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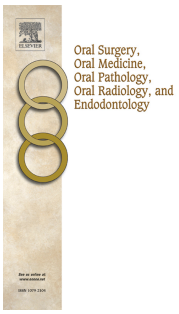

Oral squamous cell carcinoma associated with oral submucous fibrosis have better oncologic outcome than those without

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Abstract:

Objectives: Oral submucous fibrosis (OSMF) is a potentially malignant disorder associated with the use of areca nut and is mainly seen in the parts of South-East Asia and Indian sub-continent. We hypothesized that Oral cancers occurring in presence of OSMF are clinico-pathologically a distinct entity.

Study design: We analyzed 289 treatment naïve patients of oral cancer. They were followed up for a median of 44 months. Association of presence of OSMF with other histopathological factors was done using Chi square test. Kaplan Meier analysis was used for survival analysis.

Results: Oral squamous cell carcinoma along with OSMF was seen more often in younger patients ($p<0.001$), males ($p<0.007$) and had a lower T ($p<0.002$), N stage ($p<0.000$). These were thinner ($p<0.002$), less infiltrative ($p<0.04$) tumors and required adjuvant therapy less frequently ($p<0.017$). The mean disease specific survival, overall for those with and without OSMF was 58.8 and 48.6 months ($p<0.002$) and specifically for stages III, IV was 49.4 and 38.5 months respectively ($p<0.053$).

Conclusion: Oral squamous cell carcinomas associated with OSMF are associated with good clinico-pathological profile and have better prognosis and oncological outcomes.

Introduction:

Oral sub-mucous fibrosis (OSMF) is a potentially malignant disorder associated with the use of areca nut. Areca nut has been labelled as a group I human carcinogen. [1, 2] Its use is mainly seen in the Indian sub-continent and parts of South-East Asia where chewing of areca nut along with tobacco is prevalent. [3] Use of areca nut results in juxta-epithelial inflammation and progressive fibrosis of submucosa. Being a potentially malignant condition certain patients with OSMF develop oral squamous cell carcinoma. Oral squamous cell carcinomas (OSCC) associated with OSMF are characteristically seen in those who chew areca nut. We believe that such tumors which occur in the background of OSMF due to use of areca nut are different from OSCC not associated with areca nut and OSMF. We have previously published a study that demonstrated that oral cancers associated with OSMF are a clinico-pathologically distinct entity from oral cancer without OSMF. [4] We followed up the patients of the above mentioned study for a period of 5 years and analyzed the overall prognosis with reference to presence or absence of OSMF.

Methodology:

This was a retrospective analysis of prospectively collected data on oral cancer patients. We had previously published a study of 371 patients comparing prevalence of prognostic factors in patients of oral cancer with and without OSMF. Present study involved long term follow up of those patients with an aim to evaluate differences in outcome. We excluded 82 patients from this study as they did not have adequate follow up details (<6 months). Therefore, this was an analysis of 289 treatment naïve patients

of oral cavity squamous cell carcinoma. These patients were operated between June 2010 and April 2011 at our institution. All patients had histologically proven diagnosis of squamous cell carcinoma. These included both patients with and without OSMF. Patients having OSMF were diagnosed clinically based on whether they had intolerance to hot and spicy foods, pale looking oral mucosa, palpable fibrotic bands and chronic progressive trismus. Patients not having these clinical features were diagnosed as not having OSMF. We excluded all patients with non squamous histology, history of prior treatment, recurrences, multiple or second primaries. Patients who died due to any other cause except due to the disease were excluded. As mentioned earlier, patients whose adequate follow up details were not available were also excluded from the study. The patient's last follow up status was updated till March 2016.

All the demographic details of the patients were recorded viz age, gender, addictions, date of registration and surgery details. The final histopathology report of all patients was analyzed and presence or absence of all prognostic factors was documented. All the patients were staged as per the AJCC 7th edition. The decision for adjuvant therapy was based on the standard evidence based guidelines. The patients were then kept on follow up quarterly for first two years and thereafter 6 monthly thereafter. As the study involved retrospective analysis of data without any active intervention on the patients, IRB approval was not sought for. The study was in compliance with Helsinki declaration.

The data was analyzed using SPSS 21 software. Association of presence of OSMF with other histopathological factors was done using Chi square test. P value of less than 0.05 was considered significant. Man Whitney-U test was used to check for association between tumor thickness and OSMF. Kaplan Meier analysis was used for survival

analysis. Multivariate analysis was done using cox-regression proportional hazard model.

Result:

Demography

There were 289 patients in this analysis. The mean follow up for all the patients was 38.7 months and the median follow up was 44 months. OSMF was present in 30.5% (88) patients. The age of patients ranged from 18 years to 81 years. Median age of patients in OSMF group was 43 years and of those without OSMF was 49 years. Age-group wise distribution is given in table 1. OSMF was seen more often in younger age-groups ($p < 0.001$). The majority of the patients were males (82.4%). The percentage of males in OSMF and non OSMF group was 90% and 72.8% respectively. Thus, the incidence of OSMF was significantly higher in males ($p < 0.007$).

Association with various factors (table 1)

T stage distribution of the cohort was as follows - T1 in 27.7%, T2 in 29%, T3 in 8.9% and 34.3% had T4 lesions. OSMF was associated with a higher incidence of early stage cancer. Majority (70.5%) of patients in OSMF group were of T1-T2 stage as compared to 50.7% in patients without OSMF. This association of OSMF with early T-stage cancer was found to be statistically significant ($p < 0.002$). The pathological nodal status of the patients was as follows - 54.3% (157) patients were pN0, 17.3% (50) were pN1 and 28.4% (82) were having pN2 status. In patients with OSMF, 71.5% (63) patients were pN-zero whereas in patients without OSMF only 46.7% (94) were pN-zero. Patients with OSMF were found to have significantly better N stage ($p <0.000$). In patients with early

stage tumors (T1, T2), we noticed that patients with OSMF were more likely to be node negative ($p<0.03$). On evaluating, T3 and T4 stages separately, it was observed that OSMF group had more pathologically node negative patients (65.4%) as compared to non OSMF group (36.4%). Perineural invasion was present in 15.6% of the patients. Its association with OSMF was not found to be significant. (table 1). Extracapsular spread was present in 27.6% (80) of the entire group. On evaluating just the node positive patients, the distribution of ECS in OSMF and non-OSMF group was not found to be of significance ($p<0.332$). Tumors were also classified based upon the gross morphology as; ulcerative, proliferative, ulcero-proliferative, infiltrative, ulcero-infiltrative and verrucous. Infiltrative and ulcero-infiltrative morphology was seen less often in patients with OSMF. Linear by linear association of tumor morphology with OSMF was found to be significant ($p < 0.049$).

Adjuvant therapy was administered to 75.4% patients (n=218). Out of these, 71.1% received adjuvant radiotherapy and 28.9% patients received adjuvant chemo-radiotherapy. Correlation between adjuvant therapy received and OSMF was significant and adjuvant therapy was required less often in the patients having OSMF ($p <0.017$). Mean thickness of the primary tumor in presence of OSMF was found to be 1 cm (0.2-2.5 cm). In those patients without OSMF, mean thickness was 1.3 cm (0.1-4 cm). Association between tumor thickness and presence of OSMF was assessed using Man Whitney-U Test. Tumors without OSMF were found to be significantly thicker. ($p < 0.003$). Tumor differentiation was assessed in both the groups. It was observed that incidence of well differentiated tumors was higher in patients with OSMF, this association was found to be significant ($p < 0.002$). We analyzed the margin status in

the two groups. We found that in patients having OSMF, clear margins were obtained in 95.5% of the patients and in those without OSMF it was obtained in 89.6% of the patients No statistically significant difference between the two groups existed (p<0.11).

Effect on survival (Table 2)

Mean disease specific survival of the entire cohort was found to be 53.9 months and the median disease specific survival was 68 months. Patients having OSMF had a mean disease specific survival of 58.8 months and those without OSMF had mean disease specific survival of 48.6 months. This difference between the two groups was found to be statistically significant (p value < 0.002).

On evaluating patients with node positive neck, ECS was seen in 80 patients and mean survival in patients who had co-existing OSMF was 42 months and in those without OSMF it was 23 months. The difference was statistically significant (p <0.02). In patients not having ECS no statistically significant difference in survival was noted (p<0.72).

PNI was seen in 45 patients. Mean survival in these patients with co-existing OSMF was 38.4 months and in those without OSMF was 30 months. The difference was not statistically significant. In patients without PNI but with OSMF survival was 61.2 months and in those without OSMF it was 50.7 months. This difference was found to be statistically significant (p < 0.003).

No statistically significant difference was seen between the OSMF and the non-OSMF groups with regard to distribution of well differentiated or poorly differentiated tumors. In those having moderately differentiated tumors, survival in those with OSMF was 60

months and in those without OSMF it was 50.7 months. This difference was statistically significant ($p < 0.014$).

Based upon T stage, patients were grouped as those having T1, T2 tumors (early lesions) and T3, T4 tumors (advanced lesions). For patients with and without OSMF the difference in survival between the two groups (early and advanced lesions) was not statistically significant. P values were 0.08 and 0.06 respectively. Even though statistically not significant, there was a trend toward better survival in the OSMF group.

While comparing the survival between OSMF and non OSMF group with respect to their nodal status, we found that among the pN0 patients, there was no statistically significant difference in survival between the two groups. Whereas, among pN+ patients the survival in those with OSMF was significantly higher than in those without OSMF ($p < 0.037$).

On being grouped based upon the adjuvant therapy offered, no statistically significant difference in survival was seen between the OSMF and non-OSMF group.

In order to negate the effects of other prognostic factors we evaluated the survival in patients with stage T1 T2 and N0. Survival in patients with OSMF was 59 months and in those without OSMF was 70 months. The difference between the two was not significant ($p<0.37$).We compared survival after dividing the patients according to stage; that is early (stage I and II) and advanced stage (stage III and IV). (Figure 1 and 2) In early stage disease, the difference between OSMF and non-OSMF group was not significant. For advanced stages, OSMF group had a trend towards better survival, though the difference was not statistically significant ($p<0.053$).

Multivariate analysis was done to evaluate the impact of OSMF on survival and it was not found to be an independent predictor of survival.

Discussion:

OSMF has been defined by WHO as a “slowly progressive disease in which the fibrous bands form in the oral mucosa, ultimately leading to severe restriction of movement of the mouth, including tongue.” [(5)] It is an oral potentially malignant disorder which is seen predominantly in parts of South East Asia and more so in Indian sub-continent due to prevalent use of areca nut. OSMF presents with progressive reduced mouth opening, burning sensation, blanching of oral mucosa and development of fibrotic bands in advanced stages. Annual malignant transformation rate has been reported to be around 0.5%. OSMF has direct dose-dependent association with areca nut usage. Areca nut may be used alone or in combination with tobacco or as betel quid (slaked lime, tobacco and betel leaves) or as pan masala (grounded form of areca nut with tobacco). Simultaneous use of tobacco and alcohol along with betel quid has been found to increase the odds of malignant transformation of OSMF. [(6)] Areca nut itself has been labelled as group I carcinogen by the IARC. Association of OSMF and areca nut use has been proven. There is an increased collagen formation and juxta-epithelial inflammation and deposition of collagen matrix in the submucosa and its decreased degradation. There is also an increase in local cytokine levels.[(7, 8, 9, 10)] All this results in intense submucosal fibrosis. Malignant transformation in OSMF may occur due to changes in the cell cycle, DNA, keratinocytes, and keratin, tumor-cell proliferation and survival, angiogenesis, fibrosis through epithelial-mesenchymal transitions (EMTs), and

tissue hypoxia. [11] We believe that the OSCC developing in the background of OSMF is biologically a different cancer compared to other OSCC not associated with OSMF.

In a previous study from our institution we had shown that oral squamous cell carcinoma occurring in background of OSMF was a clinico-pathologically distinct entity. We had found that patients of oral cancer with OSMF present in a younger population. It is seen more often in males and is associated with better prognostic factors such as better grade of tumor differentiation, lesser incidence of nodal metastases, and extracapsular spread. We also noted that presence of OSMF was an independent factor influencing the nodal metastases.[4]

There have been no other studies which have looked at the long term impact of OSMF in patients of OSCC. In this study we followed up these patients for 5 years. We looked for association between the presences of OSMF with adverse histological factors. The impact of co-existing OSMF on survival in these patients of OSCC was also evaluated.

We found that patients of OSCC with co-existing OSMF presented at an earlier stage. These patients had an early T and N stage at presentation with lower incidence of ECS. It may be tempting to attribute this to early presentation of the patients with OSMF because of their nagging symptoms. However, significantly low incidence of nodal metastases in the group with early diseases (T1/T2) points to better biology of those with OSMF ($p<0.03$). Even in advanced T stage tumors the group with OSMF had more patients with pathologically node negative neck (65.4% vs 36.4%). We do not know the exact cause for this but we speculate that as fibrosis in OSMF constricts the blood vessels, probably due to similar mechanism lymphatic supply is also blocked due to pre-

existing fibrosis resulting in lower incidence of nodal metastasis. [12] We found that the tumors associated with OSMF had higher chances of being well differentiated than those associated without OSMF. Patients with OSMF not only had lesser chances of being morphologically infiltrative but were also associated with thinner tumors. This could again be attributed to sub-mucosal fibrosis that may restrict an infiltrative growth pattern and result in tumors with lesser thickness. [13] The patients with OSMF had less thick tumors as compared to those without OSMF. Thicker tumors have been found to have poor prognosis. [14] Due to presence of fibrosis in mucosa adjoining the tumor, it can be technically challenging to ascertain tumor margin by digital palpation. This is further complicated by the trismus associated with OSMF. Despite this no statistically significant difference with respect to margins was seen in the OSMF and the non-OSMF group. Patients with OSMF had lesser chances of receiving adjuvant therapy thus demonstrating better clinico-pathological profile of tumors associated with OSMF. This could be due to OSMF patients having better differentiation, lower stage, lesser nodal metastases and thinner tumors.

In order to further assert our hypothesis that OSCC patients with OSMF are a clinico-pathological distinct entity, we looked at disease specific survival in these patients. The patients with OSMF had statistically better mean survival than the patients without OSMF (58.8 months vs 48.6 months, $p < 0.002$) thus proving our hypothesis. We stratified the patients based upon various known prognostic factors and compared survival between the two groups in these strata. Patients with OSMF had better survival even when stratified on the basis of T stage, N stage, ECS, PNI and adjuvant therapy. Though, statistical significance was achieved only in few strata such as nodal positivity,

absence of PNI and presence of ECS (Table 2). Absence of statistical significance in other groups could be due to lesser number of patients in each stratum. We assessed the patients with stage T1, T2 and N0 separately so as to negate the effect of other more powerful prognostic factors. We found that there was no statistically significant difference between the OSMF and non-OSMF groups. On comparing survival in early and advanced stages of cancer, OSMF group had a trend towards better survival in advanced disease. We believe that the survival advantage in OSMF group was seen more clearly in advanced stages of disease because they had lesser chances of nodal metastasis and were associated with good prognostic factors. This depicts the better clinico-pathological profile and prognosis of the OSMF patients. In early stage tumors the difference in survival was not that apparent because due to early stage even the non-OSMF group had lesser nodal metastasis and lesser association with poor prognostic factors.

Multivariate analysis for survival was done to assess the impact of OSMF on survival. It was not found to be an independent predictor for survival. This happened because relatively OSMF was a weaker prognostic factor as compared to other stronger prognostic factors like N stage, ECS, differentiation and PNI.

Conclusion:

In this study, we found that OSCC with OSMF are more often seen in younger males and are associated with good clinic-pathological factors. These patients are more likely to have lower T and N stage and are generally well differentiated. Lesions in patients with OSMF are less likely to be thicker or infiltrative. Requirement of adjuvant therapy in

patients with OSMF patients is less frequent. The patients with OSMF have better mean disease specific survival compared to the non-OSMF group, the better survival is more apparent in advanced stages of disease. Thus, patients of OSCC with OSMF have better clinico-pathological profile and prognosis compared to OSCC without OSMF.

Acknowledgements: none

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Legends:

Table 1: Patient distribution according to different parameters along with p value of association with presence of OSMF

Table 2: Difference in survival with respect to different parameters between the group of patients having OSMF and not having OSMF

Figure 1: Kaplan Meir survival curves showing mean disease free survival in patients with and without oral submucous fibrosis in stage I & II

Figure 2: Kaplan Meir survival curves showing mean disease free survival in patients with and without oral submucous fibrosis in stage III & IV

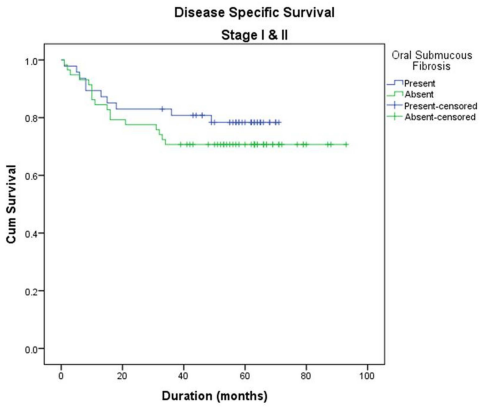
Parameter		Number of patients		P value	Confidence Interval-Mean (Range)
		OSMF present (n=88) (percentage)	OSMF absent (n=201) (percentage)		
Gender				0.007	2.72 (1.22-6.06)
	Male	80 (91)	158 (78.6)		
	Female	8 (9)	43 (21.4)		
Age group				0.001	2.26 (1.42-3.62)
	<30 years	6 (6.8)	8 (3.9)		
	31-50 years	62 (70.5)	102 (50.8)		
	51+	20 (22.7)	91 (45.3)		
T stage				0.002	2.31 (1.35-3.95)
	T1-T2	62 (70.5)	102 (50.8)		
	T3-T4	26 (29.5)	99 (49.2)		
N stage				0.000	1.86 (1.34-2.57)
	N0	63 (71.5)	94 (46.8)		
	N1	11 (12.5)	39 (19.4)		
	N2	14 (16)	68 (33.8)		
Margin status				0.11	2.45 (0.815-7.36)
	Positive/Close (<5mm)	4 (4.5)	21 (10.4)		
	Clear (>=5mm)	84 (95.5)	180 (89.6)		
Tumor thickness		-	-	0.003	-
Tumor differentiation				0.002	1.92 (1.97-2.90)
	Well differentiated	20 (22.7)	24 (12)		
	Moderately differentiated	54 (61.4)	115 (57.2)		
	Poorly differentiated	14 (16)	62 (30.8)		
PNI				0.648	1.17 (0.59-2.31)
	Present	15 (17)	30 (14.9)		
	Absent	73 (83)	171 (85.1)		
ECS (in N+)				0.332	-0.068 (-0.207-0.070)
	Present	13 (52)	67 (62.6)		
	Absent	12 (48)	40 (37.4)		
Tumor morphology				0.049	1.186 (1.001-

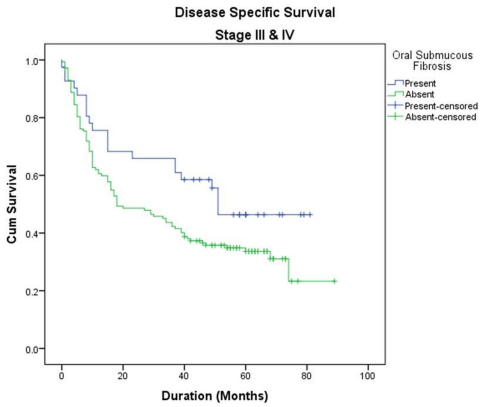
					1.41)
	Ulcerative	13 (14.8)	22 (11)		
	Proliferative	6 (6.8)	8 (4)		
	Ulceroproliferative	30 (34.1)	50 (24.8)		
	Infiltrative	5 (5.7)	16 (8)		
	Ulceroinfiltrative	28 (31.8)	97 (48.2)		
	Verrucous	6 (6.8)	8 (4)		
Adjuvant therapy				0.017	0.96 (0.71-1.3)
	None	27 (30.7)	44 (21.9)		
	RT	51 (58)	104 (51.7)		
	CTRT	10 (11.3)	53 (26.4)		

Table 1: Patient distribution according to different parameters along with p value of association with presence of OSMF

Parameter		**Survival in OSMF present (months)**	**Survival in OSMF absent (months)**	**P value**
Mean survival		58.8	48.6	0.002
Stage				
	Stage I, II	59.1	70.2	0.37
	Stage III, IV	49.4	38.5	0.053
T1T2 N0		59	70	0.37
T stage				
	T1, T2	62.3	57.8	0.08
	T3, T4	48.8	38.3	0.06
N stage				
	N0	60.4	64.1	0.28
	N+	49.2	31.4	0.03
ECS (in N+)				
	Yes	42	23	0.02
	No	39.1	39.2	0.72
PNI				
	Yes	38.4	30	0.20
	No	61.2	50.7	0.003
Grade				
	Well differentiated	64.9	70.3	0.44
	Moderately differentiated	60	50.7	0.014
	Poor differentiated	26.8	30.6	0.73
Adjuvant therapy				
	None	52.6	53.4	0.198
	RT	58.2	54.8	0.124
	CTRT	49.7	25.4	0.08

Table 2: Difference in disease specific survival with respect to different parameters between the group of patients having OSMF and not having OSMF





Statement of clinical relevance: This study shows that, OSMF related oral cancers are a biologically distinct entity. They are associated with good clinico-pathological profile and better prognosis.

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