostic strategies to improve the clinical decision-making and the management of patients.
- Although, tumor size, depth of invasion and margin status are important for prognostication, assessment of invasive tumor front (ITF) can give added value in predicting mortality and morbidity. Further research and studies might be helpful in this area to look for tumour aggresiveness and high risk patients group.
- Attractive features of invasive tumour front analysis includes that there are no extra processing charges to lab and analysis can be done on routine H and E stained slides, results are reproducible and there is no extra cost to patient.
- Therefore, PNI, POI and LHR though not included in AJCC staging, should be included in standard reporting and are important in prognosis and management of SCC of tongue.
- Limitations of this study includes reterospective analysis, heterogenous sample (includes stage T1-T4) and no clinical follow up of patients therefore this study could not include late cervical metastasis.

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