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Original Article

Dentistry Section

Prognostic Role of Tumour Stroma Ratio in Oral Squamous Cell Carcinoma Arising in the Background of Oral Submucous Fibrosis: A Retrospective Study

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ABSTRACT

Introduction: Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder with an increased risk of malignant transformation. Oral Squamous Cell Carcinoma (OSCC) arising in the background of OSMF shows distinct clinical presentation and behaviour. The present study was done with the rationale to understand the disease progression and assist in treatment planning using Tumour Stroma Ratio (TSR).

Aim: This study aimed to evaluate the role of TSR in OSCC arising in the background of OSMF.

Materials and Methods: This retrospective study was conducted in the Department of Oral Pathology and Microbiology, Saveetha Dental College and Hospitals, Chennai, Tamil Nadu from January 2024 to June 2024. Only patients reported with conventional OSCC with detailed clinicopathological and survival data were included in this study. A total of 120 slides were retracted from the departmental records and grouped into Group-1- OSCC arising in the background of OSMF (30 cases), Group-2- Well Differentiated OSCC (WDSCC) (30 cases), Group-3- Moderately Differentiated OSCC (MDSCC) (30 cases), and Group-4- Poorly Differentiated OSCC (PDSCC) (30 cases). Group-2, 3 and 4 cases showed no clinical signs or histopathological features of OSMF. The TSR was evaluated at the invasive front of the tumour and recorded as stroma-high and stroma-low. The survival data for these patients were retrieved from the medical records. Kappa statistics, Chi-square and Kaplan-Meier survival analysis were performed to statistically analyse the results. A p-value of ≤0.05 was considered statistically significant.

Results: A total of 26 (86.6%) cases of OSCC arising in the background of OSMF showed stroma-low and 4 (13.3%) cases showed stroma-high TSR. The WDSCC group exhibited a predominance of stroma-low tumours with 24 cases (80%) of stroma-low and six cases (20%) of stroma-high TSR. In MDSCC group, 20 cases (66.6%) showed stroma-low and 10 (33.3%) cases showed stroma-high TSR. Notably, the PDSCC group had a significantly higher proportion of stroma-high tumours, with four cases (13.3%) of stroma-low and 26 cases (86.6%) of stroma-high TSR. This difference between the four groups was statistically significant (p<0.001). On survival analysis, it was noted that the stroma-low cases had a better survival rate than stroma-high TSR.

Conclusion: OSCC arising in the background of OSMF are low-grade tumours and TSR can be helpful in predicting the survival rate of OSCC patients.

Keywords: Carcinoma, Fibrosis, Prognosis, Tumour microenvironment

INTRODUCTION

The OSCC which develops from the oral mucosa accounts for approximately 90% of oral malignancies [1]. OSCC arises as a result of the use of different types of tobacco, alcohol, chronic trauma, human papillomavirus infections, and genetic factors [2,3]. OSCC arises from various precancerous lesions and conditions. The most common ones affecting the oral cavity are leukoplakia, actinic keratosis, Oral Lichen Planus (OLP), oral human papilloma virus infection and OSMF [4]. OSMF shows marked progressive fibrosis of the oral mucosa leading to trismus, difficulty in swallowing, and inability to speak. OSMF can remain stable or progress to an advanced disease [5]. Complex, multifactorial oncogenesis signalling pathways are involved in the malignant transformation of submucous fibrosis. This involves various genetic and epigenetic alterations and a dysregulated tumour microenvironment. Collagen maturation, fibrosis driven vascular changes, hypoxia, and interaction of various cells like myofibroblasts play an important role in this mechanism of malignant transformation [6]. Oral cancers arising in the background of OSMF are mostly well differentiated tumours [7]. Chourasia NR et al., reported that almost 25.77% of cases of oral carcinoma arise in the background of submucous fibrosis [8]. These are better grade tumours with lesser incidence of local and distant metastasis. Interestingly, these patients also show less chance of deeper invasion owing to the fact that the fibrosis in OSMF blocks and prevents tumour spread [7].

Tumour microenvironment plays an important role in the malignant cell invasion and metastasis. The stroma controls the proliferation and survival of malignant cells and provides a scaffold for the tumour cells to grow. The TSR is a recent entity introduced in the field of cancer biology and is an important prognostic factor in various carcinomas [9]. TSR represents the proportion of stroma surrounding the cancer cells and is classified as high and low stroma [10]. The stroma-high TSR in tumours represents a more aggressive and invasive tumour [11]. A recent meta-analysis reported that TSR represents an independent predictor for survival in OSCC, gastric adenocarcinoma, laryngeal squamous cell carcinoma and invasive breast cancers [12]. Furthermore, TSR is known to have good interobserver reproducibility [13]. TSR is evaluated at the invasive tumour front with the highest amount of stroma [12].

However, implication of TSR in patients with OSCC arising in the background of OSMF is not well recognised. This research aimed to study the role of TSR in OSCC arising in the background of OSMF.

The null hypothesis of the present study is that the tumour-stroma ratio is similar between OSCC arising in the background of OSMF and the different grades of OSCC.

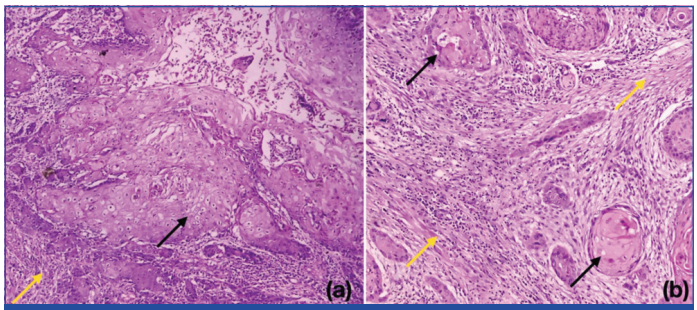
The alternative hypothesis posits that a significant difference exists in the TSR between OSCC arising in the background of OSMF and different grades of OSCC.

This is the first study of its kind to evaluate the role of tumour-stroma in OSCC arising in the background of OSMF. This will help in understanding the disease progression of this distinct clinicopathological entity and assist in treatment planning. Comparing the TSR with patient survival will aid in prognosticating outcomes for these patients.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Oral Pathology and Microbiology, Saveetha Dental College and Hospitals, Chennai, Tamil Nadu from January 2024 to June 2024. The study was approved by the Institutional Ethical Committee (SRB/SDC/UG-2113/24/OPATH/192). A total of 120 patient records and slides were retrieved from the departmental archives for analysis. The patients were divided into four groups: Group-1- OSCC arising in the background of OSMF, Group-2- WDSCC, Group-3- MDSCC, and Group-4- PDSCC [14,15]. Each group consisted of 30 subjects. Furthermore, the WDSCC, MDSCC, and PDSCC groups showed no clinical signs or histopathological features of OSMF.

Only histopathologically confirmed patients with OSCC along with detailed clinicodemographic details and survival data records were included in the study. Patients who underwent radio/chemo therapy or naturopathic treatment prior to surgical excision and patients diagnosed with variants of OSCC (e.g., verrucous, spindle cell, clear cell, basaloid, acantholytic) and recurrent OSCCs were excluded. The clinicopathological details including age, gender, laterality, site and histopathological diagnosis were collected from the medical records. The slides were re-evaluated by two pathologists and confirmed the diagnosis. TSR was also evaluated by these two pathologists at the invasive tumour front on the slide with the deepest invasion using 10x objective (100x magnification). The area with the highest percentage of stroma containing the tumour cells on all four sides of the microscopic field was identified. Tumour with more than 50% of stroma was considered as stroma-high and less than 50% at the invasive tumour front was deemed as stroma-low [11] [Table/Fig-1]. The same two pathologists independently evaluated each case and scored the TSR. Major vascular structures and muscle tissue were visually excluded during the evaluation. The survival data for all the 120 patients were recorded in months until death or till June 2024.



[Table/Fig-1]: Photomicrograph of H&E stained sections show: (a) stroma-low TSR; (b) stroma-high TSR; the black arrow denotes the tumour and the yellow arrow denotes the stroma. {Magnification-10x objective (100x magnification)}.

STATISTICAL ANALYSIS

The data was entered in Microsoft Excel and statistically analysed using SPSS version 23. The interobserver agreement was determined using Kappa statistics, and Chi square was used for qualitative analysis. A p-value of less than or equal to 0.05 was considered statistically significant. The Kaplan Meier analysis was used for survival analysis.

RESULTS

Thirty cases in each group were compared for clinico-demographic details and TSR [Table/Fig-2]. OSCC arising in the background of OSMF was commonly reported in the buccal mucosa {26 cases (86.6%)} followed by the lateral border of tongue and gingivobuccal sulcus {2 cases (6.7%) each}. The WDSCC was commonly reported in the lateral border of tongue {9 cases (30%)} followed by buccal mucosa {7 cases (23.3%)} and gingivobuccal sulcus and retromolar trigone {5 cases (16.7%) each}. Three cases (10%) of WDSCC were reported in the floor of mouth and one case in the maxillary alveolus (3.3%). Eleven cases (36.7%) each of MDSCC were reported in the buccal mucosa and lateral border of tongue; three cases (10%) each in the gingivobuccal sulcus and retromolar trigone; and two cases (6.6%) in the maxillary alveolus. The PDSCC was commonly reported in the buccal mucosa {15 cases (50%)} followed by retromolar trigone {7 cases (23.3%)}, floor of mouth {4 cases (13.3%)}, lateral border of tongue and maxillary alveolus {2 cases (6.7%) each}. The mean age of occurrence was noted to be 47.31±6.56 years for OSCC-OSMF group, 57.04±11.54 years for WDSCC, 56.02±9.86 years - MDSCC and 55.97±9.8 years - PDSCC groups.

The TSR was evaluated at the invasive front of the tumour and graded as stroma-high and stroma-low. Kappa statistics showed k value of 0.92 (near perfect agreement) [16]. Twenty six cases (86.6%) of OSCC-OSMF showed stroma-low and four cases (13.3%) showed stroma-high invasive front. WDSCC group showed 24 cases (80%) of stroma-low and six cases (20%) of stroma-high TSR [Table/Fig-3]. On evaluation of MDSCC group, it was noted that 20 cases (66.6%) showed stroma-low and 10 (33.3%) showed stroma-high TSR [Table/Fig-4]. The PDSCC group showed four cases (13.3%) of stroma-low and 26 cases (86.6%) of stroma-high TSR [Table/Fig-5]. Most of the cases of OSCC arising in the background of OSMF showed stroma-low and PDSCC cases showed stroma-high TSR at the invasive tumour front. This difference between the four groups collectively (OSCC arising from OSMF, WDSCC, MDSCC and PDSCC) was statistically significant ($p<0.001$). When individual comparisons were made between OSCC arising from OSMF and different grades of OSCC; the p-value was obtained as 0.365 (not significant) for WDSCC, 0.063 (not significant) for MDSCC and $p<0.001$ (statistically significant) for PDSCC [Table/Fig-5].

Upon analysing the entire dataset, survival analysis showed that the stroma-low TSR cases had better survival rate than stroma-high TSR; the stroma-low TSR cases showed a mean survival of 28.27±1.3 months and stroma-high TSR showed a mean survival of 23.25±2.09 months [Table/Fig-6]. The patients with OSCC arising from OSMF showed a mean survival of 32.15±0.95 months, WDSCC- 24.07±1.2 months, MDSCC- 20.5±1.3 months, and PDSCC cases had a mean survival of 15.2±1.6 months [Table/Fig-2,7].

DISCUSSION

The tumour-host interface and the importance of tumour microenvironment have been studied by various researchers over

Parameter		OSCC arising in the background of OSMF (n=30)	Well differentiated squamous cell carcinoma (n=30)	Moderately differentiated squamous cell carcinoma (n=30)	Poorly differentiated squamous cell carcinoma (n=30)
Age (years)		47.31±6.56 years	57.04±11.54 years	56.02±9.86 years	55.97±9.8 years
Gender	Male N (%)	28 (93.3%)	22 (73.3%)	23 (76.7%)	25 (83.3%)
	Female N (%)	2 (6.7%)	8 (26.7%)	7 (23.3%)	5 (16.7%)

Site	Buccal mucosa N (%)	26 (86.6%)	7 (23.3%)	11 (36.7%)	15 (50%)
	Lateral border of tongue N (%)	2 (6.7%)	9 (30%)	11 (36.7%)	2 (6.7%)
	Gingivobuccal sulcus N (%)	2 (6.7%)	5 (16.7%)	3 (10%)	0
	Maxillary alveolus N (%)	0	1 (3.3%)	2 (6.6%)	2 (6.7%)
	Retromolar trigone N (%)	0	5 (16.7%)	3 (10%)	7 (23.3%)
	Floor of mouth N (%)	0	3 (10%)	0	4 (13.3%)
Tumour Stroma Ratio (TSR)	Stroma-low	26 (86.6%)	24 (80%)	20 (66.6%)	4 (13.3%)
	Stroma-high	4 (13.3%)	6 (20%)	10 (33.3%)	26 (86.6%)
Mean survival (in months)		32.15±0.95	24.07±1.2	20.5±1.3	15.2±1.6

[Table/Fig-2]: Clinicodemographic and histopathological comparison between OSCC arising in the background of OSMF, WDSCC, MDSCC and PDSCC.
OSCC: Oral squamous cell carcinoma; OSMF: Oral submucous fibrosis; WDSCC: Well differentiated squamous cell carcinoma; MDSCC: Moderately differentiated squamous cell carcinoma; PDSCC: Poorly differentiated squamous cell carcinoma

	Stroma-low	Stroma-high	Chi-square value	p-value
OSCC-OSMF	26	4	0.480	0.365
WDSCC	24	6		

[Table/Fig-3]: Comparison of TSR between OSCC arising in the background of OSMF and WDSCC.
Test applied- Chi-square; p-value of <0.05 was regarded as statistically significant, OSCC: Oral squamous cell carcinoma; OSMF: Oral submucous fibrosis; WDSCC: Well differentiated squamous cell carcinoma

	Stroma-low	Stroma-high	Chi-square value	p-value
OSCC-OSMF	26	4	3.354	0.063
MDSCC	20	10		

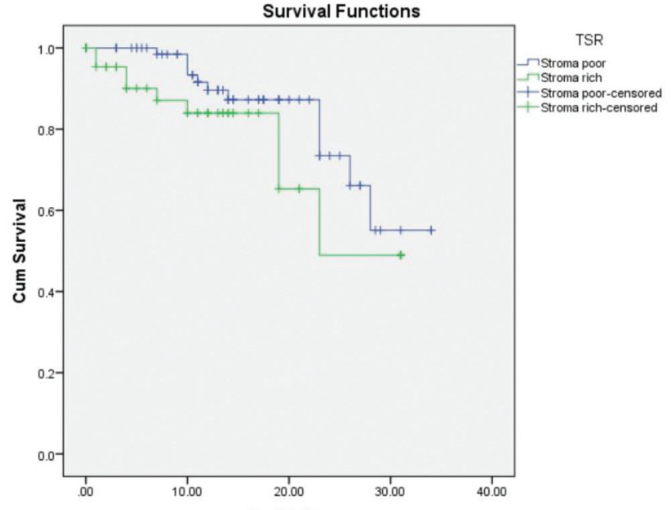
[Table/Fig-4]: Comparison of TSR between OSCC arising in the background of OSMF and MDSCC.
Test applied- Chi-square; p-value of <0.05 was regarded as statistically significant, OSCC: Oral squamous cell carcinoma; OSMF: Oral submucous fibrosis; MDSCC: Moderately differentiated squamous cell carcinoma

	Stroma-low	Stroma-high	Chi-square value	p-value
OSCC-OSMF	26	4	32.267	p<0.001
PDSCC	4	26		

[Table/Fig-5]: Comparison of TSR between OSCC arising in the background of OSMF and PDSCC.
Test applied- Chi-square; p-value of <0.05 was regarded as statistically significant, OSCC: Oral squamous cell carcinoma; OSMF: Oral submucous fibrosis; PDSCC: Poorly differentiated squamous cell carcinoma

Groups	Estimate (in months)	Standard error (in months)	Lower bound (in months)	Upper bound (in months)
Stroma-low	28.277	1.373	25.586	30.969
Stroma-high	23.257	2.096	19.150	27.364
Overall	27.251	1.223	24.854	29.648

[Table/Fig-6]: Survival estimates from Kaplan-Meier analysis.



[Table/Fig-7]: Kaplan Meier curves for overall survival of Oral Squamous Cell Carcinoma (OSCC) patients stratified by Tumour Stroma Ratio (TSR). Patients with stroma-low TSR showed better survival than stroma-high TSR; Censored indicates lost to follow-up or death.

the last decade. The tumour environment consists of different types of cells including myofibroblasts, tumour associated macrophages, endothelial cells and immune cells [17]. The ratio of tumour and the stroma at the invasive tumour front is of utmost importance as this determines the proliferation of malignant cells, initiates Epithelial Mesenchymal Transition (EMT) and metastatic spread [18]. The tumour microenvironment also contains Cancer Associated Fibroblasts (CAFs) that release growth factors into the extracellular matrix and regulates cancer spread leading to more aggressive behaviour [19].

The characteristic histopathological changes seen in OSMF are atrophic epithelium, fibroelastic changes in the connective tissue stroma including hyalinisation and fibrosis, along with juxta epithelial inflammatory response and varying degrees of vascularity [20]. The co-interaction of the components of areca nut, fibroblasts, and keratinocytes is responsible for the malignant transformation of OSMF. The arecoline in areca nut releases Reactive Oxygen Species (ROS) and activates various signalling pathways like NF-κB, P38 MAPK, and JNK pathway leading to its malignant transformation [21]. OSCC arising in the background of OSMF are low-grade tumours with a different molecular mechanism of carcinogenesis related to the areca-nut chewing [7]. These patients usually present at an earlier stage, and show less chance of distant metastasis [22].

TSR determines the proportion of stromal components around the cancer cells. A high amount of stroma at the invasive tumour front is typically associated with poor overall survival and disease free survival [11]. Furthermore, some studies have reported increased tumour stage, deep invasion, perineural and lymphovascular invasion in tumours with high stroma in the invasive tumour front [11-13,18]. The stromal cells provide a scaffold for the cancer cells to survive, grow and spread, and lay down glycoproteins, collagen, and integrins [23]. High TSR represents an epiphenomenon for loss of adhesion and EMT [24]. This enables the cancer cell to acquire more infiltrative properties. We found that the OSCC arising in the background of OSMF showed a stroma-low TSR, similar to WDSCCs. This further supports the fact that OSCC arising in the background of OSMF are well differentiated tumours [7]. Possibly, in these tumours, the malignant cells invade the underlying connective tissue stroma as large islands. Perhaps this helps in the collective movement of the tumour cells through fibrosed and hyalinised connective tissue stroma. These groups of cells generate force to facilitate its movement through the dense collagen bundles of OSMF. In the present study, PDSCCs showed a stroma rich TSR. PDSCCs are reported to show increased tumour budding and EMT when compared to WDSCCs [25]. These tumours also exhibit increased migratory and invasive properties. Wang S et al., have reported that the proportion of TSR is an independent factor in the prognosis of oral cancer patients [26]. Another study observed increased cancer mortality and recurrence in OSCC patients with stroma rich TSR [27]. Lv Z et al., reported that the rate of advanced pathological stage was seen in patients with stroma rich TSR when compared to stroma-low TSR [28].

Hence, we made an attempt to compare the proportion of stroma at the invasive tumour front and the overall survival of patients with OSCC. It was noted that patients with stroma-low TSR showed better survival than stroma rich TSR. The better survival of patients with OSCC associated with OSMF could be attributed to the decreased tumour thickness, depth of invasion, lesser nodal spread, and distant metastasis [29]. Furthermore, the stroma rich TSR shows abundant connective tissue stroma around the tumour cells with increased active interactions between the two components. Ichikawa T et al., in their study reported that low TSR significantly correlated with favourable behaviour of lung adenocarcinoma [30].

Limitation(s)

The main weakness of this research concerns the limited sample size and retrospective nature of the study. As all the samples were collected from a single institution of a specific demographic area, the results cannot be generalised to the entire global population. Furthermore, the confounding factors like the tobacco or alcohol consumption, the clinical and histopathological grades of OSMF, nutritional factors, and comorbidities that affect the prognostic outcome could not be considered.

CONCLUSION(S)

These results conclude that OSCC arising from OSMF are low-grade tumours with stroma-low TSR. TSR can be helpful in predicting the survival rate of patients with OSCC. TSR can be easily evaluated in H&E stained sections routinely without the need of any advanced techniques or procedures. Further studies with increased sample size and more standardised histopathological criteria will help in treatment planning of oral cancer patients.

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