Relationship between Tumor-stroma Ratio and Cervical Lymph Node Metastasis in Oral Squamous Cell Carcinoma

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Abstract

Background: Regional metastasis of oral squamous cell carcinoma most likely occurs in cervical lymph nodes. The tumor-stroma ratio describes the proportion of stroma in comparison to the neoplastic cells at the deepest invasive front of tumor. There is no available data on the relationship between tumor-stroma ratio and cervical lymph node metastasis.

Objective: To assess correlation between tumor-stroma ratio and cervical lymph metastasis in oral squamous cell carcinoma. Methods: This cross-sectional analytic study was carried out in Oral and Maxillofacial Surgery Department of Bangladesh Medical University. A total of 25 oral squamous cell carcinoma patients were enrolled by purposive sampling. The sample size was calculated using a two-sided exact test with a 5% significance level and 80% power. Tumor-stroma ratio was categorized as high tumor-stroma ratio >50% (stroma poor) and low tumor stroma ratio <50% (stroma rich). The number of metastatic lymph nodes was calculated after neck tissue histology. Descriptive statistics and Pearson correlation was obtained between the tumor-stroma ratio and cervical lymph node metastasis.

Results: The mean age of the participants was 56.68 (±9.10) year. Among all, 68% was female and 32% was male. Most of the oral squamous cell carcinoma were located on buccal mucosa (56%). The mean tumor-stroma ratio was 53.12 (±6.45). Low tumor-stroma ratio was reported in 36% cases and high tumor-stroma ratio was reported in 64% cases. Cervical lymph node metastasis was reported in 32% case. A significant relation was found between cervical lymph node metastasis and tumor stroma ratio (R = -0.6142 and p = 0.001).

Conclusion: Tumor-stroma ratio showed a significant association with lymph node metastasis. TSR can be used to evaluate the prognosis of patients with oral squamous cell carcinoma and may help to consider the treatment plan accordingly.

Keywords: Oral Squamous Cell Carcinoma, Tumor-Stroma Ratio, Cervical Lymph Node, Metastasis.

Introduction

Oral cancer encompasses the cancer affecting the lips, tongue, palate, and other areas of the oral cavity, as well as the oropharynx. It is the 13th most common cancer worldwide [1]. Histologically, OSCC makes up more than 90% of all types of oral cancers (Aaboubout et al., 2021). Among all OSCC, buccal mucosa accounted for 59.9% is the most common site and 49% patients with OSCC involving buccal mucosa manifest with occult metastases in the cervical lymph nodes [2,3].

The cervical lymph nodes metastases in oral cancer, is considered as the most reliable independent prognostic marker, reducing

a patient's survival rate by half [4]. Regional metastasis is an important predictor of overall survival in patients with OSCC [5]. Several factors can influence the rate of metastasis and survival in OSCC, including tumor size, location, grade, T stage, and various biological tumor markers [6]. Although, histopathological features like surgical margins involvement, depth of invasion (DOI), lymph vascular invasion (LVI), and more recently the tumor-stroma ratio (TSR).

The Tumor-stroma ratio describes the proportion of stroma in comparison to the neoplastic cells at the deepest invasive front of tumor. The analysis of such cellular and stromal features of the invasive tumor front can be utilized to presume prognostic value in addition to the TNM staging [7]. Previous studies have shown that stroma rich tumor morphology negatively impacts the prognosis of oral, esophageal, breast, endometrial, ovarian epithelial, cervical, and colorectal cancers [8,9].

Therefore, tumor-stroma ratio could be an important histological factor for predicting occult cervical lymph node metastasis in OSCC [10]. The aim of this study was to analyze the relationship of TSR with cervical lymph node metastasis to provide appropriate ground for therapeutic decision making.

Material And Methods

This cross-sectional analytic study was conducted in the Department of Oral and Maxillofacial Surgery, Bangladesh Medical University, Dhaka, over one year (September 2023–August 2024). The sample size was calculated using a two-sided exact test with a 5% significance level and 80% power. Twenty-five histopathologically confirmed OSCC patients were enrolled using purposive consecutive sampling based on predefined eligibility criteria. Data were obtained from patient history, clinical examination, and histopathology reports. Tumor-stroma ratio was categorized as high tumor-stroma ratio >50% (stroma poor) and low tumor stroma ratio <50% (stroma rich). Cervical lymph node metastasis rate was also calculated. Statistical analysis was performed using SPSS version 26, applying descriptive statistics, Chi-square tests, and Pearson correlation, with significance set at p<0.05. Ethical approval was obtained from the IRB, Bangladesh Medical University and informed written consent was taken from all participants.

Results

The mean age of the patients was 56.68 (±9.10) years. Among the 25 participants, 17 (68%) were female and 8 (32%) were male. Most of the OSCC were located on the buccal mucosa (56%) (Figure 1). The mean TSR was 53.12 (±6.45). Low TSR was reported in 36% cases and high TSR was reported in 64% cases. No cervical lymph node metastasis was found in 17 (68%) patient and 8 (32%) patient was reported at least 1 positive lymph node. The mean lymph node metastasis rate was 14.75 (±9.81). There was no significant relation between age group and TSR (P = 0.973) or between sex and TSR (p = 0.431). But a strong and significant relation was found between cervical lymph node metastasis and TSR (p-value 0.00002). A significant relation was also reported between PNI and TSR (p-value 0.0055). However, no significant relation was found between tumor grading and TSR (P = 0.1317). Pearson correlation analysis revealed a strong significant negative relationship between TSR and the cervical

lymph node metastasis rate (R = -0.6142, p = 0.001). This indicates that higher TSR scores tend to be associated with lower cervical lymph node metastasis rates, and vice versa.
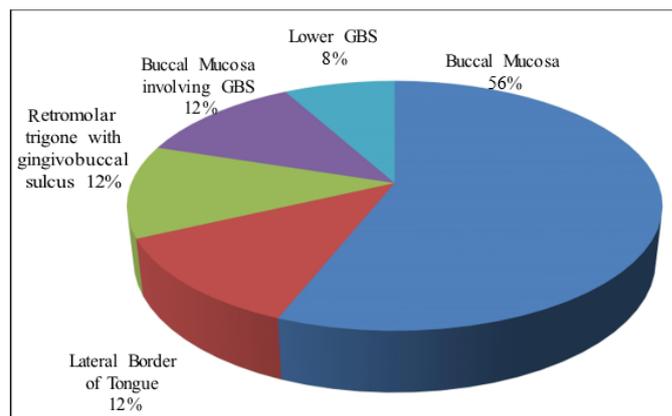

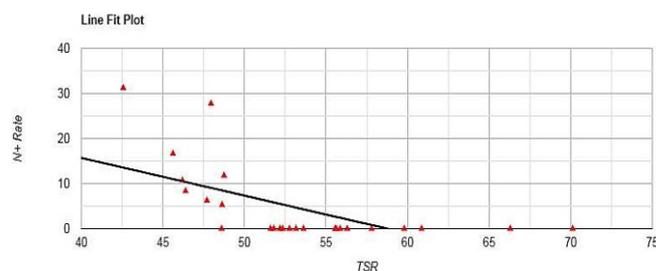**Figure 1:** Distribution of OSCC according to sites of oral cavity (N=25)

Figure 2: Linear association between TSR and cervical lymph node metastasis.

Table I. Distribution of lymph nodes in participants (N=25)

Distribution of lymph nodes in study participants			
Node positive (n=8)	Total excised nodes	Positive node	Node density
Mean SD	18 ±4.56	2.62 ±1.68	14.75 ±9.81
min-max	12-28	1-5	5.26- 31.25
Node negative (n=17)			
Mean SD	18.82 ± 6.68	0	0
min-max	12-37	0	0

*Significant at p < .05

Table II: Relation of TSR with demographic variables and cervical lymph node metastasis (N = 25)

	Low TSR (N=9)	High TSR (N=16)	Total (N=25)	
Variable	N (%)	N (%)	N (%)	p*
Age (Years) < 60	5 (20%)	9 (36%)	14 (56%)	0.9732
≥ 60	4 (16%)	7 (28%)	11 (44%)	
Sex Male	2 (8%)	6 (24%)	8 (32%)	0.4318
Female	7 (28%)	10 (40%)	17 (68%)	

Cervical LN Metastasis Present	8 (32%)	0	8 (32%)	0.00002*
Absent	1 (4%)	16 (64%)	17 (68%)	

*Significant at p < .05

Table IIII: Relation of TSR with Clinicopathological characteristics (N = 25)

	Low TSR (N=9)	High TSR (N=16)	Total (N=25)	
Variable	**N (%)**	**N (%)**	**N (%)**	**p***
PNI Present	5 (20%)	1 (4%)	6 (24%)	0.0055*
Absent	4 (16%)	15 (60%)	19 (76%)	
Anne Roth Grading Grade 1	1 (4%)	6 (24%)	7 (28%)	0.1317
Grade 2	8 (32%)	9 (36%)	17 (68%)	
Grade 3	0	1 (4%)	1 (4%)	

Discussion

Cervical lymph node metastasis is a crucial factor that can affect disease prognosis. If cervical node metastasis can be predicted, treatment planning and outcome would be better. The proliferative activity and morphological properties of the tumor stroma in the invasive tumor front could be considered as important predictors of cervical node metastasis in oral cancer [11,12]. Therefore, the possible relationship between tumor stroma ratio and cervical lymph node metastasis was discussed with greater attention in recent studies [13,14].

The present study reported that most of the patient were found without cervical lymph node metastasis and the mean lymph node metastasis rate was 14.75 (±9.81). Similar observations were also reported by different other studies [15-17]. According to present study high TSR was reported in most of the case. All the patients with cervical lymph node metastasis (8/8) were stroma-poor in this present study. Observation of this present study was supported by previous studies [15,17,18].

In this study, no significant relation between age group and TSR (P = 0.973) or between sex and TSR (p = 0.431) was found. This observation was also supported by previous studies [16,17]. Almangush et al. reported no significant association (P > .05) between TSR and other clinic-pathologic factors, including sex, tumor size and histological grade [13]. Rani et al. also found no significant correlation between TSR and grade of the tumor, lymph node metastasis, lymph vascular invasion and perineural invasion [19]. But a strong and significant relation between cervical lymph node metastasis and TSR was found in this present study (R = -0.6142 and p = 0.001). Moreover, a significant relation between PNI and TSR was also reported (p = 0.005). Similar result was reported by Obayashi et al. and Wang et al. [18,20]. They also showed that there was a significant relationship between the cervical node metastasis and TSR. Furthermore, they also found a strong correlation between the PNI and TSR.

This present study focused on histopathological features that can be found in Hematoxylin and Eosin-stained slides of invasive tumor front and as well as in resected cervical lymph nodes. Invasive tumor front reflects morphological features that demonstrated prognostic value of the cancer. A high proportion of stroma or low TSR in the invasion front had significant association with worse clinical outcome and thus considered as adverse prognostic factor in OSCC. Verma et al. suggested that assessing TSR is a good reproducible technique and hence, recommended it as a reliable independent prognostic indicator in OSCC [16]. Almangush et al. also advocated TSR as a prognostic indicator beside the common clinic-pathological parameters [13].

The observations of this study indicate that TSR is a powerful prognosticator and an important parameter in outcome prediction. In accordance with previous study, the present study on OSCC also showed that TSR has the potential prognostic value. Besides, the laboratory procedure of TSR is also cost-effective, reliable, and requires minimum effort from the pathologist. The present findings should be validated in independent large multicenter cohorts to allow for consideration of TSR in clinical decision making.

Conclusion

In this present study, TSR showed association with cervical lymph node metastasis and perineural invasion. However, any significant relationship cannot be established between TSR and age, sex, site and grade of the tumor. TSR is highly reproducible and reliable. Thus, TSR can be used to assess the prognosis of OSCC and may help to consider the treatment plan accordingly.

Author Contributions

All authors declared equal contribution to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Conflict of Interest

All authors declared that there is no financial interest or any conflict of interest.

Ethical Approval

Ethical approval was obtained from the IRB, Bangladesh Medical University and informed written consent was taken from all participants. All procedures performed in the study were in accordance with the ethical standards of the institutional guidelines and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed written consent was taken from all participants.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

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