

# Evaluation and Correlation of Clinicopathological Parameters of Oral Squamous Cell Carcinoma of Gingivobuccal Sulcus with Lymph Node Status - A Retrospective Institutional Analysis in Navi Mumbai

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## ABSTRACT

### BACKGROUND

Mortality and Morbidity rates in the patients diagnosed with oral cancers remain static despite availability of advanced diagnostic and treatment modalities. For improving the survival status of the patients, a thorough understanding of the factors that predicts the progression of oral cancer is necessary to determine appropriate line of treatment. To do so in practise, critical knowledge regarding the prognostic factors that has high sensitivity holds immense importance. For determination of prognosis in oral cancer patients, clinical and histopathological parameters are widely used for assessment of treatment strategies. The primary objective of this study was to determine the clinical and histopathological prognostic factors in patients of oral squamous cell carcinoma of gingivobuccal sulcus (GBSSCC) treated by surgical intervention (neck dissection).

### METHODS

Histopathological evaluation of archived samples of 60 GBSSCC patients which were treated by surgical intervention (Neck Dissection) in the time period from January 2011 to December 2020. Recurrent cases were excluded. Clinicopathological parameters such as age, sex, habit, tumour site, tumour size, tumour differentiation, depth of invasion, bone invasion, muscle invasion, perineural invasion & extracapsular spread were evaluated & then correlated with lymphnode status.

### RESULTS

Among all the parameters, variables like habit (tobacco use) ( $P = 0.045$ ), tumour size ( $P = 0.003$ ), perineural invasion ( $P = 0.000$ ) emerged as independent prognosticators and significantly correlated to the lymph node status of the patients.

### CONCLUSIONS

This analysis suggests that habit, tumour size, perineural invasion to be consistent, easy to assess and reliable independent prognosticators which are significantly correlated to the lymph node status. To conclude, it is of paramount importance to include the aforementioned prognosticators in histopathological reports for the prediction of clinical outcome and archiving of valued data for future analysis.

### KEY WORDS

Oral Squamous Cell Carcinoma, Gingivobuccal sulcus, Lymph Node Status, Clinico-Pathological Prognosticators

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**BACKGROUND**

Oral squamous cell carcinoma (OSCC) is the most common oral malignant neoplasm, constituting up to 80 – 90 % of all malignant neoplasias of the oral cavity.<sup>1</sup> The incidence of oral cancer is highly variable globally. It is generally established that oral cavity is one of the prominent anatomical locations for squamous cell carcinoma which also depends significantly on the geographic location (even specifically, regions in some countries) and demographic criteria of the individuals.<sup>1</sup> In spite of its mean incidence, it represents the most common location for cancer in some specific regions, especially in southeast Asia.<sup>1</sup>

Clinical site of placement of the tobacco quid may differ according to different tobacco habits and products. The various sites of placement of tobacco include lingual sulcus, maxillary gingivobuccal sulcus and the mandibular gingivobuccal sulcus. The chemical and mechanical irritants of the tobacco plays an important role in oral carcinogenesis.

The gingivobuccal sulcus complex usually consists of buccal mucosa, gingivobuccal sulcus, gingiva and retro molar trigone. In Indian subcontinent, mandibular gingivo-buccal sulcus (GBS) is the most common site affected by oral squamous cell carcinoma (OSCC) and hence, it is called as Indian Oral Cancer.<sup>2</sup> An early gingivobuccal sulcus complex squamous cell carcinoma (GBSSCC) is often asymptomatic with most cases being usually identified in advanced stages sometimes involving nearby local regions and lymph node (LN) involvement. It comprises of total 40 % of all OSCC with survival rate of 63 % and 53 % for 2 yr and 5 yr respectively. Similarly the 5-yr survival rate in GBSSCC patients with lymph node metastasis (20 - 36 %) is comparatively less than those with no metastasis (63 - 86 %).<sup>3</sup>

Mortality and morbidity rates in the patients diagnosed with oral cancers remain static despite the availability of advanced diagnostic and treatment modalities. In spite of the easy accessibility of the oral cavity for examination, OSCC is rarely diagnosed at initial stages. For improving the survival status of the patients, a thorough understanding of the factors that predict the progression of oral cancer is necessary to determine appropriate line of treatment. To do so in practise, critical knowledge regarding the prognostic factors that has high sensitivity holds immense importance. For determination of prognosis in oral cancer patients, clinical and histopathological parameters are widely used for assessment of treatment strategies. Lymph node (LN) metastasis is one of the most accepted and reliable prognostic markers for overall prognosis of cancer patients. The metastasis within the lymph node may be dependent, in turn, on various clinicopathological factors such as age, gender, site, treatment, habit, staging, etc., which help in determining the survival outcome of the patient.

Till now, various studies have been conducted to analyze the prognostic ability of various clinical and pathological factors associated with oral squamous cell carcinoma affecting different oral sub-sites. Hence the primary objective of this study was to evaluate and correlate the role of various clinicopathological factors with LN status with or without metastasis in GBSSCC patients.

**METHODS**

The present study is an institutional retrospective observational study. 78 patients were surgically intervened for SCC from January 2011 to December 2020. All the demographic details were retrieved for these 78 patients. After meeting the inclusion (Neck dissection cases only) and exclusion criteria (systemic diseases, recurrent cases and metastatic lesions) 60 cases of surgically operated for GBSSCC were selected for this retrospective study based on convenient sampling. Histopathological slides were retrieved for reanalysis. Clinicopathological parameters like age, gender, site, habit, clinical staging, tumour differentiation, bone invasion, skeletal muscle invasion, perineural invasion and extracapsular involvement were noted. Evaluation and correlation of the factors with lymph node status were statistically assessed. Two independent pathologists reviewed the data and any discrepancy was solved by mutual consensus. Age of the patients was categorised into two groups i.e.  $\leq 40$  and  $> 40$  yrs. Habits were categorised into 3 groups i.e. Smokeless, Smoke form and both. Clinical tumour size (cT) staging was given as per the AJCC 7th edition mainly. Tumour differentiation was graded by broders system (1927) for ease of analysis. Presence or absence of invasion in bone, muscle, and nerve was also assessed. Histopathological lymph node status was classified as positive or negative with or without extracapsular spread. This study protocol was approved by the institutional research review board. As the study is a retrospective observational one, the ethical approval for the same was not applicable. Though, the individuals informed consent for the surgery and use of the specimen for research purpose were acquired.

**Statistical Analysis**

Microsoft word and Excel were used to store the data and to generate graphs and tables. The descriptive and inferential statistical analyses were performed by using SPSS software version 21 (IBM, Armonk, NY, USA). Analysis of data with continuous measurements were presented as Mean SD whereas data with categorical measurements were depicted in numbers (%). The level of significance was fixed at  $P = 0.05$  and any value less than or equal to 0.05 was considered to be statistically significant. Chi-square analysis and Multivariate logistic regression analysis were run to find the significance of study parameters on a categorical scale.

**RESULTS**

Descriptive analysis of patient data showed that maximum study participants had a history of tobacco consumption in the form of smokeless tobacco (76.66 %) whereas only (16.66 %) used tobacco in smoke form. Out of 60 study samples, 68.33 % were moderate tumour differentiation types followed by well and poor differentiation types 15 % and 16.66 % respectively. 61.66 % of study samples did not show any evidence of bony, muscle or perineural invasions or extracapsular spread in metastatic lymph node. Only (38.33 %) of cases showed positive evidence of histopathological lymph node status. (Table 1).

Variables	Sub - Groups	N	%
Gender	Male	40	66.66
	Female	20	33.33
Age	≤40 years	13	21.66
	>40 years	47	78.33
Habits	Smokeless	46	76.66
	Smoke form	10	16.66
Tumour Differentiation	Both	4	6.66
	Well	9	15
	Moderate	41	68.33
Tumour Size	Poor	10	16.66
	T1	4	6.66
	T2	24	40
	T3	10	16.66
Bone Invasion	T4	22	36.66
	Evident	23	38.33
	Not evident	37	61.66
	Evident	20	33.33
Muscle Invasion	Not evident	40	66.66
	Evident	9	15
Perineural Invasion	Not evident	51	85
	Positive	23	38.33
Histopathological Lymph Node Status	Negative	37	61.56
	Evident	23	38.33
Extra capsular Spread	Not evident	37	61.66

**Table 1. Distribution of Study Variables**

On comparison of lymph node status with other clinicopathological parameters, positive association was found in relation with different forms of habits. Within all metastatic lymph node cases, smokeless habit was found to be associated with lymph node metastasis as compared to other forms of tobacco habits. But when forms of habit were compared with positive and negative lymph node status, again smokeless form was found to be the most prevalent form of habit. In case of tumor size, the association with lymph node status could not be ascertained due to varied distribution of number of samples although the association was found to be statistically significant. On comparison with tumor differentiation, moderate and poor tumor differentiation cases showed higher instances of lymph node metastasis as compared to cases showing well tumor differentiation. Perineural invasion showed no association with occurrence of lymph node metastasis. (Table - 2).

Variables	Histopathological Lymph Node Status		χ <sup>2</sup> - Value	P - Value	
	Positive (N = 23)	Negative (N = 37)			
Habit	Smokeless	16	30	1.051	0.043*
	Smoking	05	05		
	Both	02	02		
Tumour Size	T1	00	04	4.198	0.041*
	T2	12	12		
	T3	03	07		
	T4	08	14		
Tumour Differentiation	Well	01	08	7.116	0.004*
	Moderate	15	26		
	Poor	07	03		
Perineural Invasion	Evident	09	10	5.960	0.043*
	Not evident	14	27		
Extracapsular Spread	Evident	09	01	13.551	0.000*
	Not evident	14	36		

**Table 2. Comparison of Histopathological Lymph Node Status with Different Variables Using the Chi-Square Test. (Variables Which Showed Significant Correlation Are Only Included)**

(P < 0.05 - Significant\*)

To check the independency of the prognostic factors, we performed a multivariate logistic regression analysis of the obtained data. As a result, we found that prognosticators such as habit, tumour size, perineural invasion were independent and were significantly correlated to the lymph node status of the patient.

Effect	Model Fitting Criteria - 2 Log Likelihood of Reduced Model	Likelihood Ratio Tests		
		Chi - Square	df	Sig.
Age	46.308	.003	1	0.959
Gender	46.657	.351	1	0.863
Habit	11.620	1.032	2	0.045
Tumour Size	54.874	8.569	3	0.003
Tumour Differentiation	46.320	.014	1	0.905
Bone Invasion	46.558	.252	1	0.615
Muscle Invasion	46.595	.289	1	0.591
Perineural Invasion	62.117	15.812	1	0.000
Extracapsular Spread	46.659	.354	1	0.552
Intercept	46.326	.020	1	0.887

**Table 3. Multivariate Logistic Regression Analysis with Predictable Variables of Oral Squamous Cell Carcinoma**

## DISCUSSION

Oral potentially malignant lesions and frank carcinoma occurs as a result of highly irritating mixtures of tobacco and slaked lime, which are widely used in Indian subcontinent. The major subsite for OSCC in India is gingivo-buccal sulcus because of placing / chewing habits of various tobacco forms.<sup>4,5</sup> The recurrence and survival rate depends on various clinicopathological parameters such as age, gender, habits, site, tumour size, differentiation, bone invasion, muscle invasion, perineural invasion, extracapsular spread and lymph node status.

The present study has included cases that have undergone neck dissection for GBSSCC (N = 60) out of which N = 23 have shown positive lymph node involvement and N = 37 have shown negative lymph node status. Lymph node metastasis is an established prognosticator of OSCC. But, the role of other clinicopathological factors in the prognosis of the tumours is yet to be determined. Thus, in our study we tried to evaluate and correlate clinicopathological factors with LN metastasis & to understand their role in prognosis. We compared the clinicopathological prognostic factors with the lymph node status by using chi square test.

In our study most patients were above 40 yrs. of age i.e. approximately 78 % of total patients which proved that age is an established risk factor for the cancers mainly because of accumulation of mutational changes throughout the life years and diminishing immune system. 67 % of the patients were males and the rest were females which showed the predilection of cancers in males. Poor socio-economic status, easy acceptance of habits and labour associated tobacco consumption are attributed for male predilection. Habits and tumour site can be directly correlated in our study as 77 % patients had a habit of smokeless tobacco chewing and all had common site to place it i.e. mandibular gingivo-buccal sulcus hence included in the study.

Among the total patients, the clinical tumour size ranged from T2 to T4 out of which T2 had the predominance suggesting that neck dissection was necessary despite the small clinical size of tumour thus improving prognosis of the patients. In this study, Broders system was used to grade the tumours and as a result moderate differentiation was found in 68 % of cases. In correlation with the lymph node status it was not statistically significant but there was positive inclination from well to poor differentiation. Fang et al. Rikardsen et al. Choi et al. observed that cell differentiation was the most significant factor for lymph node metastasis, affecting prognosis and survival of OSCC.<sup>6,7,8</sup>

In OSCC, two different types of bone invasion is seen in mandible. In one type, saucerization of cortical bone occurs via osteoclastic resorption. In the other, bone marrow is infiltrated by tumour cells through the periodontal space or enlarged Volkmann and Haversian canals or by replacing the marrow spaces directly by cortical bone resorption.<sup>9,10</sup> In the current study, bone invasion was found among 38 % of the total patients studied. Bone invasion was identified as a prognostic factor in cervical metastases in the study conducted by Ogura et al.<sup>11</sup>

Muscle invasion occurs by the infiltration of extrinsic skeletal muscle bundles by malignant cells.<sup>12</sup> Studies exclusively on muscle invasion are rarely done, rendering its clinical relevance and its prognosis unknown. Therefore, its exact prognostic value or outcome has not been assessed. A study done by Min et al. has described that muscle invasion by a squamous cell carcinoma involving posterior mandibular alveolar ridge was associated with a cervical nodal metastasis.<sup>13</sup> 33 % of the patients showed histopathologic evidence of muscle invasion in our study suggesting that along with other established prognosticators, muscle invasion could be the reliable prognostic factor for determining the prognosis of the patient. Chandler k et al. hypothesized that the muscle invasion as a surrogate prognostic factor for depth of invasion can be correlated similarly for occult lymph node metastasis.<sup>14</sup>

In squamous cell carcinoma of head and neck the prognostic significance of perineural invasion has been investigated thoroughly. Perineural invasion was found to be positively correlated with lymph node status and recurrences.<sup>15,16</sup> But few studies reported no difference in outcome when perineural invasion was histopathologically evident.<sup>17,18</sup> In the present study, perineural invasion was seen in only 15 % of the total patients. Some studies aimed to determine the prognostic value of extracapsular spread through comparison of macroscopic and microscopic extracapsular spread.<sup>19,20</sup> These studies proposed that extracapsular spread had prognostic significance when it was macroscopically recognized, whereas microscopic extracapsular spread was rejected as a significant prognosticator in these studies. Several other studies found no difference in prognosis of the patients when compared between microscopic and macroscopic extracapsular spread.<sup>21,22,23,24</sup> In the current study, 38 % of patients had histopathological evidence of extracapsular spread.

Among the above mentioned clinicopathological parameters, habits ( $P = 0.043$ ), tumour differentiation ( $P = 0.004$ ), tumour size ( $P = 0.041$ ), perineural invasion ( $P = 0.043$ ) and extracapsular spread ( $P = 0.000$ ) were significantly correlated with lymph node status of the patients by using chi square test. To check the independency of the prognosticators we conducted multivariate logistic regression analysis which concluded that prognostic factors such as habits ( $P$  value-0.045), clinical tumour size ( $P$  value - 0.003) and perineural invasion ( $P$  value - 0.000) were independent prognosticators.

For Indian population, both chewable and smoke form of tobacco act synergistically in oral carcinogenesis in those individuals with mixed habits which eventually form a high risk population.<sup>25,26</sup> All the patients in our study had a history of tobacco consumption (predominantly smokeless). The various epidemiological studies conducted by various authors

reported use of smokeless tobacco as an important causative factor of oral cancer particularly in india and the risk of developing oral carcinomas in chewers (combinations of areca nut, betel leaf, tobacco and lime) was 2 - 4 times higher as compared to those individuals with no tobacco habits.<sup>26,27,28</sup> In a retrospective study conducted by Shenoj et al.<sup>29</sup> Gingivo-buccal sulcus is the commonly involved site in tobacco chewers because of the placement of the tobacco quid which acts as a contact carcinogen. Other patients had tobacco habits associated with alcohol consumption. Alcohol alone is not a risk factor for oral carcinomas but tobacco in combination with alcohol have synergistic effect for carcinogenesis. As nicotine promotes lymph node metastasis, individuals with existing malignant lesion with habit continuation will directly affect the cancer progression, metastasis and prognosis. Habit has been recognised as an independent prognosticator in our study and is significantly correlated to the lymph node status.

38.33 % of patients in our study had metastatic lymph nodes out of which majority had clinical tumour size of 2 - 4 cm (T2). A radiology based study conducted by Khan SA et al. showed a strong positive significant correlation in between the tumor size (more than 4 mm transversely) and lymph node metastasis.<sup>30</sup> Madana J et al. compared the radiological (CT) measurements of tumor thickness with histopathology and found them closely related to each other.<sup>31</sup> Clinical tumour size has been significantly correlated with lymph node status in our study and recognised as an independent prognostic factor. Similar observations were noted in the retrospective study conducted by Alessandro Menna Alves.<sup>32</sup>

Perineural invasion is usually defined as a microscopic identification of small unnamed peripheral nerves within the vicinity of an invasive tumor.<sup>33</sup> It is a well-recognized factor associated with poor prognosis. A study conducted by G Deepthi et al. 63.6 % and 50 % showed positivity for perineural invasion in T3 and T4 tumour stages with high significance.<sup>34</sup> Whereas in our study only 15 % cases showed perineural positivity and all of them were in T2 tumour stage. It was significantly correlated with the lymph node status in our study and was recognised as an independent prognosticator.

## CONCLUSIONS

This analysis suggests that habit, tumour size and perineural invasion to be consistent, easy to assess, and reliable independent prognosticators that are significantly correlated to the lymph node status. To conclude, it is of paramount importance to include the aforementioned prognosticators in histopathological reports for the prediction of clinical outcome and archiving of valued data for future analysis.

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