Original Article

Clinicopathological correlation of tumor-stroma ratio and inflammatory cell infiltrate with tumor grade and lymph node metastasis in squamous cell carcinoma of buccal mucosa and tongue in 41 cases with review of literature

ABSTRACT

Introduction: Several studies regarding tumor-stroma ratio (TSR) in colorectal, esophageal, breast, endometrial, and cervical carcinomas have been done in the past with significant results.

Objectives: The objectives of this study were to (1) study and grade TSR in buccal mucosa and tongue squamous cell carcinoma (SCC), (2) grade inflammatory cell infiltrate surrounding the tumor, and (3) correlate the above two parameters with tumor grade, lymph node metastasis, lymphovascular invasion (LVI), and perineural invasion (PNI).

Materials and Methods: Totally, 25 patients of buccal SCC and 16 cases of tongue SCC were included in the study. TSR was assessed visually on the hematoxylin and eosin-stained tissue sections by two independent observers. Cases were categorized into two groups: One with high TSR >50% (stroma poor) and the other with low TSR <50% as the stroma-rich group. TSR was correlated with tumor size, lymph node metastasis, inflammatory cell infiltrate, LVI, and PNI. Data were analyzed by the Statistical Package for the Social Sciences version 16.0 (Chicago, IL, USA) for Windows. The Chi-square and Fischer's exact tests were applied in the analysis of categorical variable.

Results and Conclusion: SCC of buccal mucosa showed a significant correlation between TSR and size of the tumor ($P = 0.001$). We found that smaller the tumor size ≤2 cm (Stage T1), lesser the TSR, and size >2 cm was found to be associated with higher TSR. Hence, higher TSR (stroma poor) was associated with an adverse pathological characteristic, i.e., advanced T significantly. There was no significant correlation between TSR and inflammatory infiltrate with grade of the tumor, lymph node metastasis, LVI, and PNI. In 16 cases of SCC of the tongue; no correlation was observed between TSR and inflammatory infiltrate with tumor size, grade of the tumor, lymph node metastasis, LVI, and PNI. TSR has been studied in various malignancies (mostly adenocarcinomas) including laryngeal SCCs; however, it has never been studied on oral SCCs.

KEY WORDS: Squamous cell carcinoma buccal mucosa, squamous cell carcinoma-tongue, tumor stroma ratio

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Submitted: 10-May-2016
Revised: 29-Jun-2016
Accepted: 05-Aug-2016
Published: 24-May-2017

INTRODUCTION

Oral cancer is the sixth most common cancer worldwide and its annual incidence is more than 300,000 cases. The age-adjusted incidence rate of oral cancers in India is approximately over 20/100,000 population.[1] Approximately, 263,900 new cases and 128,000 deaths from oral cavity cancer (including lip cancer) occurred in 2008 worldwide.[2] Oral cancer is a major problem in India and accounts for 50–70% of all the cancers diagnosed. The major risk factors for oral cavity cancer are smoking, smokeless tobacco products, alcohol use, and human papillomavirus infection. In India and neighboring countries, tobacco, betel

Cite this article as: Rani P, Gupta AJ, Mehrol C, Singh M, Khurana N, Passey JC. Clinicopathological correlation of tumor-stroma ratio and inflammatory cell infiltrate with tumor grade and lymph node metastasis in squamous cell carcinoma of buccal mucosa and tongue in 41 cases with review of literature. J Can Res Ther 2020;16:445-51.

Access this article online
Website: www.cancerjournal.net
DOI: 10.4103/0973-1482.193113
Quick Response Code:

quid, and smokeless tobacco products are the major risk factors for oral cavity cancers.[3] Squamous cell carcinomas (SCCs) contribute up to 90% of all oral cavity cancers.[4]

The tumor microenvironment or stroma plays a very important role in tumor progression and metastasis. The recent literature clearly proves that stroma promotes epithelial–mesenchymal transition and metastasis by favoring proliferation and survival of neoplastic cells.[5]

More recently, tumor-stroma ratio (TSR) is coming up as an independent prognostic factor in various solid cancers. Its prognostic significance has been studied in various carcinomas including colorectal, esophageal, breast, endometrial, ovarian epithelial, cervical, laryngeal, nasopharyngeal, and hepatocellular carcinoma.[6-13]

Several studies have shown that the presence of a lymphocytic infiltrate in cancer tissue is associated with improved outcome[14] and that the immune system participates in the elimination of tumor cells and control of tumor growth.

Objectives

The main objectives were to (1) study and grade TSR in buccal mucosa and tongue SCC, (2) to study and grade inflammatory cell infiltrate surrounding the tumor, and (3) to correlate the above two parameters with tumor grade, lymph node metastasis and lymphovascular invasion (LVI), and perineural invasion (PNI).

MATERIALS AND METHODS

It was a retrospective analysis with tumor specimens obtained from the past 2 years (2013–2015) records.

In total, 25 cases of buccal mucosa SCC and 16 cases of tongue SCC with lymph node dissection were retrieved from the records in the past 2 years received routinely by the Department of Pathology, Maulana Azad Medical College, New Delhi. These hematoxylin and eosin (H and E)-stained slides prepared already from the specimens were examined for TSR, inflammatory cell infiltrate, tumor grade, lymph node metastasis, LVI, and PNI by two individual observers, blinded to each other's findings.

TSR was assessed visually on the H and E-stained tissue sections. The deepest area of invasion of the tumor was identified in each case using a low-power magnification of microscope (×100 including the eyepiece magnification), in which tumor was present at all the four corners of the field. TSR was scored and divided into two categories using a 50% cut off value as high TSR (≥50% or stroma poor) [Figure 1] and low TSR (<50% or stroma-rich) [Figure 2].

The inflammatory infiltrate was graded as mild, moderate, intense, and germinal center formation, subjectively assessed by two pathologists.[15] [Figures 3-6]. The tumor was whole processed in every case and all the tumor sections were

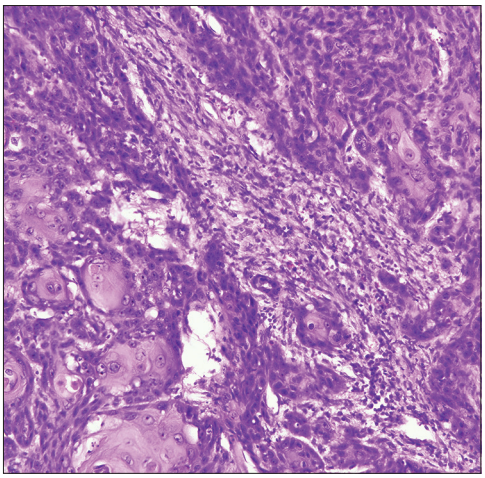

Figure 1: High tumor-stroma ratio (stroma poor) in moderately differentiated squamous cell carcinoma-tongue (H and E, ×200)

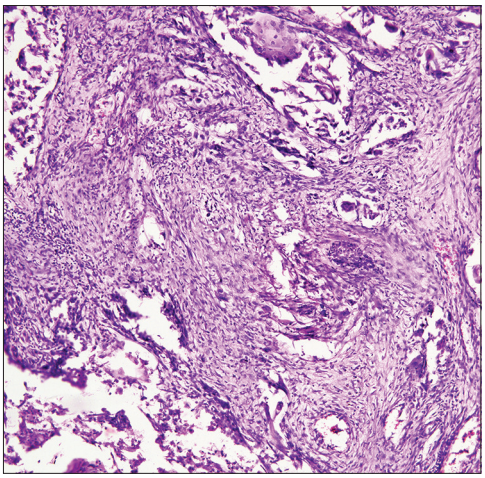

Figure 2: Low tumor-stroma ratio in squamous cell carcinoma buccal mucosa (stroma rich) (H and E, ×100)

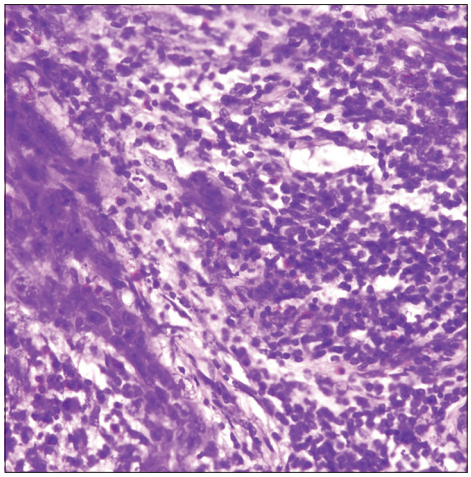

Figure 3: Intense (Grade 3) lymphocytic infiltrate in tumor stroma, in moderately differentiated squamous cell carcinoma buccal mucosa (H and E, ×400)

examined for inflammatory infiltrate grading. The areas of cystic change and necrotic material were excluded. TSR was correlated with TNM stage including tumor size, lymph node metastasis, inflammatory cell infiltrate, LVI, and PNI. The data regarding lymph node metastasis, number of lymph nodes involved, perinodal extension, LVI, and PNI were reconfirmed. The tumors with size ≥1 cm and no presurgery chemo/radiotherapy given were included while small biopsies without lymph node dissection, largely necrotic tumors, and very small size tumors were excluded.

Statistical analysis

For statistical analysis, the Statistical Package for the Social Sciences, version 16.0 (Chicago, IL, USA) for Windows was applied. The results were considered significant with a probability of <0.05.

The Chi-square and Fischer's exact tests were applied in the analysis of categorical variable. Fisher's exact test was used when we had small cell sizes (expected values <5) and Chi-square test was used when the cell sizes were expected to be large in a 2×2 table.

RESULTS

In total, 25 cases of buccal mucosa SCC and 16 cases of tongue SCC with lymph node dissection were retrieved from the records and examined. As per the American Joint Committee on Cancer Cancer Staging Manual,[16] Stage T1 for cancers of the oral cavity is when tumor size is ≤2 cm and T2 is >2 cm. We graded tumor size as 1: ≤2 cm, 2: >2 cm.

Results of buccal mucosa squamous cell carcinoma

The age range was 26–73 years with a male:female ratio of 8:1. The tumor size ranged from 1 to 8 cm. There were 11 cases of well-differentiated SCC (WDSCC), 12 moderately differentiated SCC (MDSCC), and 2 cases of poorly differentiated SCC. LVI [Figure 7], PNI [Figure 8], and lymph node metastasis were seen in 7, 16 and 11 cases, respectively. *P* value of 25 cases of buccal mucosa as per statistical analysis is given in Table 1.

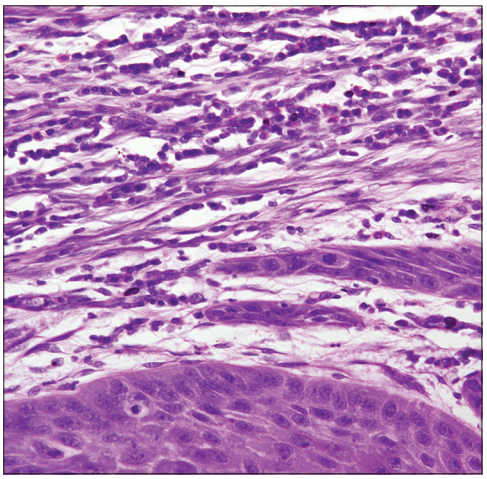

Figure 4: Plasma cells in tumor stroma in squamous cell carcinoma-tongue (H and E, ×400)

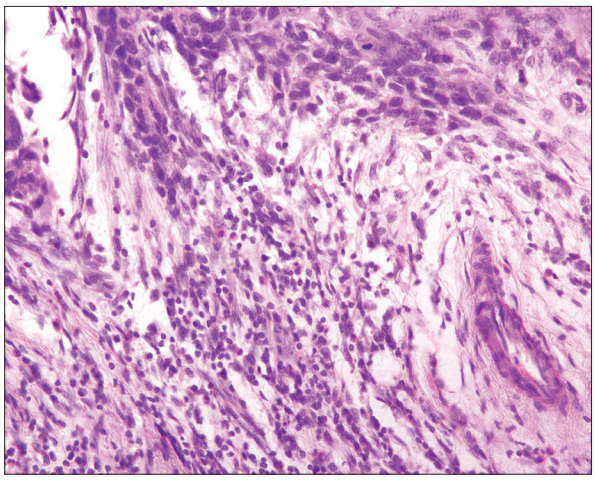

Figure 5: Lymphocytic and eosinophilic infiltrate in tumor stroma in squamous cell carcinoma buccal mucosa (H and E, ×400)

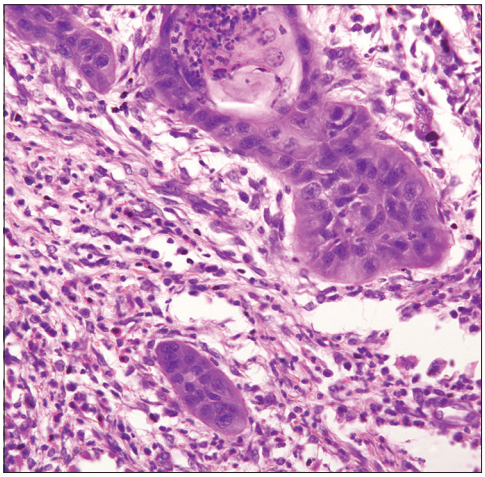

Figure 6: Mixed inflammatory infiltrate including neutrophils in tumor stroma, in squamous cell carcinoma buccal mucosa (H and E, ×400)

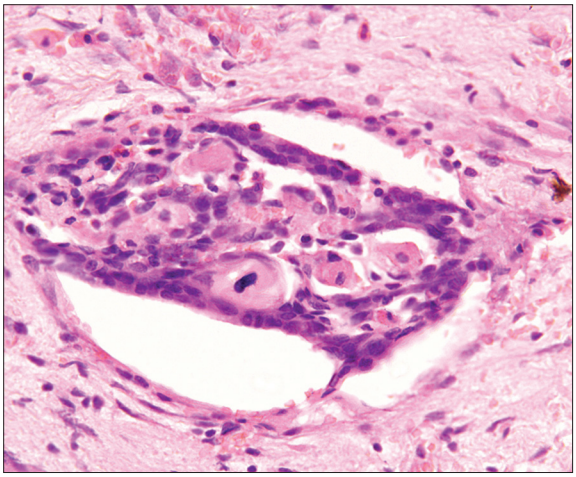

Figure 7: Lymphovascular invasion by tumor, in squamous cell carcinoma buccal mucosa (H and E, ×600)

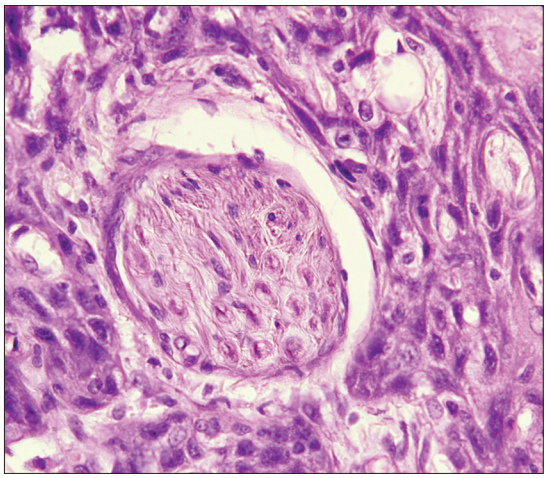

Figure 8: Perineural invasion by tumor in moderately differentiated squamous cell carcinoma buccal mucosa (H and E, ×600)

The significant correlation between TSR and size of the tumor was found with a *P* value of 0.001. There were 8 cases with size ≤2 cm and 17 cases of >2 cm size. In 88% cases, TSR was <50% in cases with Stage T1 while it was >50% for Stage T2. There were two exceptions with tumor size ≤2 cm where TSR was found to be >50%. Both cases were WDSCC without any lymph node metastasis, and both showed mixed inflammatory infiltrate of the variable grade. One case of Stage T2 which has a size of 8 cm showed TSR <50%. This case was a 26-year-old male with a history of smoking and tobacco chewing. On histopathological examination, the tumor was MDSCC. Lymph node metastasis was present only in one lymph node out of 21 nodes examined. In the tumor, lymphocytic inflammatory infiltrate (Grade 3) was seen. PNI was present while LVI was not found. Ten out of 16 cases with size >2 cm (Stage T2) showed regional lymph node metastasis while only 1 case of Stage T1 showed lymph node metastasis.

There was no significant correlation between TSR and inflammatory infiltrate with grade of the tumor, lymph node metastasis, LVI, and PNI.

Results of 16 cases of tongue squamous cell carcinoma

The age range was 28–62 years with a male:female ratio of 7:1. There were 4 cases of WDSCC and 12 cases of MDSCC. The tumor size ranged from 1.8 to 4 cm. LVI, PNI, and lymph node metastasis were seen in 5, 10, and 6 cases, respectively.

P value of 16 cases of tongue SCC as per statistical analysis is given in Table 2. There was no significant correlation between TSR and inflammatory infiltrate with grade of the tumor, tumor size, lymph node metastasis, LVI, and PNI.

DISCUSSION

Tumors are composed of cancer cells and the surrounding microenvironment. Under physiological and pathological conditions, a reciprocal dynamic interplay occurs between

Table 1: Statistical analysis of different variables of buccal mucosa squamous cell carcinoma (25 cases)

Parameters	*P*
TSR	
Size of the tumor	0.001
Grade of the tumor	0.116
Lymph node metastasis	0.688
lymphovascular invasion	0.673
PNI	0.200
Inflammatory infiltrate	0.445
Tumor size	
Lymph node metastasis	0.404
Lymphovascular invasion	0.825
PNI	0.588
Grade of the tumor	0.382
Inflammatory infiltrate	0.396
Lymph node metastasis	
Lymphovascular invasion	0.202
PNI	0.688
Grade of the tumor	0.411
Inflammatory infiltrate	1.00
Inflammatory infiltrate	
Grade of the tumor	0.230
PNI	0.445
Lymphovascular invasion	
PNI	0.205
Grade of the tumor	0.221
Inflammatory infiltrate	0.179

TSR: Tumor-stroma ratio, PNI: Perineural invasion

Table 2: Statistical analysis of different variables of tongue squamous cell carcinoma (16 cases)

Parameters	*P*
TSR	
Size of the tumor	0.596
Grade of the tumor	0.308
Lymph node metastasis	0.302
lymphovascular invasion	0.596
PNI	0.633
Inflammatory infiltrate	0.081
Tumor size	
Lymph node metastasis	0.596
Lymphovascular invasion	1.00
PNI	1.00
Grade of the tumor	0.622
Inflammatory infiltrate	0.760
Lymph node metastasis	
Lymphovascular invasion	0.538
PNI	0.554
Grade of the tumor	0.062
Inflammatory infiltrate	0.262
Size of the tumor	0.532
Inflammatory infiltrate	
Grade of the tumor	0.361
PNI	0.457
Lymphovascular invasion	0.760
Lymphovascular invasion	
Grade of the tumor	0.119
PNI	0.093
Inflammatory infiltrate	0.760

TSR: Tumor stroma ratio, PNI: Perineural invasion

the cancer cells and their surrounding stroma. The stroma comprised extracellular matrix (including collagens, laminin, and fibronectin) and cellular tissue including fibroblasts, myofibroblasts, microvasculature, adipocytes, and immune effector cells. In recent years, the concept has come up that the tumor progression depends on the interplay between tumor cells, stromal cells, and host inflammatory cells. Cancer-associated fibroblasts (CAFs) are different from normal fibroblasts as they enhance tumor proliferation and metastasis by modulating immune polarization and production of growth factors as well as extracellular matrix proteins.[17,18] This fact is supported by the difference in molecular signatures between stromal cells from normal tissues and tumors. The tumors exhibit "Reverse Warburg Effect" suggesting that the tumor cells induce pseudohypoxia in the tumor microenvironment through $H_2O_{2\ sec}$retion and simultaneously producing and presenting lactate, ketones, fatty acids, and amino acids, such as glutamine to the tumor cells as a result of aerobic glycolysis. In addition, tumor cells induce an oxidative stress on surrounding fibroblasts promoting cytokine production, which in turn, provides nutrients to anabolic tumor cells.[18] There is evidence that stromal myofibroblasts promote tumorigenesis in oral SCC by secreting activin A.[19] Tumor invasion and angiogenesis is promoted by smooth muscle actin (SMA)-positive myofibroblasts than SMA-negative myofibroblasts. CAFs and myofibroblasts play an important role in tumor progression as they can produce various cytokines and growth factors, angiogenic molecules, and proteolytic enzymes. In addition, they can induce epithelial to mesenchymal transition of carcinoma cells and thus facilitate tumor growth, local invasion and increase metastatic spread.[20]

Myofibroblasts help tumor cells in escaping immune-mediated death by preventing infiltration of immune cells in the tumor. Hence, increased stromal component of the tumor may promote the aggressive potential of the tumor leading to the poor outcome.[21] All these above-mentioned data support the stroma as an important predictor of tumor behavior.

TSR is a relatively new entity and it was first described by Mesker *et al*.[22] in 2007 as a prognostic factor in colorectal carcinomas; however, now, its prognostic significance has been studied in various carcinomas including esophageal, breast, endometrial, ovarian epithelial, cervical, laryngeal, nasopharyngeal, and liver carcinoma.

In various studies done on TSR, variable results were found and prognostic significance was also variable. Our study shows significant association of stroma-poor buccal mucosa SCC with higher T stage which is itself an independent prognostic marker, while in colorectal carcinomas and epithelial ovarian carcinomas, high stromal content was found to be associated with higher T stage. The studies done on endometrial carcinoma, cervical adenocarcinoma, and laryngeal SCC do not find any association between TSR and T stage.

Majority of research work point toward poor prognosis in tumors with high stromal content such as studies on early stage cervical adenocarcinoma,[23] colorectal carcinoma,[6] and nonsmall cell lung carcinoma[24] depicted stroma-rich tumors to be associated with poor survival, while in endometrial carcinoma,[9] estrogen receptor-positive breast carcinoma[7] and pancreatic ductal adenocarcinoma,[25] high stromal content was associated with better survival.

This paradigm that CAFs play an active role in tumor progression and metastasis does not necessarily apply to all tumor types. Studies done on pancreatic carcinoma demonstrated the tumor-suppressive role of CAFs and fibrosis. Bever *et al*.[25] reported a good prognosis in stroma-rich pancreatic ductal adenocarcinoma cases suggesting variable tumor-stroma interactions in different cancer types. A recent molecular study in endometrioid endometrial carcinoma depicted that macrophage response signature was associated with worse prognostic features rather than the activated stromal signature.[26]

Considering the role of inflammatory infiltrate in the tumor, numerous studies have been done which explain that tumor stroma promotes tumorigenesis by preventing immune cell infiltration in the tumor. The stromal myofibroblasts and fibroblasts create a physical barrier against immune cells due to their contractile properties, hence promoting tumor progression.[21] This fact is supported by various studies which elicit relation between inflammation and tumor stroma. In colorectal and breast ductal carcinomas, stroma-rich cases were inversely related to local inflammation.[27] In prognostic studies, the presence of intratumoral T cells correlated with a good clinical outcome in ovarian carcinoma[14] while no correlation was found in oral SCC.[28] de Matos *et al*. illustrated, from their study on tongue SCC, a significant correlation between scarcity of the lymphocytic infiltration and PNI with nodal metastasis ($P < 0.05$).[29] In our study, there was no significant correlation of inflammatory cell infiltrate with TSR and other parameters studied.

This fact that tumor stroma promotes tumorigenesis is difficult to validate; hence, mechanisms underlying the prognostic ability of stroma should be explored.

Table 3 summarizes the results of previous studies. All these studies correlated TSR with survival; however, in our study, we correlated histological parameters with TSR and among themselves. To summarize, variable TSR results drawn from different tumor types suggest that the stroma plays different roles among epithelial tumors, and their effect on prognosis hence is not universal.

CONCLUSION

Our study is based on the correlation of TSR with inflammatory infiltrate, lymph node metastasis, and LVI. We found TSR

Table 3: Comparison of studies regarding tumor-stroma ratio in various malignancies

Sn	Tumor site	Year	Conclusion
1	Triple negative breast carcinoma[31]	2012	Stroma rich-poor survival Stroma poor- better survival
2	Esophageal SCC[32]	2012	Stroma-rich tumors were associated with poor prognosis and an increased risk of relapse
3	Larngyeal SCC [8]	2013	No significant difference in survival between low and high TSR
4	Nasopharyngeal carcinoma [11]	2014	Stroma rich : poor prognosis
5	Colorectal carcinoma[6]	2014	Stroma rich tumors – reduced survival
6	ER+breast carcinoma[7]	2014	Stroma rich tumors : better survival.
7	Endometrial carcinoma[9]	2015	High TSR (stroma poor): low survival Stroma rich : better survival No correlation between TSR and other parameters.
8	Epithelial ovarian carcinoma[10]	2015	Stroma rich tumor- poor prognosis
9	Hepatocellular carcinoma[12]	2015	Stroma poor : better survival
10	Cervical carcinoma [13]	2015	Stroma-rich tumors had worse prognosis and higher risk of relapse compared with those having stroma-poor tumors.
11	Cervical Adenocarcinoma [23]	2015	Low TSR (stroma rich): low survival No correlation between TSR and grade, LVI, PNI or LN metastasis.
12	Non small cell lung carcinoma [24]	2015	Stroma rich tumors : poor prognosis and incresed risk of relapse.
13	Pancreatic ductal carcinoma[25]	2015	Stroma rich tumors- good prognosis
14	Inflammatory breast carcinoma [30]	2015	No significant difference in survival with TSR
15	Our cases (Buccal mucosa and tongue SCC)	2016	Significant correlation between TSR and size of the tumor was found with a *P* value of 0.001 in buccal mucosa SCC cases suggesting higher TSR (stroma poor) to be associated with adverse pathological characteristic i.e; advanced T significantly. No significant correlation between TSR and inflammatory infiltrate with grade of the tumor, lymph node metastasis, LVI and PNI.

SCC: Squamous cell carcinoma, TSR: Tumor-stroma ratio, LVI: Lymphovascular invasion, PNI: Perineural invasion, ER: Estrogen receptor

to be significantly associated with an adverse pathological characteristic, i.e., advanced T, but independent of other parameters studied. TSR has been studied in various malignancies (mostly adenocarcinomas) including laryngeal SCCs; however, it has never been studied on oral SCCs; hence, it needs to be studied in oral SCC cases on a larger number of cases and if possible with follow-up of patients to assess prognosis.

The assessment of the proportion of tumor stroma using routine pathological specimens may act as a surrogate for tumor stroma activity and its subsequent effect on survival and chemoresistance. Together, inflammatory cell infiltrate and TSR can help assess the response of oral SCCs to radiotherapy and chemotherapy. Their correlation with lymph node metastasis and LVI may form an important indicator for overall patient survival.

A major limitation of our study is small sample size and retrospective nature; hence, a larger prospective study along with prognosis and study on different sites of oral SCC are warranted.

TSR is an important factor that needs further evaluation in oral SCC, and various therapeutic agents which target tumor microenvironment may have great potential in clinical practice. Moreover, an effective antitumor treatment should target a specific stromal component rather than targeting the stroma in general.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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