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ORIGINAL ARTICLE

ROLE OF TUMOR-STROMA RATIO IN ORAL SQUAMOUS CELL CARCINOMA – A CROSS SECTIONAL STUDY

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is one of the most common oral cancers. Tumor microenvironment plays a significant role in the initiation and progression of OSCC. The interaction of malignant epithelial cells and the tumor environment modulates angiogenesis, epithelial mesenchymal transition, and tissue invasion. The present study aimed to evaluate tumor-stroma ratio in oral squamous cell carcinoma and correlate it with the clinico-histopathological features.

Materials and methods: 64 histopathologically confirmed cases of OSCC were included in the study. Tumor stroma ratio (TSR) was evaluated at the invasive tumor front and grouped as stroma-rich and stroma-poor. The TSR was compared with tumor grade, clinicodemographic details, lymphovascular invasion, perineural involvement, and nodal metastasis. Statistical analysis was performed with SPSS software 23.

Results: Most of the cases of well-differentiated OSCC showed stroma-poor TSR, and poorly differentiated OSCC showed stroma-rich TSR; this correlation was statistically significant ($p = 0.033$). It was noted that the stroma-rich TSR cases tend to have a higher incidence of lymphovascular invasion and nodal metastasis when compared to stroma-poor cases. Stroma-rich TSR also showed a significant correlation with perineural invasion ($p=0.045$).

Conclusion: The ratio of tumor and stroma at the invasive tumor front reflects the biological behavior of the OSCC. Evaluation of TSR might help in better treatment planning of patients with OSCC.

Keywords: oral, OSCC, cancer, tumor stroma ratio, invasion

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common head and neck cancer, and is characterized by its invasive potential and ability to metastasize to distant sites¹. OSCC arises from the mucosal lining of the oral cavity and poses a major public health challenge, particularly in areas where

tobacco use and betel quid chewing are prevalent². Key risk factors for OSCC include the consumption of tobacco and alcohol, which together amplify the risk of cancer development^{3,4}. Other contributing factors include infection with high-risk strains of human papillomavirus (especially HPV-16), chronic irritation, poor oral

hygiene, and nutritional deficiencies⁵. Despite the advancements in diagnosis and treatment, OSCC patients are often diagnosed at a late stage. Based on the Global Cancer Statistics 2022 and data from the GLOBOCAN database, which analyzed 36 types of cancer across 185 countries, about 20 million new cancer diagnoses and 9.7 million cancer-related deaths were reported globally⁶. Lip and oral cavity tumors rank 16th with 389,485 new cases worldwide⁶. This highlights the increasing global health threat posed by this cancer, and the importance of targeted public health strategies. Furthermore, all forms of SCC have the potential to invade nearby tissues and spread to other parts of the body, making early diagnosis and effective treatment essential for better patient outcomes.

Recent research has focused on the tumor microenvironment (TME), the complex network of surrounding connective tissue cells and molecules, which significantly influences tumor growth, immune system evasion, and the spread of cancer⁷. Tumor-associated alterations in the extracellular matrix (ECM) include enhanced ECM production and proteinase remodeling of ECM proteins, such as matrix metalloproteinases (MMPs), which mostly caused by cancer-associated fibroblasts that have been stimulated by the tumor microenvironment⁸. The TME comprises of various cellular and non-cellular components, including reprogrammed stromal cells, immune cells, extracellular matrix proteins, and signaling molecules. Stromal cells within the TME, such as cancer-associated fibroblasts (CAFs), endothelial cells, pericytes, and immune suppressor cells, actively interact with tumor cells to support carcinogenesis. These interactions are facilitated by cytokines and growth factors that promote angiogenesis, epithelial-mesenchymal transition (EMT), and tissue invasion. Chronic inflammation within the TME further drives tumor progression by recruiting immunosuppressive cell types such as regulatory T cells (Tregs), M2 macrophages, neutrophils, which suppress anti-tumor immune responses⁹. Thus, the stromal component is no longer viewed as a passive scaffold but as an active participant in malignancy. Tumor-stroma ratio (TSR) describes the ratio of tumor and the adjacent stroma in the invasive tumor front. Tumors are classified as stroma-rich (>50% stroma) or stroma-poor (<50% stroma)¹⁰. Research indicates that cancers with high stromal content, or low TSR, tend to have worse prognosis in various cancer types, including colorectal, breast, and esophageal cancers¹¹.

Therefore, evaluating the TSR in OSCC can provide valuable prognostic information and may help in personalized treatment approaches. The present study aimed to evaluate tumor-stroma ratio in oral squamous cell carcinoma and correlate it with the clinico-histopathological features.

MATERIALS AND METHODS

Patient Demographic Details

This retrospective study was carried out in the Department of Oral Pathology of a private Dental College and Hospital, after obtaining approval from the Institutional Ethical Committee. The demographic details of patients diagnosed with oral squamous cell carcinoma (OSCC) were collected from departmental archives. A total of 64 cases were selected for evaluation based on the availability of complete clinical and histopathological documentation. Details such as age, gender, and site of the lesion were documented for each patient.

Histopathological analysis

The OSCC cases were graded as well-differentiated, moderately differentiated, and poorly differentiated squamous cell carcinoma based on Bryne et al¹². All the H&E stained sections were reviewed independently by two oral pathologists to maintain consistency and minimize observer bias. The depth of invasion (DOI), bone invasion, lymphovascular invasion, perineural involvement, and lymph node status for all the patients were also noted.

Evaluation of Tumor stroma ratio (TSR)

The tumor-stroma ratio was determined at the invasive front of the tumor for all the cases. A field showing the most invasive tumor portion was selected, and the ratio of tumor to stromal tissue was visually assessed. To maintain consistency, the area with the most abundant stroma was chosen. TSR was defined as the percentage of stromal tissue in relation to the combined area of tumor and stroma. Cases were grouped into stroma-rich or stroma-poor. Tumors with more than 50% stroma were labeled stroma-rich, while those with 50% or less were considered stroma-poor. The evaluations were conducted independently by two observers to reduce subjectivity, and any inconsistencies were resolved.

Statistical Analysis

Following data collection, all clinical and

histopathological parameters, including TSR, were recorded in an excel datasheet. Statistical analysis was performed using SPSS software. Descriptive statistics were used to summarize the demographic and histopathological findings. Associations between TSR and other categorical factors, such as tumor grade and lymphovascular or perineural invasion, were analyzed using Chi-square tests. A p-value below or equal to 0.05 was considered statistically significant.

RESULTS

Demographic details

A total of 64 histopathologically confirmed cases of oral squamous cell carcinoma (OSCC) were included in this retrospective study. The mean age of the patients was 54 ± 9.42 years. Male predominance (M

= 48, F = 16) was noted with an M:F ratio of 2.18:1. The most common site was the buccal mucosa (n = 25; 39.06%), followed by the gingivobuccal sulcus (n = 17; 26.5%) and the lateral border of the tongue (n = 15; 23.4%).

Tumor stroma ratio and tumor grade

Out of 64 cases included in this study, 38 cases (59.37%) showed stroma-poor TSR, and 26 (40.62%) showed stroma-rich TSR. Among the WDSCC cases,

25 (64.1%) showed stroma-poor TSR, whereas 14 (35.9%) were classified as stroma-rich. MDSCC showed 6 (40%) cases of stroma-poor, and 9 (60%) cases of stroma-rich. PDSCC had 1 (25%) stroma-poor and 3 (75%) stroma-rich cases, while all 6 VC (100%) into SCC cases were found exclusively in the stroma-poor category (Table 1).

Table 1. Comparison of tumor stroma ratio and histopathological parameters.

Parameters		Stroma poor	Stroma rich	P value
Grades of OSCC	WDSCC	25 (64.1%)	14 (35.9%)	0.033
	MDSCC	6 (40%)	9 (60%)	
	PDSCC	1 (25%)	3 (75%)	
	VC into SCC	6 (100%)	0	
Lymphovascular invasion	Absent	37 (97.37%)	23 (88.46%)	0.179
	Present	1 (2.63%)	3 (11.54%)	
Nodal metastasis	Absent	28 (73.7%)	15 (57.7%)	0.143
	Present	10 (26.3%)	11 (42.3%)	
Perineural invasion	Absent	35 (92.1%)	19 (73.08%)	0.045
	Present	3 (7.9%)	7 (26.9%)	

A statistically significant correlation was observed between tumor grade and TSR, with $p = 0.033$. This indicates that most of the cases with stroma-poor TSR were well-differentiated, and stroma-rich were poorly differentiated OSCCs.

Tumor stroma ratio and histopathological parameters

The study further examined the relationship between TSR and various other histopathological parameters, such as nodal metastasis, bone involvement, perineural invasion, and lymphovascular invasion. The lymphovascular invasion (LVI) was observed in only 1 of 38 (2.63%) stroma-poor cases, whereas 3 of 26 (11.54%) stroma-rich cases exhibited LVI. Although the chi-square analysis did not show a statistically significant correlation ($p = 0.179$), the findings suggest that stroma-rich TSR cases tend to have a higher incidence of lymphovascular invasion compared to stroma-poor cases (Table 1).

When nodal involvement was compared between stroma-rich and stroma-poor TSR, increased nodal metastasis was noted in stroma-rich cases (fig1). 10 out of 38 stroma-poor cases (26.3%) and 11 out of 26 stroma-rich cases (42.3%) showed nodal metastasis.

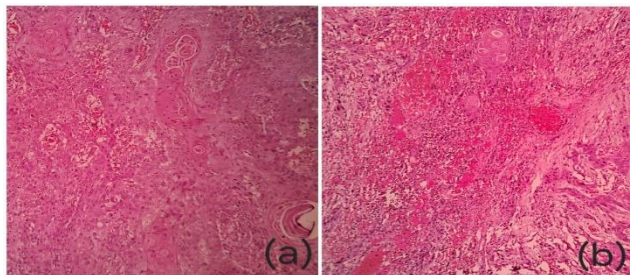


Figure 1. Photomicrograph of (a) Stroma poor and (b) stroma rich TSR

However, the difference was not statistically significant ($p = 0.143$). The perineural invasion was also more frequent in stroma-rich cases (7/26, 26.9%) compared to stroma-poor cases (3/38, 7.9%). The difference between the two groups showed p -value of 0.045 (statistically significant) (Table 1).

DISCUSSION

Oral squamous cell carcinoma (OSCC) is one of the aggressive malignancies of the head and neck region. OSCC arises from the epithelial lining of the oral cavity¹³. The tumor microenvironment modulates the tumor development, lymph node spread, and distant metastasis.

The mean age of the patients included in this research was noted as 54 ± 9.42 years. Various studies have reported that middle-aged and older people show a higher incidence of OSCC. South Asia reported the highest age-standardized incidence rate (ASIR), age-standardized mortality rate (ASMR), and age-standardized disability-adjusted life years (DALYs) rate in 2019¹⁴. A study by Krishnan et al. reported an increased prevalence of oral squamous cell carcinoma (OSCC) among younger individuals (under 40 years) in India. This study reported the mean age for younger patients as 36.43 ± 3.32 years and older patients as 55.80 ± 9.7 years¹⁵. It is believed that human papilloma virus, chronic irritation, immunosuppression, syndromes (such as Bloom syndrome), hereditary disorders, Fanconi anemia, and genetic vulnerability plays a major role in the etiopathogenesis of OSCC in the younger patients.

Cultural customs, tobacco use, and viral infections significantly influence the anatomical location of OSCC. As betel quid is commonly used in South India, the most common site for OSCC in this population is the buccal mucosa. In the present study, the buccal mucosa was the common site (39.06%), followed by the gingivobuccal sulcus (26.5%) and the lateral border of the tongue. Sharma P et al also reported the common site of OSCC as buccal mucosa followed by retromolar trigone and floor of mouth¹⁶.

The tumor-stroma ratio (TSR) is a histological measure that quantifies the percentage of stromal to tumor tissue. The stroma-rich tumors are often associated with aggressive behavior, poor immune response, and resistance to therapy¹⁰. In the present study, a total of 64 OSCC cases were retrospectively analyzed to determine the clinical significance of TSR. 38 cases (59.37%) showed stroma-poor TSR, and 26 (40.62%) showed stroma-rich TSR. A statistically significant difference was noted in the TSR between WDSCC, MDSCC and PDSCC groups. Most of WDSCC showed stroma poor TSR, whereas the PDSCC showed stroma rich TSR.

According to these findings, less differentiated tumors tend to interact more with the surrounding stromal cells and modulate angiogenesis, extracellular matrix remodeling, and immune evasion. Additionally, these stromal components release various growth hormones and cytokines that promote tumor growth and treatment resistance. Qiu et al linked the stromal component directly

to the clinical behavior and highlighted the function of cancer-associated fibroblasts (CAFs) in enhancing tumor invasiveness and immune evasion in stroma-rich environments¹⁷. Wang et al. found that stroma-rich tumors in OSCC was associated with increased lymph node metastasis and poorer survival¹⁸. Similarly, Kang et al. reported that TSR was an independent prognostic marker for disease-specific survival in patients with oral tongue squamous cell carcinoma¹⁸.

Further results of our study showed that OSCC with stroma rich TSR showed increased incidence of lymphovascular invasion, nodal metastasis and perineural invasion. A significant association was noted between TSR and perineural invasion ($p=0.045$). This association with histological parameters reinforces the potential of TSR an important factory for tumor aggressiveness and differentiation. The relationships that exist within the tumor microenvironment provide the biological foundation for TSR. Factors secreted by tumor cells attract and activate stromal cells, including immune suppressor cells, fibroblasts, pericytes, and endothelial cells. Through immunological regulation, epithelial-mesenchymal transition (EMT), and matrix metalloproteinase (MMP) activation are essential for advancing tumor growth^{19,20}. While a stroma-poor tumor may imply less contact with the supporting microenvironment and hence correlate with a better prognosis, a stroma-rich tumor frequently reflects an environment favorable to tumor advancement.

CONCLUSION

Our findings show that OSCCs, tumor stroma ratio reflects the biological behavior of the oral squamous cell carcinoma. TSR can be easily evaluated in H&E stained sections and mentioning this in the histopathology might help in better treatment planning of patients with OSCC.

DECLARATIONS

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Conflicts of interest/Competing interests

There is no conflict of interest between the authors

Ethical approval

Ethical approval obtained from Institutional Ethical

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Availability of data and material

Not Applicable

Authors' contributions

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