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### A retrospective study of clinicopathological features of oral squamous cell carcinoma with and without oral submucous fibrosis

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#### Abstract

**Context:** Oral submucous fibrosis (OSF) is strongly associated with areca nut usage; the existence of OSF in patients with oral squamous cell carcinoma (OSCC) is an indicator of areca nut-induced carcinogenesis. As areca nut follows a discrete molecular path for oral carcinogenesis, this could be the basis why OSCC patients with OSF are different and are currently projected to constitute a distinct clinicopathologic entity. **Aim:** This study aims to analyze and compare the demographics, risk factors and clinicopathologic features of OSCC patients with and without OSF. **Materials and Methods:** A retrospective review of OSCC cases treated in the institution from 2008 to 2013 was done. Sixty OSCC of buccal mucosa were selected, of which 30 were with concomitant OSF and 30 without OSF. Demographics, risk factors and clinicopathological features were studied. The data were analyzed by SPSS-20 software, using the Pearson Chi-square, Fisher's exact and Mann-Whitney U-tests. **Results:** OSCC cases with OSF were younger (mean age 40.5 vs. 54 years) compared to those without OSF ( $P < 0.05$ ). Risk factors and other clinicopathological parameters did not differ between the two groups. There was significant difference in the two groups with regard to tumor differentiation ( $P = 0.000$ ). Tumors in OSCC with OSF were more likely to be well differentiated. **Conclusion:** Although majority of OSCC patients with OSF were young with a better grade of tumor differentiation, other clinicopathologic features having prognostic significance did not differ significantly between the two groups. Therefore, OSCC arising in background OSF as a distinct entity is uncertain.

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#### Full Text

### Introduction

Oral submucous fibrosis (OSF) is a potentially malignant disorder of the oral cavity.[1] It is mainly associated with chewing of areca nut, an ingredient of betel quid, and is prevalent in South Asian populations.[2] A high incidence of OSF is linked to areca chewing in the Indian subcontinents.[3],[4] The areca nut alkaloid arecoline is now identified as a principal causative factor in OSF.[4]

OSF may cause atrophy in the epithelium, thus increasing the carcinogen penetration.[5] Arecoline is a desiccating agent and may shrink the cells enough to permit percolation of carcinogens through the epithelium to reach the basal layer, which is the dividing cell layer where neoplastic cellular transformation may occur. The permeability of the epithelium to carcinogens is a potent mechanism that may play a role in arecoline-related carcinogenesis.[6]

Studies suggest that dysplasia is seen in about 25% of biopsied OSF cases.[5] Epithelial dysplasia has been reported to occur in 7%–43% of OSF in different studies.[6] However, the rate of transformation to malignancy varies from 3% to 19%.[6],[7] The incidence of oral squamous cell carcinoma (OSCC) concomitant with OSF was found to be 25.77% in a recent study from India, and it is evident that the malignant potential of OSF is underestimated.[8] Since areca nut follows a distinct molecular pathway for oral carcinogenesis, this could be the basis why patients with OSF-OSCC have different morphology, histology and biology.[3] In few studies on OSCC arising in the background of OSF, it was noted that patients with OSF-OSCC were younger males with better prognostic factors such as better grade of tumor differentiation, lesser incidence of nodal metastases and extracapsular spread (ECS).[1],[3] Contradictory data stating that OSCC originated from OSF is clinically more invasive and also exhibits higher metastasis and recurrence rate than OSCC not originated from OSF have been reported from China.[9] Currently, it has been proposed that OSCC arising in OSF constitutes a clinicopathologically distinct disease; the differences of which are believed to arise from differential mechanisms of areca nut carcinogenesis.[3],[10],[11] Considering the controversy that exists in the literature regarding OSCC arising in the background of OSF and based on the proportion of OSCC-OSF reported during clinical practice in the institution motivated the authors of this study to analyze the demographics, risk factors and clinicopathologic features of OSCC occurring with and without OSF.

### Materials and Methods

The study protocol was approved by the Institutional Ethics Committee SDMCDSh-IEC (IRB No: 2013/UG/OP/17). A retrospective review of OSCC cases treated in the institution during a 5-year period from 2008 to 2013 was done. Out of 537 OSCC cases reported in the institution, 60 OSCC (stage matched) cases primarily affecting the buccal mucosa were selected. Of which, thirty carcinomas occurring in the background of OSF and another thirty without OSF were chosen. An a priori testing was done to calculate the sample size. OSCC cases arising in OSF background were selected based on the history and clinical features of OSF transforming into OSCC mentioned in the patient records. Parameters for analysis included demographics, risk factors, clinical details, clinical staging and histopathology.

Histopathological analysis included:

Grading: Broder's grading, invasive front grading (IFG)[12] and Martinez–Gimeno score system (MGSS)[13] Tumor thickness (TT) measured using ocular micrometer: Microscopic TT was defined as the maximum TT excluding the keratin coat, taking the vertical extent of the tumor from the surface to its deepest extent in a perpendicular fashion[14] Lymph node metastasis (LNM); ECS; surgical margin status; Recurrence Sections obtained from surgical specimens of 30 OSCC-OSF were compared with 30 OSCC without OSF. In each case, all the parameters of IFG and MGSS were analyzed in detail and scored. The sum of the scores was used to decide the grade of the tumor or risk associated with metastasis.

Inclusion criteria

Patients with untreated OSCC who reported to the institution from 2008 to 2013 were included in the study. These patients underwent surgical excision of the lesion along with neck dissection in the craniofacial unit of the institution from 2008 to 2013.

Exclusion criteria

OSCC patients with multiple primaries and second primary; patients who were treated elsewhere before reporting to the institution; patients with preoperative chemotherapy or radiotherapy; patients with local resection without neck dissection; patients with previous malignancies in or outside the oral cavity and histologic variants of OSCC were excluded from the study.

Source of data

Clinical details were obtained from the patient records on file from departmental database. Hematoxylin and eosin stained tissue sections were obtained from archives of department for histopathological analysis. All the sections were analyzed by two researchers who followed uniform criteria and were blinded to the final outcome. Before commencement of the principal study, a pilot study was carried out to assess inter- and intra-observer consistency for scoring the histopathological parameters.

Statistical analysis

The data were tabulated and analyzed by SPSS 20.0 statistical software (IBM Corp., Armonk, NY, USA). Frequency tables of categorical data were analyzed using the Pearson Chi-square test, Fisher's exact test and Mann–Whitney test. Probability level was fixed at <0.05.

## Results

Comparative analysis of clinicopathologic characteristics of oral squamous cell carcinoma with oral submucous fibrosis and without oral submucous fibrosis

[Table 1] shows that OSCC cases with OSF were younger (mean age 40.5 vs. 54 years) compared with without OSF. There was no significant difference in the two groups with regard to various other clinical characteristics. [Table 2] shows tumors in the OSCC without OSF group were more likely to be poorly differentiated (12 cases vs. nil) than those with OSF. Tumors in OSCC-OSF were more likely to be well differentiated [Figure 1]. There was significant difference in the two groups with regard to tumor differentiation ( $P = 0.000$ ). There was no significant difference in the two groups with regard to other pathologic features. LNM was seen in larger number of cases in OSCC without OSF than with OSF. {Table 1}{Table 2}{Figure 1}

Analysis of additional histopathologic prognosticators

[Table 3] shows that of the 60 OSCC cases analyzed, 21% of cases had intravascular invasion (IVI), 47% cases with perineural invasion (PNI) and 48% of cases were >3–7 mm thick. Only 18% of the tumors had uniform front (pushing, well defined) while 82% were showing infiltrating solid cords or small groups/marked and widespread cellular dissociation [Figure 2]. Mean (actual) TT in OSCC-OSF group was 6.9 mm and OSCC without OSF was 9.2 mm ( $P = 0.113$ ) [Figure 3] and [Figure 4]. {Table 3}{Figure 2}{Figure 3}{Figure 4}

Clinicopathologic characteristics influencing lymph node metastasis

In the univariate analysis, it was observed that tumor extension, type, size, stage, tumor differentiation, MGSS score, TT, IVI and PNI emerged as significant factors associated with LNM ( $P < 0.05$ ) [Table 4]. Mean TT in pN +ve group was 10.8 mm and pN –ve was 7.3 mm ( $P = 0.001$ ). {Table 4}

## Discussion

The highest incidence of oral cancer in the world was noted in the Indian subcontinent mainly due to the high prevalence of chewing smokeless tobacco and areca nut.[15] In this study, 68% of OSCC cases were chronic tobacco and areca nut chewers; majority of them were obsessed with commercially prepared areca nut preparations. The frequency of cases with tobacco and areca nut chewing were higher in OSCC-OSF than without OSF group. The number of patients who practiced the habits for 1–10 years' duration was more in OSCC-OSF than without OSF. However, there was no statistically significant difference between the two groups with respect to parameters such as habits and duration of habits. Analyses of related "habits" in 371 OSCC patients did not offer significant information on the individual roles of smokeless tobacco and areca nut; two well-established carcinogens by Chaturvedi et al. and Gadabail et al. noted that duration of tobacco- and betel nut-chewing habit was significantly higher in OSCC compared to OSCC-OSF. Habit of smoking and alcohol was predominant in OSCC patient compared to OSCC-OSF.[16]

In this analysis out of 60 OSCC cases, 52% were ≤45 years. It indicates that a larger number of young patients are exposed early to tobacco and areca nut habituation which may imply a higher vulnerability in this area.[17] The habitual use of betel products from childhood, with duration, frequency and cumulative amount all being factors, enhances the risk of early development of OSF and with progression to more lethal variants increases the probability of transformation to frank OSCC.[18] Studies on OSCC-OSF states that individuals with OSCC-OSFs were younger when compared with OSCC alone.[3],[16] Similar findings were noted in this study. OSCC with OSF were younger (mean age 40.5 vs. 54 years) compared with OSCC alone.

In a study by Chaturvedi et al., it is mentioned that OSCC-OSF was significantly common in male patients (M:F = 10:1) compared with OSCC alone (3.2:1). There was no significant difference in gender distribution between OSCC-OSF and OSCC without OSF.[3] Overall, in this study also, OSCC was noted predominantly in males (90%) compared to females (10%) (M:F = 9:1). The higher incidence of OSCC among males (with/without OSF) can be explained by the fact that the incidence of chewing habit is higher among males.[3]

Most oropharyngeal cancers in India present in advanced stages of malignancy.[19] In this study, 52% were >4 cm and 67% of the tumors were in the advanced stage. There was no significant difference in tumor size and stage between OSCC with OSF and without OSF. Gadabail et al. found significant differences in clinical TNM staging between OSCC and OSCC-OSF. OSCC-OSF cases (46%) were significantly presented in early stage compared to OSCC (18%) whereas OSCC cases (82%) were significantly presented in advanced stage compared to OSCC-OSF (54%).[16] Chaturvedi et al. observed that 3 of every 4 patients with OSCC with OSF (74%) presented in early stages and nearly half of patients with OSCC (47%) presented in the advanced stage.[3]

There was a significant difference in the study groups with respect to tumor differentiation in this analysis. These findings were similar to Chaturvedi et al.'s observations that patients of OSCC-OSF are with better grade of tumor differentiation.[3] Zhou et al. reported a higher proportion of well-differentiated tumors in OSCC-OSF.[20] Gadabail et al. found that histological

presentation of well-differentiated carcinoma was significantly more in OSCC-OSF compared to OSCC.[16]

Sarode and Sarode, in an observation of 381 OSCC cases, observed that 34 OSCC cases were associated with OSF, of which 30 cases showed well-differentiated tumor. Sarode and Sarode proposed a hypothesis to correlate atrophy, turnover rate and surface keratinization in OSF with degree of tumor differentiation in OSCC. High proliferative activity and basal cell hyperplasia in conjunction with rapid exfoliation of superficial cells and epithelial atrophy suggest that epithelial turnover is very high in OSF. Rapid rate of maturation of epithelium is evidenced by the existence of surface keratinization. Hence, these epithelial cells are genetically tuned for a higher turnover rate and keratin formation. In the process of OSF changing into malignancy, these altered epithelial cells possibly keep the genetic memory of rapid rate of maturation or differentiation leading to well-differentiated tumors.[1]

Cells at the invasive front of the tumors with and with OSF did not differ with regard to morphology. This raises the query, whether the extracellular matrix in at least a subset of OSF is different and resistant to normal invasive mechanisms. This area needs further investigation.[10],[11] The mean TT in OSCC with OSF group was lesser compared to OSCC without OSF (6.93 vs. 9.26 mm) though statistically insignificant. Probably dense fibrosis of stroma could be responsible for the tumors to be thin, in OSCC with OSF consequently exhibiting exophytic growth pattern with superficial invasive features. Many authors have reported TT to be significant prognostic factor for the occurrence of subclinical and clinical metastasis.[14],[21] The present study also reveals the association between the microscopic TT and LNM. In this analysis, it was also observed that tumor extension, type, size, stage, tumor differentiation, MGSS score, TT, IVI and PNI emerged as significant factors associated with LNM. Similar findings have been mentioned in the literature.[3],[13],[22]

Cervical LNM is one of the most important prognostic factors in OSCC, and the presence of ECS is a marker of poor prognosis.[23] In this study, 50% of the cases showed LNM, with 20% of the cases showing ECS; all were in advanced stage. LNM were seen to a great extent in OSCCs than in OSCC-OSF (45% vs. 30%). Due to smaller sample, the actual difference could not be highlighted as statistically significant. Chaturvedi et al. observed that patients with OSCC-OSF were less likely to present with a metastatic neck node compared to OSCC. Even in advanced stage disease, OSCC-OSF had less chance of metastasis and ECS. They also found that the risk of LNM in the absence of OSF is higher.[3] A similar observation was reported by Zhou et al. who showed that patients with OSCC-OSF had no neck nodal metastases.[20] Gadbail et al. also found that regional LNM was significantly higher in OSCC compared to OSCC-OSF[16] and believed that this difference exists because of the protective effect of OSF. They hypothesize that the lesser incidence of LNM is because of the blockage of submucosal lymphatics as a result of fibrosis.[3] It is also expected that reduced and blocked submucosal vascularity may be a beneficial effect on overall prognosis.[24] Singh et al. have further stated that nodal metastasis is significantly less in T4 stage patients with OSF where the percentages were 28.6% versus 81.1% in OSCC without OSF.[25] Siriwardena et al. showed that nodal metastasis was less in patients with OSF compared to the ones without (22.6% vs. 30.8%).[26] However, OSCC originating from OSF is clinically more invasive and also exhibits higher metastasis; this has been stated by Guo et al.[9]

#### Limitations

Limitations of this study were small sample size and data regarding other parameters such as disease-free survival, overall survival and quality of life (QOL) issues which could not be retrieved completely for evaluation. Assessing these along with all the clinicopathologic features would have helped to precisely define OSCC-OSF as a distinct entity or otherwise, so as to formulate different treatment plan for this distinct group, as the chances of recurrence or second primary in the upper aerodigestive tract are more with OSF. Prospective studies with large sample size will eliminate the selection bias and may emphasize the differences between the study groups.

## Conclusion

The rate of occurrence of OSF and OSCC arising from this disease in this region of the world shows an ample range of clinical forms and behavior. Observations of this study suggest that OSCC patients with OSF are younger males with better grade of tumor differentiation. Risk factors and other clinical and pathological parameters did not differ significantly between the groups. Hence, observations of this study are not that supportive to consider OSCC arising in the background OSF as a distinct clinicopathologic entity.

Although OSCC-OSF may have a lower rate of LNM as mentioned by several authors, they have a higher chance of local recurrence and second primary cancer as OSF is considered as a premalignant condition. Furthermore, it is difficult to treat the QOL issues because trismus associated with OSF adds significant morbidity and occasional mortality to this group. Hence, OSCC with OSF should not be considered as a less destructive cancer and should not be treated less aggressively.

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#### Conflicts of interest

There are no conflicts of interest.

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