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Effect of Clinical, Demographic and Pathological Factors on Disease Free Survival Rate of Patients Having Oral Squamous Cell Carcinoma with Oral Submucous Fibrosis:- A Retrospective Study

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[doi: 10.33472/AFJBS.6.Si1.2024.268-277](https://doi.org/10.33472/AFJBS.6.Si1.2024.268-277)**ABSTRACT:**

Introduction-The oral cavity is the site where food is received and therefore an area of body where contact with exogenous materials is particularly intense. In response to exogenous materials protective mechanisms are an increased capacity for epithelial regeneration, and increased keratinization. These epithelial changes are reactive and reversible, but with progressive loss of normal control mechanism they lead to precancerous states and oral carcinoma. More than 90% of all oral cancers are squamous cell carcinoma (SCC). The most important risk factors for oral SCC are use of tobacco or betel quid which is also responsible for oral submucous fibrosis(OSMF). There has been increased incidence of concomitant association of OSCC & OSMF in recent times. Thus the aim of this study is to evaluate the effect of individual variables on disease free survival in patients having SCC alongwith OSMF.

Material and Methods-A retrospective observational study was carried out in which records of patients were retrieved from 2011 to 2014. A total of 78 patients having OSCC with OSMF were taken up for the study.

Patients present clinical information was obtained through telephone calls. Patients were evaluated on demographic, clinical and pathological fronts and its effect on disease free survival was studied.

Results- Out of 78 patients overall 3 year disease free survival was found to be 84.62%. Patients with negative margins had substantially low recurrence as compared to those who had positive surgical margins.

Regards to present study recurrence was present in 12 patients which was found to be the sole factor having profound impact on survival. Rest all variables did not have impact on disease free survival.

Conclusion- Good survival rate can be obtained with primary surgical treatment. Pre operative assessment of factors such as stage of lesion, cervical lymph node metastasis, extracapsular spread, staging of OSCC, grading of OSMF play a crucial role in predicting recurrence post- operatively. Thus, to improve survival rates, recurrence has to be minimized which in turn is controlled by above factors

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1. INTRODUCTION

The oral cavity is the site where food is received and therefore an area of body where contact with exogenous materials, microorganisms and harmful agents is particularly intense. The oral mucosa functions as mechanical as well as immunological barrier. Protective mechanisms are an increased capacity for epithelial regeneration, and increased keratinisation. These epithelial changes are reactive and reversible, but with progressive loss of normal control mechanism they lead to precancerous states and oral carcinoma. Oral cancer is the sixth most common cancer worldwide¹ⁱ. More than 90% of all oral cancers are squamous cell carcinoma (SCC). The most important risk factors for oral SCC are use of tobacco or betel quid. Use of betel-nut stiffens oral mucosa, a ubiquitous precancerous condition known as oral submucous fibrosis (OSMF). OSMF is an established pre-cancerous condition. There has been increased incidence of concomitant association of OSCC & OSMF in recent times. In patients having OSCC with OSMF, dense fibrosis and less vascularity of the corium, in the presence of an altered cytokine activity creates a unique environment for carcinogens from both tobacco and areca nut to act on the epithelium. Despite the development of diagnostic screening equipment, operation techniques, and postoperative care, there are a high number of patients manifesting advanced-stage oral cancer as well as high mortality. Thus the aim of this study is to evaluate the impact of clinical, demographic and pathological factors retrospectively on survival rate of patients having Oral squamous cell carcinoma with Oral submucous fibrosis.

2. MATERIALS AND METHOD

The retrospective observational studies present study was conducted in the Department of Oral and Maxillofacial Surgery, Datta Meghe Institute of Medical Sciences (Deemed University) and Acharya Vinoba Bhave Rural Hospital, Sawangi(M), Wardha. Data of patients having OSCC associated with OSMF who were treated between between 2011 to 2014 was retrieved from the MRD(Medical records department) and discharge cards for studying the three years survival. A total of 78 patients having OSCC with OSMF were taken up for the study. Present clinical information was obtained through telephone calls. Histopathologically established diagnosis of squamous cell carcinoma with oral submucous fibrosis, who had clinically positive neck node at first presentation and did not receive any treatment for the primary tumour were included for the study. While patients with multiple primaries or second primary tumours and previous history of treatment of OSCC or OSMF were excluded

Method

Disease free survival-Disease free survival was calculated from the first day of treatment to the date of disease recurrence.

Socio demographic evaluation

- 1) Age-Number of patients less than or more than 50 years were calculated and grouped accordingly
- 2) Sex-Number of males and females affected by the pathology were grouped separately.

Clinical evaluation

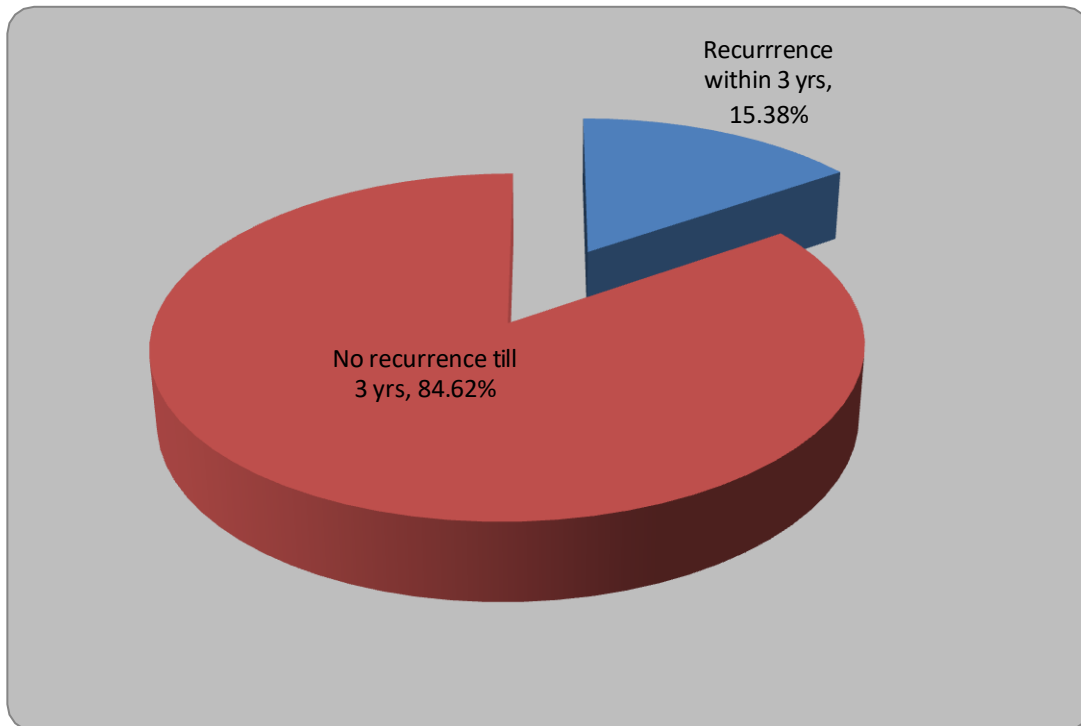
- 1) OSCC grading- (According to TNM staging Recommended by AJCC staging manual 7 th edition)
- 2) OSMF grading
Khanna and Andrade classification Grade I-Very early cases
Grade II-Early cases(26-35mm)

Grade III-Moderately advanced cases(15-25mm) Grade IV-Advanced cases(Less than 15 mm)

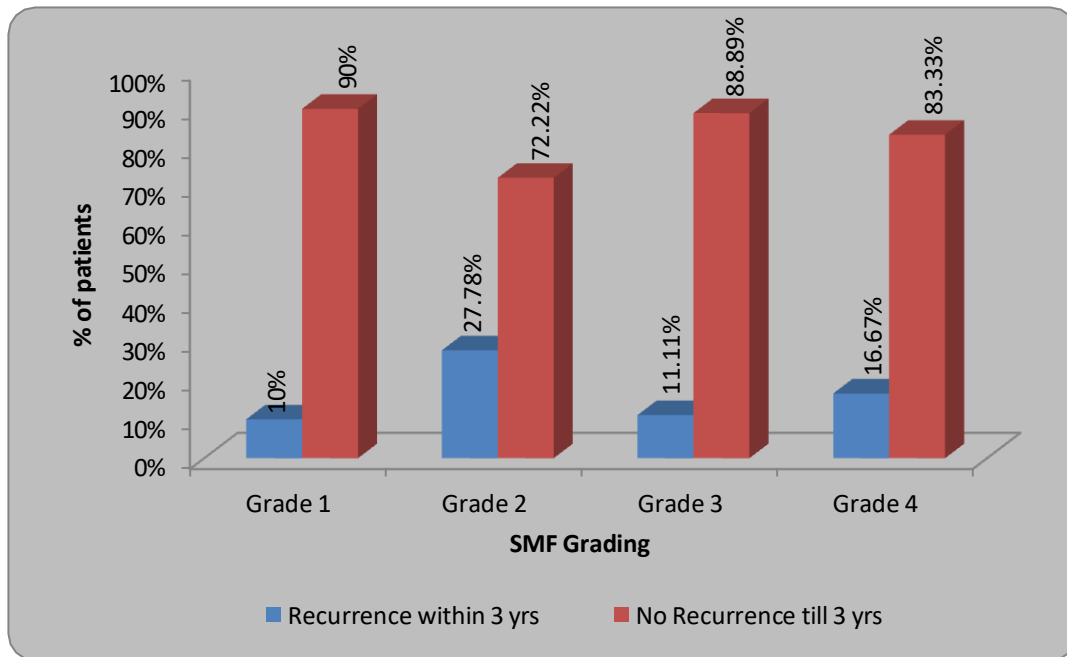
- 3) Recurrence-New lesion or growth at the operated site which was histopathologically proven to be squamous cell carcinoma was considered to be local recurrence. It was determined from surgery to pathologically confirmed diagnosis of squamous cell carcinoma.
 - 4) Type of habit- Form of tobacco which the patient consumes has a pivotal role in developing squamous cell carcinoma. Thus grouping of habit was done as follows
Betel nut alone
Betel nut with tobacco Pathological evaluation
- 1) OSCC grading-(According to Broders classification)
 - 2) Extracapsular spread(ECS)
 - 3) Tumor margins- Margins less than 5 mm were considered positive whereas margins more than 5 mm were considered as negative margins.

3. RESULTS

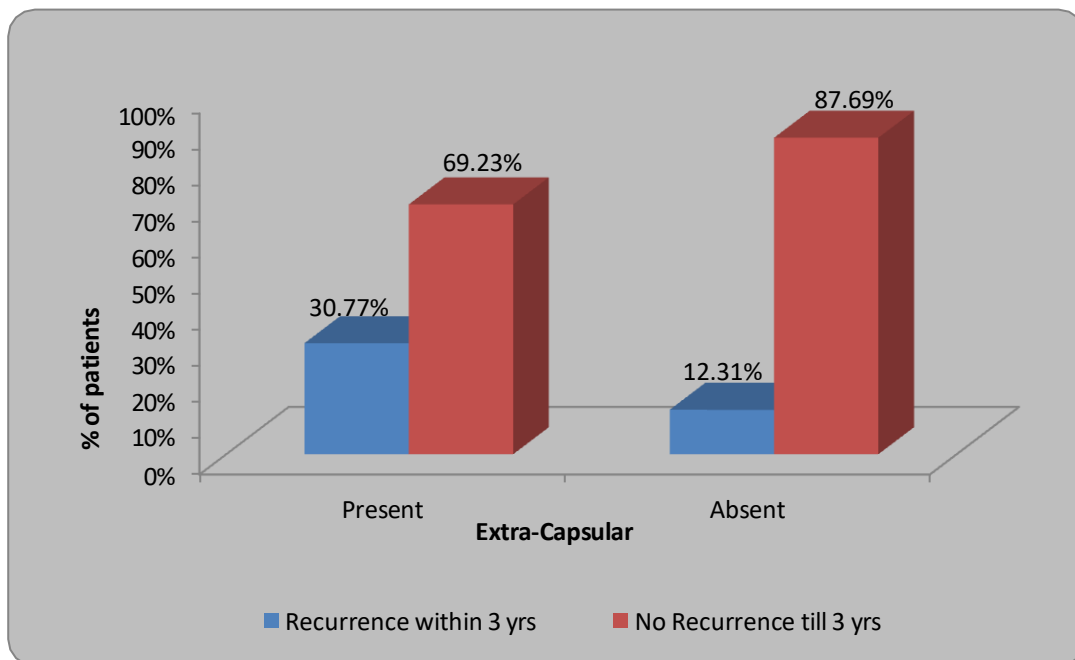
Graph 1: Disease free survival rates



Graphs 2: Correlation of SMF grading with disease free survival



Graph 3 : Correlation of disease free survival with extra-capsular spread.



Graph 4: Correlation of disease free survival with tumor margins.

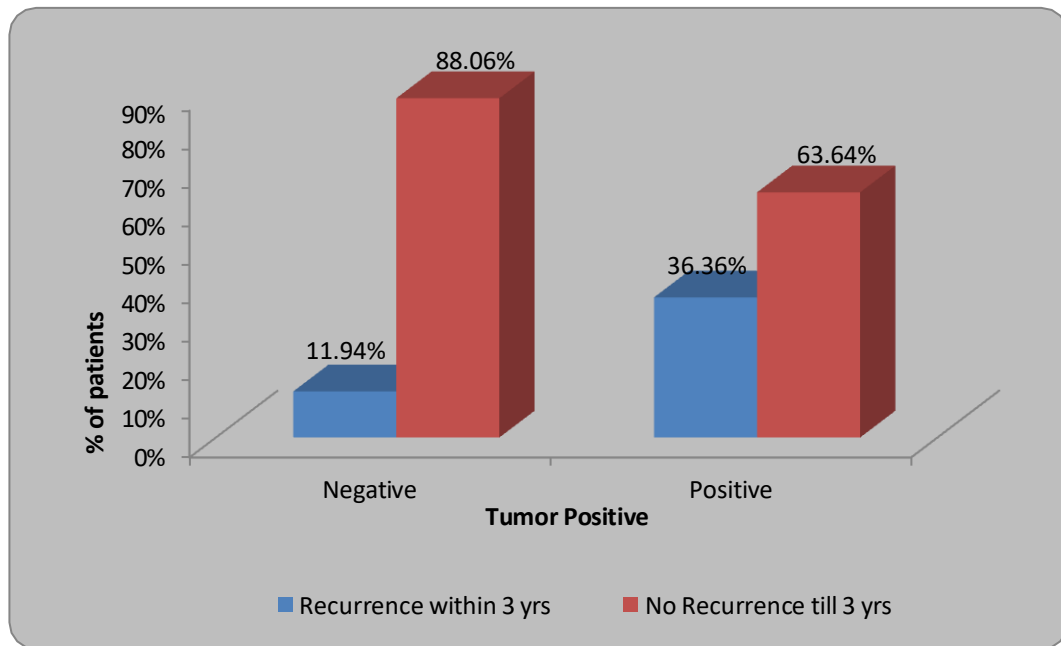


Table 1: Correlation of disease free survival with age

Age in yrs	Recurrence within 3 yrs		No Recurrence till 3 yrs		χ ² -value	p-value
	No of patients	Percentage	No of patients	Percentage		
≤50 yrs	5	13.51	32	86.49	0.18	0.36 NS,p>0.05
>50 yrs	7	17.07	34	82.93		

Table 2: Correlation of disease free survival with type of habit

Type of habit	Recurrence within 3 yrs		No Recurrence till 3 yrs		χ ² -value	p-value
	No of patients	Percentage	No of patients	Percentage		
Betel Nut	9	20.93	34	79.07	2.26	0.13 NS,p>0.05
Betel Nut Tobacco	3	8.57	32	91.43		

Table 3: Correlation of stage of tumor with recurrence

Stage of Tumor	Recurrence within 3 yrs		No Recurrence till 3 yrs		χ ² -value	p-value
	No of patients	Percentage	No of patients	Percentage		
Stage 1	0	0.00	3	100.00	8.51	0.036 S,p<0.05
Stage 2	1	25.00	3	75.00		

Stage 3	6	37.50	10	62.50		
Stage 4	5	9.09	50	90.91		

Table 4: Correlation of disease free survival with OSCC grading.

OSCC Grading	Recurrence within 3 yrs		No Recurrence till 3 yrs		χ ² -value	p-value
	No of patients	Percentage	No of patients	Percentage		
Poor	0	0.00	2	100.00	2.30	0.31 NS,p>0.05
Well	6	11.76	45	88.24		
Moderately	6	24.00	19	76.00		

Out of 78 patients overall 3 year disease free survival was found to be 84.62% (66) (*Graph I*). Statistical analysis was done using Chi square test and software used in the analysis were SPSS 22.0 version and EPI-INFO 6.0 version and $p < 0.05$ is considered as level of significance ($p < 0.05$).

7 out of 41 patients having age more than 50 years and 5 out 37 patients being below 50 years of age had recurrence in less than 3 year .In spite of these findings, they did not have a significant correlation with disease free survival (*Table I*). 7 out of 56 males and 5 out of 39 females had recurrence within 3 years. Gender too ceased to have a significant impact on disease free survival.

Out of 43 patients with betel nut chewing habit 9 patients were found to have recurrence within 3 years. Tobacco in smokeless form along with betel nut was consumed by 35 patient out of which only 3 had recurrence. (*Table II*) 37.50% patients having Stage III lesion had recurrence within 3 years. Staging of lesion had a significant impact on recurrence. (*Table III*). Maximum 27.78% patients having grade II SMF had recurrence within 3 years. Correlation of grading of SMF with recurrence was not significant although majority of patients were found to have grade I SMF. (*Graph II*). Equal number of patients I,e 6 belonging to well and moderately differentiated category out of 51 and 25 respectively had recurrence within 3 years still these gradings ceased to have a significant impact on disease free survival. (*Table IV*). In all 13 patients out of 78 patients had presence of extra-capsular spread out of which 4 patients had recurrence within 3 years. Presence of extra-capsular spread too did not have a significant impact on disease free survival. (*Graph III*). 11 patients out of 78 were found to have positive margins. 4 of these 11 patients had recurrence within 3 years which had a profound impact on recurrence rate. (*Graph IV*)

4. DISCUSSION

Many oral squamous cell carcinomas variants are preceded by clinically evident oral potentially malignant disorders. It is very important to prevent malignant change in people diagnosed with potentially malignant disorders (PMD). In the present study out of 78 patients overall 3 year disease free survival was found to be 84.62%. In terms of clinical factors majority of patients were found to have grade I SMF (Submucous fibrosis) ie 30. Maximum 27.78% patients having grade II SMF had recurrence within 3 years. Maximum 90 % patients having grade I SMF had disease free survival. Correlation of grading of SMF with recurrence was not significant. This may be attributed to incidental clinical diagnosis of intial SMF changes in patients with established malignant lesion. In 1995, Lumerman et al ⁱⁱ reported that

6.6-36 % of epithelial dysplasia may transform to invasive SCC.

Type of habit too did not have any effect as the disease was already established although betel nut chewing was found to be most prevalent in the present study. Out of 43 patients having habit of betel nut chewing 9 patients were found to have recurrence within 3 years. Although, type of habit failed to have a statistical significance on disease free survival. Shui et alⁱⁱⁱ in 2000 indicated that betel quid chewing as a significant factor influencing malignant transformation in hyperkeratosis or epithelial hyperplasia, dysplasia. Lee et al^{iv} in 2003 also concluded that betel quid chewing has been specifically correlated with poorer prognosis.

Demographically majority of patients were above 50 years of age with a male preponderance in the present study however they ceased to change the course of disease. 7 out of 41 patients having age more than 50 years were found to have recurrence in less than 3 years. In spite of these findings did not have a significant correlation with disease free survival. 7 out of 56 males and 5 out of 39 patients had recurrence within 3 years. Gender too ceased to have a significant impact on disease free survival.

Nguyen et al^v found no prognostic differences between males and females, although they reported lower survival rates in females, attributed to delay in seeking medical care and lower acceptance of treatment. Tabatabaei et al^{vi} in their study found 60 % of patients to be females afflicted with Oral squamous cell carcinoma. Correlation of age with Oral squamous cell carcinoma seems controversial. Rogers et al^{vii} reported that as the age of patient increased, disease specific 5 year survival decreased but Liu et al^{viii} reported that there was no significant difference statistically.

In spite of 51 patients having well differentiation it failed to have an improved outcome in terms of survival for the patients in the present study. Equal number of patients i.e 6 belonging to well and moderately differentiated category out of 51 and 25 respectively had recurrence within 3 years still these grading`s ceased to have a significant impact on disease free survival.

Degree of differentiation is used to predict the clinical behavior of OSCC for decades but its prognostic value is still controversial. Degree of cell differentiation, keratinization pattern and stage of invasion and lympho-plasmocytic infiltration are mainly taken into account. Most authors have established a significant correlation between poor degree of differentiation and lower prognosis^{ix,x} but others did not find any such correlation^{xi,xii}. Sarode et al^{xiii} hypothesized that OSCC arising in background of OSMF shows better grade of tumor differentiation. Genetic memory associated with epithelial biology in OSMF is carried forward during malignant transformation which is responsible for a better grade of tumor differentiation.

About two thirds of oral SCC are already of substantial size and will have clinically detectable metastasis to cervical lymph nodes at the time of diagnosis^{xiv}. The affected lymph nodes are firm and non tender to palpation and if extra capsular spread into the surrounding connective tissue has occurred, they will be fixed and matted^{xv}. The presence of extracapsular lymph node spread is associated with a high degree of local and regional recurrence, distant metastasis and mortality^{xvi}. In the present study In all 13 patients out of 78 patients had presence of extra-capsular spread out of which 4 patients had recurrence within 3 years. Presence of extra-capsular spread too did not have a significant impact on disease free survival.

Radicality in neoplasm surgical treatment is the most important principle in oncologic surgery. The completeness of removal clearly requires a cuff of healthy tissue around the neoplastic tissue, whose dimensions generally vary depending on several factors such as the type of tumor. In the present study 67 of 78 patients were found to have negative margins out of which 8 had recurrence within 3 years and out of 11 patients with positive

margins 4 had recurrence within 3 years. Patients with negative margins had substantially low recurrence as compared to those who had positive surgical margins. Loree et al^{xvii} found that the local recurrence rate for the close margin category (less than 5mm) was significantly different from the negative margin rate. On the other hand, using the same margin size (less than 5mm) for two anatomical oral cavity subsites namely floor of the mouth and oral tongue, Zelefsky et al^{xviii} concluded that this prognostic factor did not have a significant impact on local control. Nason et al^{xix} demonstrated that recurrence free survival for SCC was similar for patients with involved and with close margins and significantly worse than that observed in patients with negative margins.

Prognosis of OSCC is poor due to aggressive local invasion and metastasis, leading to recurrence. Thus it is an important prognostic factor in patients with OSCC. Camisasca et al^{xx} have reported that the 5 year survival rate was 92% in OSCC patients without recurrence and 30 % in patients with recurrence. Lindenblatt et al^{xxi} also reported similar findings in their study. Ebrahimi et al^{xxii} have reported that T stage and N stage were important factors affecting regional recurrence in OSCC. Thus identifying factors that affect the recurrence of OSCC to reduce post-operative recurrence is an emerging issue. Regards to present study recurrence was present in 12 patients which was found to be the sole factor having profound impact on survival.

5. CONCLUSION

Good survival rate can be obtained with primary surgical treatment. Pre operative assessment of factors such as stage of lesion, cervical lymph node metastasis, extracapsular spread, staging of OSCC, grading of OSMF play a crucial role in predicting recurrence post-operatively. Thus to improve survival rates, recurrence has to be minimized which in turn is controlled by above factors. In the future, there is a need to collect more patient data to determine the survival rate of each patient by treatment method and analyse how, given the same primary site and cervical lymph node metastasis status, the combined treatment method such as chemotherapy and radiotherapy performed with primary tumor resection affects the patients survival rate.

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