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ORIGINAL ARTICLE

A CROSS SECTIONAL STUDY ON MALGINATE TRANSFORMATION OF ARECA NUT CHEWING SYNDROME

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Abstract

Background: Oral Submucous Fibrosis (OSMF) is a chronic and progressive condition with a significant potential for malignant transformation, primarily affecting populations in South and Southeast Asia. The condition is closely linked to habitual areca nut consumption, tobacco use, and nutritional imbalances. Characterized by excessive fibroelastic deposition, OSMF leads to restricted oral opening, mucosal stiffness, and an increased susceptibility to developing Oral Squamous Cell Carcinoma (OSCC). While the causative factors of OSMF are well established, the precise biological mechanisms driving its malignant progression remain insufficiently understood. Given its widespread prevalence in India, there is a critical need for further research to identify key risk factors contributing to the transformation of OSMF into OSCC, enabling early diagnosis and targeted therapeutic interventions.

Objective: The study aims to assess the malignant transformation of OSMF into OSCC, identify risk factors influencing this progression, and analyze the demographic, clinical, and histopathological characteristics of affected individuals.

Materials and Methods: This study analyzed OSCC cases, focusing on malignant transformation from OSMF. Patient data were categorized based on demographics, clinical features, and pathology. Cases with concurrent oral lesions, incomplete records, or other malignancies were excluded. Statistical analysis using SPSS (version 23) was performed to assess significant correlations among clinical parameters. Statistical analysis was performed using t-test and chi-square test in SPSS software to assess associations between variables.

Results: This cross-sectional study analysed 119 OSCC patients**,** identifying 13% malignant transformation from OSMF. Pan chewing (55.9%) was the most common habit. 53.3% exhibited nodal involvement**.** Organism presence (*Pseudomonas aeruginosa, Streptococcus epididymis*) significantly correlated with OSCC (p=0.00). Gender, habits, and age showed no significant impact on tumour grading (p>0.05).

Conclusion: The findings reinforce the malignant potential of OSMF and highlight the critical role of early detection and intervention. Areca nut and tobacco consumption significantly contribute to disease progression. Future research should focus on molecular and genetic factors influencing malignant transformation to develop targeted preventive strategies.

Keywords: Areca nut, Malignancy, Oral squamous cell carcinoma, Oral submucous fibrosis

INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder predominantly affecting individuals in South and Southeast Asia[1]. It is characterized by fibroelastic changes leading to stiffness of the oral mucosa, trismus, and an increased risk of malignant transformation into Oral Squamous Cell Carcinoma (OSCC)[2]. Despite its well-documented association with areca nut chewing, tobacco use, and nutritional deficiencies, the precise mechanisms underlying its progression to malignancy remain inadequately explored India has the highest global burden of Oral Submucous Fibrosis (OSMF), primarily due to the widespread consumption of areca nut (betel quid) and tobacco products[3]. The estimated prevalence of OSMF in the general population ranges between 0.2% and 6.3%, with significant variations based on geographic location, socioeconomic status, and cultural habits. The condition is particularly prevalent in states like Maharashtra, Gujarat, Andhra Pradesh, Tamil Nadu, and Uttar Pradesh, where areca nut chewing were deeply ingrained as social customs[4]. The malignant transformation rate (MTR) of OSMF in India has been reported to be 7-13%, which was higher than the global average of 5.5%[5]. This increased risk was attributed to multiple factors, including early onset of areca nut use, prolonged duration of exposure, and the presence of additional carcinogenic agents such as tobacco and alcohol[6]. Studies have indicated that OSMF patients who consume gutkha (a commercial areca nut and tobacco mixture) are at a significantly higher risk of developing Oral Squamous Cell Carcinoma (OSCC) compared to those who chew areca nut alone[7].

The incidence was notably higher in males, particularly those aged between 30 and 50 years, who exhibit a greater predisposition to malignant transformation. Several etiological factors contribute to this transformation, including areca nut and tobacco consumption, where arecoline—an alkaloid in areca nut—induces fibroblast dysfunction, increased collagen deposition, and oxidative stress, facilitating carcinogenesis[8]. Nutritional deficiencies, especially iron, zinc, and vitamin A, B-complex, and C, further impair epithelial repair mechanisms, making the oral mucosa more vulnerable to dysplasia. Genetic and epigenetic alterations, such as mutations in tumour suppressor genes like p53 and aberrant methylation patterns, have also been implicated. Additionally, elevated serum levels of trace elements like copper and zinc have been linked to increased malignant transformation rates due to their role in oxidative stress and tumour progression[9].

Previous studies on OSMF have faced several limitations, including the lack of standardized diagnostic criteria, which has led to inconsistencies in clinical staging and histopathological grading. Many studies have been confined to hospital-based cohorts, limiting their generalizability, and most fail to incorporate long-term follow-up data, making it difficult to establish precise malignant transformation rates. The study aimed to analyse the demographic, clinical, and pathological characteristics of OSCC cases while specifically identifying those that underwent malignant transformation from OSMF.

MATERIALS AND METHODS

The present study included patient data of individuals previously diagnosed with OSCC between May 2023 and December 2024 at Saveetha Dental College and Hospitals, Chennai.

Inclusion and Exclusion Criteria

Patients with a confirmed diagnosis of OSCC were included, while those presenting with concurrent oral mucosal lesions, incomplete medical records, OSMF associated with other malignant jaw lesions, or recurrent OSCC cases were excluded. Additionally, patients with other premalignant lesions were also omitted from the study to maintain data homogeneity.

Data Collection and Categorization

A total of 119 OSCC cases were identified, and relevant patient details were retrieved from the Diagnostic Imaging Accreditation Scheme (DIAS) database. The collected data were systematically categorized based on age, gender, oral habits, chief complaints, histopathological diagnosis, tumour grading, staging, and the primary site of involvement. From this dataset, cases of malignant transformation from OSMF to OSCC were filtered and analysed separately. Furthermore, a subset of patients exhibiting microbial growth associated with OSCC was also considered for evaluation.

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Statistical Analysis

The compiled data were subjected to statistical analysis using SPSS software (version 23). Chi-square test and t- test were employed to determine statistical significance across different variables, ensuring a comprehensive assessment of the correlations between clinical parameters and OSCC progression.

RESULTS

Out of 119 patients diagnosed as OSCC 13 patients came with the chief complaint of burning sensation, limited mouth opening and ulceration and had gutka and pan habits past 20 years with mucosa and tongue as a primary site of origin of tumour. Their diagnoses include epithelial dysplasia, invasive oral squamous cell carcinoma from oral submucous fibrosis, and superficially invasive oral squamous cell carcinoma associated with advanced oral squamous cell carcinoma. Of these, one has been diagnosed as moderately differentiated and the other twelve as well differentiated (Figure 1).

The gender distribution showed a clear male predominance, with 83% of the population being male and only 15.2% female. This suggests that OSMF and its progression to OSCC may be more prevalent among men, likely due to higher exposure to risk factors such as tobacco and betel nut consumption.

Regarding lifestyle habits, 55.9% of the population reported chewing pan, making it the most common habit. Tobacco consumption was also significant, with 11.8% of individuals using tobacco products, while 3.38% of the population were Bedi users, and another 3.38% consumed betel nuts. Other habits, such as alcohol consumption and smoking (1.69%), gutkha chewing (1.58%), and smoking alone (1.67%), were present in smaller proportions. Additionally, a small percentage (3.38%) reported engaging in a combination of pan, smoking, and alcohol consumption, indicating potential multiple risk factors contributing to disease progression. These findings highlight the strong association between oral habits, especially pan, tobacco, and betel nut consumption, with the development and progression of OSMF.

Tumour grading analysis indicates that 74.6% of cases were classified as well-differentiated, while 22% were moderately differentiated, and a small percentage (1.52%) were poorly differentiated. The presence of 13% of cases where OSMF turned into OSCC revealed the malignant potential of the disease. This suggests that although many cases remain in well-differentiated stages, a notable proportion progresses to more severe forms, emphasizing the need for early intervention.

The data on nodal involvement shows that 53.3% of cases exhibited nodal metastasis, indicating that more than half of the patients had some degree of lymph node involvement and none of the cases showed metastasis. This highlights the aggressive nature of OSCC in a substantial portion of the population, further emphasizing the importance of early diagnosis and monitoring of disease progression.

Lastly, the presence of organism growth was detected in 18.3% of the cases, suggesting that infections might play a role in disease pathology or could be secondary infections due to compromised oral health. The role of microbial factors in the progression of OSMF and OSCC needs further investigation, but their presence in a significant portion of patients suggests an area for further clinical research.

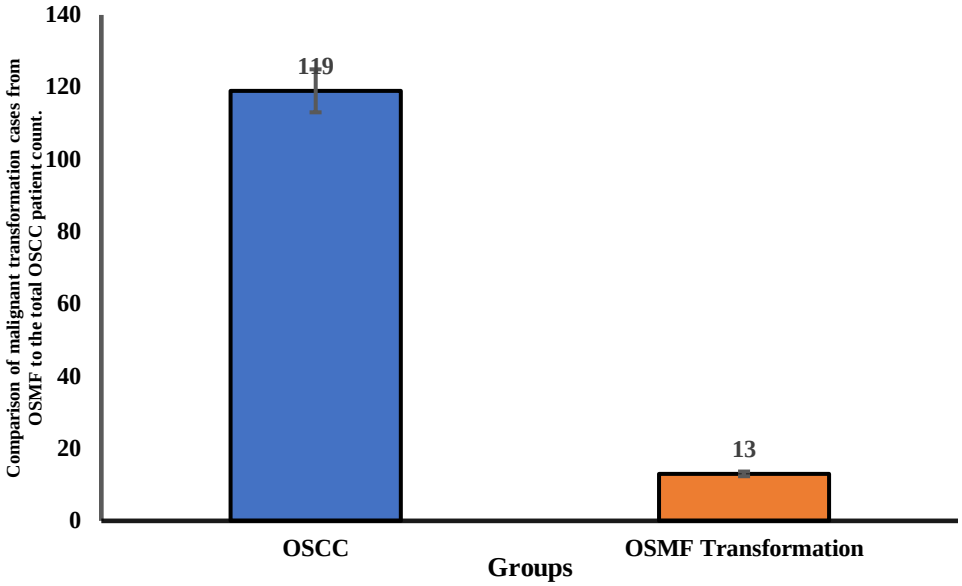

Figure 1. The bar chart compares the number of OSCC cases with malignant transformation from OSMF cases.

The analysis indicates that a large proportion of the population engages in high-risk habits, with pan and tobacco consumption being particularly prevalent. The progression of OSMF to OSCC in 13% of cases, along with 53.3% nodal involvement, demonstrates the severity of the condition. The presence of bacterial or fungal growth in 18.3% of cases may suggest an added complication in disease management. These findings emphasize the critical need for public awareness, early screening, and lifestyle modifications to reduce the burden of OSMF and its transformation into OSCC (Figure2).

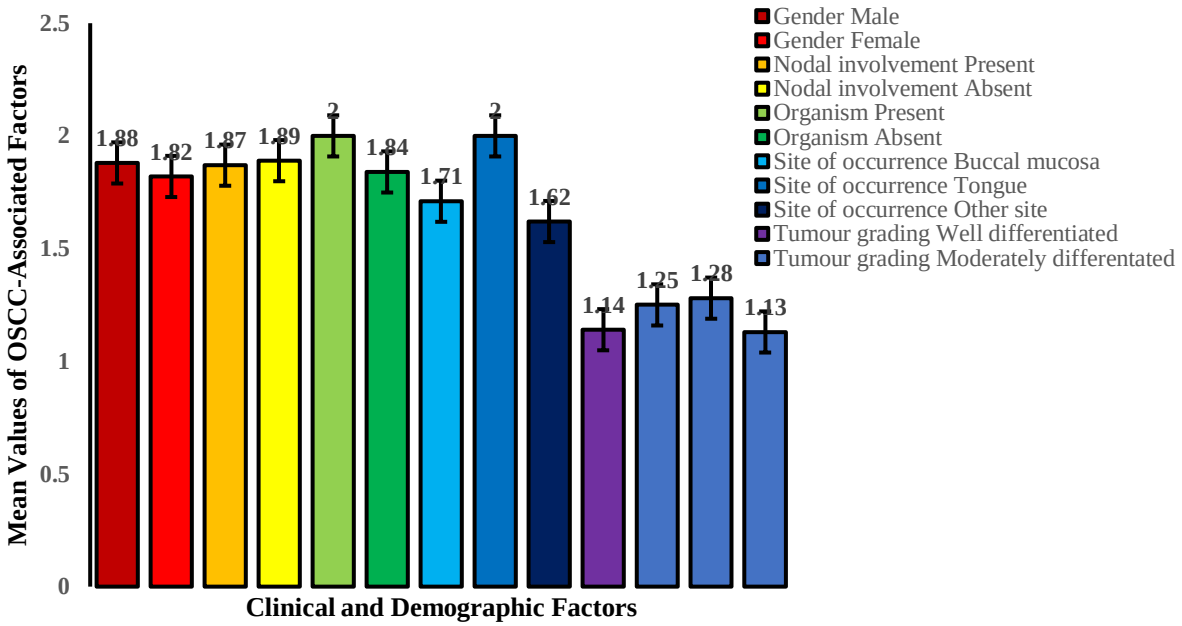

Figure 2. The bar chart presents the mean values of different factors associated with oral squamous cell carcinoma (OSCC). The factors are color-coded and categorized based on gender, nodal involvement, presence of an organism, site of occurrence, tumor grading, and habits.

Table 1. The table presents statistical comparisons (t-test) of a measured parameter across different categorical groups, including Gender, Nodal Involvement, and Organism Presence.

Clinical and Demographic Factors		N	Mean	Standard Deviation	Standard Error	Significance
Gender	Male	100	1.88	0.326	0.032	0.83
	Female	18	1.82	0.30	0.076	
Nodal involvement	Present	80	1.87	0.332	0.37	0.536
	Absent	38	1.89	0.311	0.50	
Organism	Present	26	2.0	0.00	0.00	0.00*
	Absent	92	1.84	1.84	0.037	
Site of Occurrence	Buccal mucosa	54	1.71	0.72	0.031	0.04
	Tongue	18	2	0.94	0.07	
	Other site	47	1.65	0.66	0.53	

* statistically significant ($p<0.05$)

The study analysed the effects of gender, nodal involvement, and organism presence on a measured parameter. The results showed that gender (male vs. female) had no effect, as both had the same mean value (1.88) and a high p-value (0.83), and the difference was not significant. Similarly, nodal involvement (present vs absent) also had no significant impact, with very close mean values (1.87 vs. 1.89) and a p-value of 0.536. However, the presence of an organism had a significant effect, with a higher mean value (2.0 vs. 1.84) and a p-value of 0.00, indicating a strong relationship. The low standard deviation (0.00) in the organism-present group suggests consistent results. Overall, gender and nodal involvement do not influence the measured parameter, but the presence of an organism significantly affects it (Table 1). Organism observed were predominantly *Psedomonas aeruginosa and Streptococccus epididymis.*

Table 2. Table represents the results of the **Pearson chi-square test, which examines the association between tumour grading, habits and gender**.

	Tumour grading						
Clinical and Demographic factors		**Well differentiated**	**Moderately differentiated**	**Total**	**Value**	**df**	**Significance**
Habits	Yes	76	26	100	1.868	1	0.172
	No	16	2	18			
Gender	Male	76	24	100	0.27	1	0.870
	Female	14	4	18			

The study examined whether habits (such as smoking or alcohol use) and gender have any effect on tumour grading. The results showed that there was no significant association between habits and tumour differentiation ($p = 0.172$) or between gender and tumour differentiation ($p = 0.870$). Although more people with habits had moderately differentiated tumours compared to those without habits, the difference was not statistically significant. Similarly, tumour differentiation was almost the same between males and females, meaning gender does not play a major role.These findings suggest that habits and gender do not significantly influence grading of tumour(Table 2).

Table 3. The results of a Pearson chi-square test, analysing the relationship between age groups and the progression of OSMF to OSCC.

		OSMF to OSCC	Reported as OSCC	Total	Value	df	Significance
Age	<30years	2	2	4	7.24	2	0.27
	30-50years	8	48	56			
	>50years	4	54	58			

The study analysed whether age affects the progression of oral submucous fibrosis (OSMF) to oral squamous cell carcinoma (OSCC)**.** The results showed no significant association between age and disease progression (p = 0.27). Although more cases of OSMF progressing to OSCC were seen in the 30-50 years group (8 cases) compared to <30 years (2 cases) and >50 years (4 cases) groups, this difference was not statistically significant**.** The majority of OSCC cases were in the >50 years group (54 cases)**,** likely due to longer exposure to risk factors rather than age itself being a direct cause (Table 3). These findings suggest that age alone does not play a major role in OSCC development**,** and other factors duration of tobacco use, betel nut chewing, and genetic predisposition may have a stronger influence.

DISCUSSION

The present cross-sectional study analysed the malignant transformation of OSMF to OSCC by evaluating clinical and demographic factors. The findings revealed that 13% of the OSCC cases showed malignant transformation from OSMF, with a notable male predominance of 83% and significant association with pan chewers of 55.9%. The primary site of tumour origin was the buccal mucosa and tongue, were Well-differentiated squamous cell carcinoma was the most common histological type. The malignant transformation rate (MTR) of OSMF observed in the present study was 13% aligned with the previously reported range of 7-13% in India, which is significantly above the global average of 5.5%[10]. Study by Ranganathan et al. (2004) reported similar MTRs, emphasizing the role of early-onset areca nut consumption and prolonged exposure to carcinogenic agents such as tobacco and alcohol in increasing malignancy risk[11].

The observed male predominance in this study was consistent with earlier findings, which attribute higher OSMF prevalence in males to cultural and behavioural factors, including greater exposure to areca nut and tobacco products[12]. A study by Pandiar et al. (2019) reported a similar gender distribution, with males accounting for nearly 80% of OSMF cases progressing to OSCC[13]. However, studies from other regions have reported a more balanced gender distribution, suggesting potential genetic and hormonal influences in disease progression[14]. Pan chewing emerged as the most common habit of about 55.9% among OSMF patients in the present study, in agreement with research by Hazarey et al. (2007), which highlighted the strong correlation between betel quid chewing and OSCC risk[15]. Additionally, the present study found that gutkha users had a significantly higher incidence of OSCC, corroborating findings by Gunjal et al. (2020), who reported a 4.2 times higher risk of OSCC in gutkha consumers compared to those using areca nut alone[16].

The predominance of well-differentiated OSCC cases of 74.6%) in this study was consistent with earlier studies by Arakeri et al. (2014), which suggested that OSMF-related OSCCs tend to exhibit better differentiation than tobacco-induced OSCC[17]. The buccal mucosa and tongue being the primary sites of tumour occurrence align with previous reports, further supporting the hypothesis that localized carcinogenic exposure plays a crucial role in site-specific malignancy development[18]. More than half of the patients (53.3%) in this study exhibited nodal involvement, comparable to the findings of Krishna Rao et al. (2016), who reported nodal metastasis in 50-60% of OSMF-derived OSCC cases[19]. The presence of microbial growth in 18.3% of cases suggests a potential role of secondary infections in OSCC pathogenesis. Previous studies have highlighted the involvement of bacterial species such as *Pseudomonas aeruginosa and Streptococcus epidermidis* in oral carcinogenesis, indicating a

possible link between chronic inflammation and malignant transformation[20].

While this study provides valuable insights into the malignant transformation of OSMF, certain limitations must be acknowledged. The cross-sectional design restricts the ability to establish a direct causal relationship between risk factors and OSCC development. Additionally, a larger sample size and multi-center data collection would enhance the generalizability of findings. Future research should focus on identifying molecular biomarkers for early detection and investigating the role of microbiome alterations in OSMF progression to OSCC.

CONCLUSION

The present study corroborates previous literature findings on OSMF malignant transformation, reaffirming the high-risk association with areca nut and tobacco habits, male predominance, and significant nodal involvement. The consistency of results with past studies revealed the necessity for early intervention, public awareness programs, and stringent regulations on areca nut products to mitigate the disease burden. Future studies with larger sample sizes and long-term follow-ups are essential to further elucidate the molecular mechanisms underlying OSMF progression to OSCC.

DECLARATIONS

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Conflict of Interest
The author declares that there were no conflicts of interests in the present study.

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