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Lymphocytic Host Response and other Prognostic Factors in Early Stage Squamous Cell Carcinoma of Tongue: Retrospective Analysis from a Tertiary Cancer Center

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Abstract

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Keywords

- squamous cell carcinoma
- lymphocytic host response
- Kaplan–Meier model
- disease-free survival (DFS)
- overall survival (OS)

Introduction The tongue is the most common site of malignancy in the oral cavity, and squamous cell carcinoma is the commonest histology. The prognosis remains unfavorable despite treatment, resulting in higher mortality rates. Early stage carcinoma of the tongue is a distinct entity and is primarily treated with either surgery or radiotherapy. Various factors have been implicated in the prognosis of early stage tongue carcinomas. The main objective of this study is to access whether the lymphocytic host response (LHR) and other prognostic factors influence the survival.

Patients and Methods The data of 129 patients with Stage I and Stage II (T1-2, N0) tongue cancer treated in our institute from January 2012 to December 2016 were retrospectively abstracted from the hospital case records. The various clinical and pathological factors were recorded. The Kaplan–Meier model was used for survival analysis. The disease-free survival (DFS) and the overall survival (OS) with respect to stage and LHR were calculated.

Results On multivariate analysis, site of lesion, comorbidities, habits, grade of the tumor, perineural infiltration (PNI) did not influence the survival. The main factor which was found to be significant in DFS was LHR. The DFS was better for the patients who had lymphocytic infiltration of $\geq 70\%$ (strong LHR) when compared with $<70\%$(weak LHR) ($p = 0.037$). The OS with respect to stage ($p = 0.608$) and LHR ($p = 0.164$) was not found to be statistically significant.

Conclusion The patients with weak LHR had less DFS when compared with patients with strong LHR. Larger studies are needed to evaluate whether adding adjuvant therapy may benefit the patients with weak LHR in early stage tongue cancer.

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Introduction

Oral cavity cancer is the eighth most common cancer in males worldwide[1] and is the third most common cancer in India. The survival remains poor despite treatment because the majority of the cases are diagnosed at an advanced stage.[2] In the oral cavity, the tongue is the most common site of malignancy, and squamous cell carcinoma is the commonest histology. Tongue cancers have lower survival rates probably due to incomplete response to treatment strategies.[3]

Although the etiology is multifactorial, the major risk factors associated with its development are the use of tobacco products (smoking, chewing, and snuffing) with or without alcohol intake. The TNM classification is used clinically to define therapy and estimate its response and prognosis.[4] However, it does not necessarily reflect a precise impact on prognosis. Tumors with the same stage in this classification can show different disease progression.[5]

Various pathological parameters described as tumor prognostic indicators are pathological stage, histopathological grading, presence of vascular and perineural invasion, extracapsular spread, and positive surgical margins.[6,7]

The density of lymphocytes at the interface of the tumor is quantified histologically as lymphocytic host response (LHR) in the Risk Model. LHR can be divided into weak, intermediate, and strong depending on the density of lymphocytes. LHR is inversely associated with the risk of decreased time to disease progression. There is a greater degree of adaptive cytotoxic T cell response in strong LHR when compared with moderate LHR.[8]

Early stage carcinoma of the tongue is a distinct entity and is primarily treated with either surgery or radiotherapy. The main objective of this study is to assess whether the LHR and other prognostic factors influence the survival in early stage squamous cell carcinoma tongue.

Patients and Methods

Data Collection

The data of 129 patients with Stage I and Stage II (T1-2, N0) tongue cancer treated in our institute from January 2012 to December 2016 were retrospectively abstracted from the hospital case records. The study was approved by Institutional Ethics Committee (Reference No. IEC/2021/March 01). Data were collected about patients (age, sex, comorbidities, site of disease, addictions), the tumor (site, TNM stage, degree of differentiation and perineural spread, inflammation around the tumor), treatment (margin status) and follow-up. All medical records and pathologic reports were reviewed and the data were collected.

Diagnosis and Staging

Tumor diagnosis was based on a clinical examination followed by a biopsy of the lesion and pathology. Ultrasound neck was performed to assess tumor spread and the presence of cervical nodes. Pathological data included tumor stage (pTNM). The seventh edition of the TNM Classification of Malignant Tumors (UICC staging system) was used to classify the tumors.

Inclusion and Exclusion Criteria

The patients with Stage I and II (T1-2, N0) carcinoma of the tongue were included in the study. The patients who were upstaged after surgery and with previous treatment (second primary tumor) were excluded from the study. Similarly, patients who were treated with radiation therapy for Stage I and II were also excluded.

Treatment and Follow-up

All patients underwent surgical removal of the primary lesion along with safety margins with a curative intent (wide local excision glossectomy) with or without elective neck dissection. The patients were followed up at 1, 6, and 12 months in the first year and thereafter every 6 months. For patients who underwent surgery elsewhere, the slides/paraffin blocks/entire specimen were reviewed by the pathologist of our institute. If the surgery was inadequate–when the margins were inadequate or only excision biopsy done, the patients underwent re surgery; otherwise, they were followed up. The patients who developed recurrence were salvaged either by surgery, radiotherapy, chemotherapy or a combination of two modalities.

Pathological Analysis for TILs

The tumor-infiltrating lymphocytes (TILs) in the stromal compartment (stromal TILs) were assessed using the standardized methodology for TILs assessment described by the International TILs Working Group in breast cancer by Salgado et al[9] and the International Immuno-oncology Biomarkers Working Group by Hendry et al.[10]

The tumor and stromal compartments within the borders of the invasive tumor were separated and TILs in the stromal compartment were evaluated. Assessment was done in stromal areas away from both the surface and the deep margin of the tumor, taking care to exclude areas with crush artefacts, necrosis, and hyalinization. Full assessment of all mononuclear inflammatory cells (lymphocytes, plasma cells), excluding polymorphonuclear leukocytes were carried out in the entire sections avoiding hot spots initially at 40× magnification followed by 400× magnification. The final stromal TILs were calculated at 10% intervals as the fraction of the area occupied by mononuclear inflammatory cells (numerator) over the total stroma area (denominator).

Statistical Analysis

Disease-free survival (DFS) duration was determined from the starting date of treatment to the documented date of first recurrence or death of any cause. Overall survival (OS) duration was defined as the time interval between the starting date of the treatment and documentation of the day of death or last follow-up, whichever was earlier. OS and DFS rates were calculated according to the Kaplan–Meier method and compared using the log-rank test. Analysis was done using SPSS version 20.

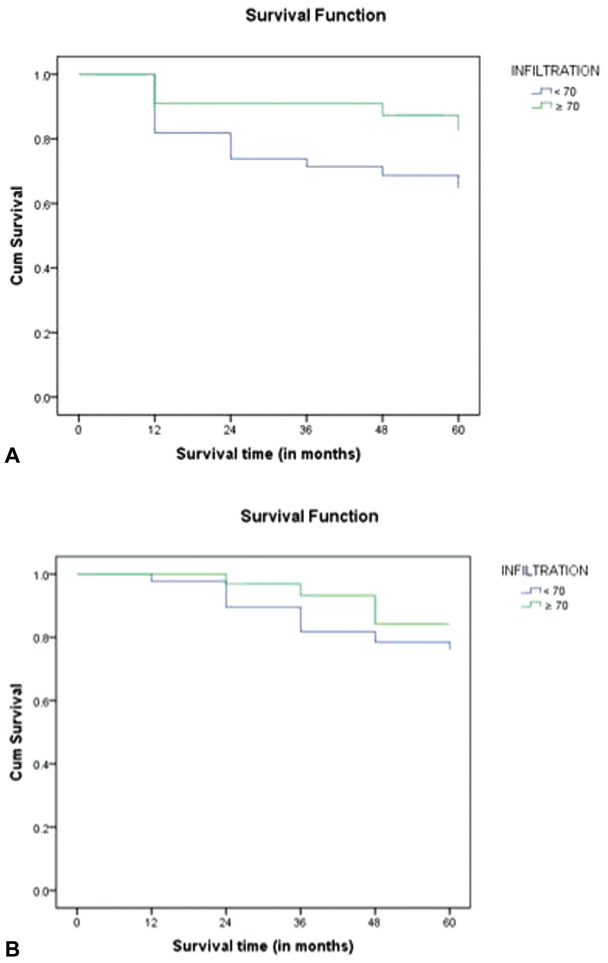

Fig. 1 (A) Disease-free survival by tumour infiltrating lymphocytes, tongue cancer, 2012-2016. (B) Overall survival by tumor-infiltrating lymphocytes, tongue cancer, 2012-2016.

Results

Our results showed that carcinoma tongue is associated with male preponderance (73.6%), and in the middle age. However, age, sex, comorbidities, habits (smoking, tobacco chewing and alcoholism) were not significant from demographic point of view. The primary treatment was surgery (wide local excision) with or without neck dissection (supraomohyoid neck dissection–SOHND/radical neck dissection–RND) in most patients. The salvage treatments were radiotherapy, chemotherapy, surgery, or a combination of these. While analyzing the pathological parameters, side of the disease (left or right), grade of the tumor, stage of the disease, PNI, close margins, margins showing dysplasia did not show any statistical significance. The DFS was better for patients who had lymphocytic infiltration ≥ 70% (strong LHR) when compared with < 70% (weak LHR) ($p = 0.037$) (►**Fig. 1A** and ►**Table 1**). The OS with respect to stage ($p = 0.608$) and LHR ($p = 0.164$) was not found to be statistically significant (►**Fig. 1B**).

Discussion

The primary treatment modality for stage I and II tongue cancer is either surgery, radiotherapy, or a combination of these modalities. However, as many as 25% and 37% of patients with stages I and II, respectively, are expected to develop locoregional recurrence, indicating that more aggressive protocols are warranted for a subset of early stage patients.[11] The decision regarding the mode of therapy depends on the treatment philosophy of the institution, the available expertise, as well as physician and patient preference. The majority of the early stage tongue cancer patients in our institute underwent surgery for the primary tumor as well as the neck during the study period.

Our study had shown male preponderance, which is in accordance with many studies. Age, gender, comorbidities, and habits did not show any statistical significance. Although there is increased incidence in old age, which may be related to the immunosuppression, occurrence of tumors in young age may be attributed to their habits.[12]

In our study, the patients with strong LHR (TILs) (70% and above) had good DFS when compared to the patients with weak LHR (< 70%). A better approach would be to quantify CD4, CD8 and Treg, which may involve more immunohistochemistry studies.

Extracapsular extension and depth of invasion are strong independent predicting factors for OS of squamous cell carcinoma of the tongue and floor of the mouth according to the eighth edition of the TNM Classification of Malignant Tumors, proposed in 2017.[7] Thus, an increase in the depth of invasion probably precedes and influences perineural and perivascular invasions.

We had analyzed various demographic variables such as age, gender, comorbidities, and habits and pathological parameters such as tumor grade, site, stage, PNI, margin status, and LHR (TILs). Among these, LHR (TILs) was the only factor that was significant ($p = 0.037$) as a prognostic indicator for early stage carcinoma of the tongue. The limitations of our study include retrospective nature of analysis, single

Table 1 Shows Disease Free Survival by Tumour Infiltrating Lymphocytes

Infiltration	No.[a]	Percentage	Disease-free survival%			*p*-Value
			1-year	3-year	5-year	
1. <70% 2. ≥70%	88 33	73 27	82 91	71 91	65 82	0.037[b]

[a]Eight slides were unavailable for analysis either broken or tissue details unclear.
[b]Statistically significant.

institute study, and lack of analysis of tumor thickness and worst pattern of invasion. Larger studies with more immunohistochemical (IHC) methods are needed to validate our results.

Conclusion

The patients with weak LHR (TILs) had less disease-free survival when compared with patients with strong LHR (TILs). Larger studies are needed to evaluate whether adding adjuvant therapy may benefit the patients with weak LHR (TILs) in early stage tongue cancer.

Conflict of Interest

None declared.

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