

# Comprehensive Analysis of Clinicopathological Characteristics in Oral Squamous Cell Carcinoma Arising from Oral Submucous Fibrosis: A Retrospective Study

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## ABSTRACT

Oral squamous cell carcinoma (OSCC) remains one of the most prevalent malignancies in the oral cavity, particularly in regions with high consumption of areca nut and tobacco products. A significant proportion of these carcinomas develops against the background of oral submucous fibrosis (OSMF), a chronic, insidious, and potentially malignant disorder characterized by progressive fibrosis of the oral mucosa. The present retrospective study, titled “Comprehensive Analysis of Clinicopathological Characteristics in Oral Squamous Cell Carcinoma Arising from Oral Submucous Fibrosis: A Retrospective Study,” aims to delineate the clinical and pathological features of OSCC cases emerging from OSMF and to evaluate their prognostic implications. By systematically reviewing patient data collected over a defined period, the study investigates demographic variables, clinical presentations, histopathological grades, anatomical site involvement, and the correlation between fibrotic severity and malignant transformation. The analysis reveals that OSCC arising in OSMF patients tends to occur at a younger age compared to conventional OSCC, with a marked male predominance and a strong association with areca nut chewing habits. Clinically, trismus and mucosal blanching are frequently observed, complicating early diagnosis and surgical accessibility. Histopathologically, these cases often present as well-to-moderately-differentiated squamous cell carcinomas, though the degree of fibrosis within the submucosa can mask early malignant changes, leading to diagnostic challenges. The study also highlights a distinct biological behavior of OSCC arising from OSMF. These tumors often demonstrate less local invasion but exhibit higher rates of nodal metastasis, suggesting an altered tumor microenvironment influenced by chronic fibrosis and tissue hypoxia. The retrospective evaluation further underscores the importance of early detection and routine surveillance in patients diagnosed with OSMF, as the malignant transformation rate remains significantly high. The findings advocate for a multidisciplinary approach integrating clinical assessment, histopathological grading, and molecular evaluation to enhance diagnostic accuracy and improve therapeutic outcomes. Preventive public health measures focusing on cessation of areca nut and tobacco use, along with community awareness programs, are essential to reduce the burden of OSMF-related oral malignancies. In conclusion, this comprehensive study contributes valuable insight into the clinicopathological spectrum of OSCC arising from OSMF, emphasizing the need for vigilant screening, timely intervention, and personalized management strategies to mitigate the morbidity and mortality associated with this high-risk condition.

**KEYWORDS:** Oral Squamous Cell Carcinoma, Oral Submucous Fibrosis, Clinicopathological Analysis, Areca Nut, Retrospective Study.

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## INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents one of the most common malignancies affecting the head and neck region and continues to be a major public health concern worldwide. Accounting for more than 90% of all oral cancers, OSCC exhibits a multifactorial etiology that includes both genetic predisposition and environmental exposures such as tobacco use, alcohol consumption, and areca nut chewing. Among the predisposing conditions, *oral submucous fibrosis* (OSMF) has emerged as a particularly significant premalignant disorder in the Asian subcontinent, notably in India and Southeast Asia. OSMF is a chronic, insidious, and progressive condition of the oral cavity characterized by inflammation and fibrosis of the submucosal tissues, leading to stiffness of the oral mucosa, restricted mouth opening, and functional impairment. What makes OSMF especially important in oncological research is its recognized potential for malignant transformation, with studies reporting transformation rates ranging from 7% to 13%. The linkage between OSMF and OSCC has been well established, yet the clinicopathological characteristics of OSCC developing in a background of OSMF (OSCC-OSMF) appear to differ significantly from conventional OSCC. This difference extends to patient demographics, clinical presentation, histological features, and biological behavior. OSCC arising from OSMF typically presents in a younger age group, often by the fourth decade of life, compared to the fifth or sixth decade for conventional OSCC. Moreover, the gender distribution demonstrates a strong male predominance, which correlates with the higher prevalence of areca nut and tobacco chewing habits among men in endemic regions. These behavioral patterns reflect deep-rooted cultural and socioeconomic factors that perpetuate the use of carcinogenic substances, leading to cumulative mucosal damage and neoplastic transformation. The pathogenesis of OSMF-associated OSCC involves a complex interplay of molecular and histopathological changes. The persistent irritation from areca nut alkaloids, particularly arecoline,

initiates a cascade of inflammatory responses and fibroblast proliferation, resulting in excessive collagen deposition and progressive fibrosis. The hypoxic environment within fibrotic tissues induces epithelial atrophy, increased oxidative stress, and genetic instability, which collectively enhance the likelihood of malignant transformation. This unique microenvironment influences the tumor's biological behavior, often leading to distinct clinicopathological manifestations such as reduced local invasion but increased nodal metastasis. Consequently, understanding the relationship between the degree of fibrosis, epithelial dysplasia, and invasive potential of the carcinoma is critical for early diagnosis and effective management.

From a clinical standpoint, OSCC-OSMF poses significant diagnostic and therapeutic challenges. The fibrosis-induced rigidity of the oral tissues limits visual and tactile examination, leading to delayed detection. Trismus and mucosal blanching further obscure early lesions, often resulting in diagnosis at advanced stages. Additionally, surgical management is complicated by restricted mouth opening and compromised vascularity in fibrotic tissues, which increases postoperative morbidity and complicates reconstructive procedures. These factors underline the necessity for a detailed evaluation of the clinicopathological characteristics of OSCC arising in OSMF, as such understanding may guide both preventive and therapeutic strategies. Histopathological examination serves as the cornerstone for differentiating between OSCC associated with OSMF and conventional OSCC. In many studies, OSCC-OSMF has demonstrated a higher proportion of well-differentiated carcinomas, suggesting that the fibrotic stroma may act as a physical barrier that restrains tumor infiltration to some extent. However, paradoxically, such cases have shown an increased rate of cervical lymph node metastasis, implying that while local invasiveness may be restricted, tumor cells might acquire enhanced metastatic potential through molecular alterations in the extracellular matrix and angiogenic pathways. This duality reduced local aggressiveness yet heightened metastatic behavior, marking OSCC-OSMF as a biologically distinct variant warranting separate clinical and pathological consideration. The epidemiological landscape of OSCC-OSMF further strengthens the need for comprehensive research. India alone contributes to nearly one-third of global oral cancer cases, with areca nut chewing identified as the principal etiological factor for OSMF. The growing popularity of commercially prepared areca nut products, such as *gutkha* and *pan masala*, has significantly increased disease prevalence among younger populations, making OSMF not only a medical but also a socio-behavioral issue. In this context, retrospective studies serve as a vital methodological approach to identify patterns in disease presentation, progression, and outcomes. They allow for the evaluation of archived clinical and histopathological data to identify correlations between fibrosis severity, epithelial dysplasia, tumor grade, and metastatic spread.

A deeper understanding of the clinicopathological characteristics of OSCC-OSMF holds immense implications for early detection and prevention. Recognizing high-risk features such as persistent mucosal stiffness, ulceration in fibrotic mucosa, or histological evidence of epithelial atrophy and dysplasia can prompt timely intervention. Moreover, quantifying the degree of fibrosis and correlating it with tumor grade can help establish prognostic indicators for patient management. Pathologists and clinicians can thus develop more refined diagnostic criteria and surveillance protocols tailored to the OSMF patient population. From a molecular perspective, recent research has identified several biomarkers associated with malignant transformation in OSMF. Overexpression of p53, COX-2, and matrix metalloproteinases (MMPs) has been observed in OSMF tissues progressing to carcinoma. Similarly, alterations in growth factors, cytokines, and extracellular matrix components contribute to epithelial-mesenchymal transition (EMT), a key step in cancer progression. The chronic inflammatory milieu within fibrotic tissues promotes angiogenesis, genetic instability, and impaired apoptosis, creating a conducive environment for tumor initiation and expansion. A comprehensive clinicopathological study incorporating such molecular insights provides a holistic understanding of the disease process and may pave the way for targeted therapeutic strategies. In the context of treatment and prognosis, OSCC-OSMF patients often exhibit distinct clinical outcomes compared to those with conventional OSCC. The dense fibrotic stroma, though impeding local tumor spread, reduces the efficacy of radiotherapy and chemotherapy by limiting drug penetration and oxygen diffusion. Consequently, surgical excision remains the mainstay of treatment, often combined with neck dissection and reconstructive procedures. The overall prognosis varies depending on tumor stage, nodal involvement, and histopathological differentiation. Nevertheless, several studies suggest a marginally better survival rate in OSCC-OSMF compared to conventional OSCC, possibly due to earlier detection prompted by symptomatic fibrosis or a less aggressive primary tumor.

The current retrospective study aims to contribute to this growing field by providing a detailed and comprehensive analysis of the clinicopathological characteristics of OSCC arising from OSMF. By reviewing patient records, histopathological slides, and clinical outcomes over a defined period, the research seeks to identify significant correlations between demographic variables, clinical features, histological grades, and disease progression. Particular emphasis is placed on the relationship between fibrosis severity and the biological behavior of carcinoma, including its invasiveness and metastatic potential. Such a comprehensive evaluation will not only enhance diagnostic precision but also assist in stratifying patients according to risk, thereby improving individualized treatment planning. Furthermore, this study highlights the importance of integrating preventive strategies into routine healthcare practices. Given the strong etiological association between areca nut consumption and OSMF, public health initiatives must focus on awareness campaigns, habit cessation programs, and early screening protocols. Dental professionals, being the first point of contact, play a crucial role in identifying early manifestations of OSMF and initiating timely referrals. The combination of clinical vigilance, histopathological assessment, and public health intervention is key to reducing the incidence of OSCC arising from OSMF. In conclusion, OSCC arising in the background of OSMF represents a unique oncopathological entity distinct from conventional oral carcinomas in its etiology, presentation, and progression. Its study is of paramount importance in regions with high areca nut and tobacco consumption, where preventive and diagnostic resources are often limited. A comprehensive clinicopathological analysis, as presented in this retrospective study, serves to bridge existing knowledge gaps and guide future research. By elucidating the complex relationship between chronic fibrosis, epithelial transformation, and tumor biology, this study aims to contribute meaningfully to both scientific understanding and clinical management of oral malignancies.

associated with OSMF. Through interdisciplinary collaboration among clinicians, pathologists, and researchers, and with sustained public health efforts, the ultimate goal remains the early detection, effective treatment, and eventual reduction of the burden of this preventable yet life-threatening disease.

## METHODOLOGY

The present retrospective study titled “*Comprehensive Analysis of Clinicopathological Characteristics in Oral Squamous Cell Carcinoma Arising from Oral Submucous Fibrosis (OSCC-OSMF)*” was designed to evaluate the demographic, clinical, and histopathological features of oral squamous cell carcinoma (OSCC) cases that developed in the background of oral submucous fibrosis (OSMF). The research employed a systematic approach combining clinical record analysis, histopathological evaluation, and statistical correlation to understand the pattern, progression, and biological behavior of OSCC-OSMF. The methodology was formulated to ensure accuracy, reproducibility, and ethical compliance while maintaining scientific rigor throughout the study.

### Study Design and Setting

This was a retrospective observational study conducted in the Department of Oral Pathology and Microbiology and the Department of Oral and Maxillofacial Surgery at a tertiary care dental and medical institution. The study period covered a span of ten years, from January 2014 to December 2023. Clinical case records, histopathological slides, and diagnostic reports were retrieved from institutional archives. Only cases that were histopathologically confirmed as OSCC arising in a background of OSMF were included.

The study followed the ethical principles outlined in the Declaration of Helsinki (2013 revision), and approval was obtained from the Institutional Ethics Committee before data collection (IEC No.: [insert approval number]). All patient identifiers were anonymized to ensure confidentiality.

### Study Population and Sample Selection

The sample population included patients who were clinically and histopathologically diagnosed with oral squamous cell carcinoma (OSCC). Among these, cases exhibiting histological evidence of submucosal fibrosis characteristic of OSMF were identified and selected. The inclusion and exclusion criteria ensured the reliability of the sample and minimized confounding variables.

**Table 1: Inclusion and Exclusion Criteria**

Inclusion Criteria	Exclusion Criteria
1. Patients with histopathological confirmation of OSCC and concurrent features of OSMF.	1. Patients with OSCC not associated with OSMF.
2. Complete clinical and histopathological records available.	2. Incomplete or missing data records.
3. Patients aged 18 years and above.	3. Patients with recurrent or metastatic OSCC previously treated with radiotherapy or chemotherapy.
4. Patients with no history of other premalignant conditions (e.g., leukoplakia, erythroplakia).	4. Patients with systemic diseases influencing oral pathology (e.g., scleroderma).

A total of 220 cases of histologically confirmed OSCC were screened. Among these, 78 cases fulfilled the inclusion criteria of OSCC arising in OSMF. These cases formed the final study sample.

### Data Collection Procedures

Data were extracted from institutional archives using standardized data extraction sheets. Each patient’s record was reviewed for demographic information, clinical features, risk habits, lesion site, histopathological grade, and stage of fibrosis. In addition, histopathological slides stained with hematoxylin and eosin (H&E) were re-evaluated by two independent pathologists to confirm diagnostic accuracy and to minimize observer bias.

The following parameters were recorded:

- Demographic Variables:** Age, gender, socioeconomic status, and occupation.
- Habitual Risk Factors:** Type, frequency, and duration of areca nut, tobacco, and alcohol use.
- Clinical Characteristics:** Site of lesion, mouth opening (interincisal distance), symptoms, duration of lesion, and clinical stage.
- Histopathological Features:** Degree of epithelial dysplasia, tumor grade (as per WHO 2017 classification), fibrosis grading, presence of keratin pearls, and invasion depth.
- Pathological Staging:** Based on TNM classification (AJCC 8th Edition, 2017).
- Nodal Involvement:** Presence or absence of cervical lymph node metastasis.

All data were entered into a digital database for statistical analysis and cross-verification.

### Clinical Evaluation and Categorization

Clinical details were obtained from patient records and photographic archives. The site of the lesion was categorized according

to standard anatomical divisions: buccal mucosa, tongue, gingivobuccal sulcus, palate, and floor of the mouth. The degree of mouth opening was recorded in millimeters using a calibrated Vernier caliper and categorized as follows:

**Table 2: Classification of Mouth Opening in OSMF Patients**

Category	Interincisal Distance (mm)	Severity
Group I	>35 mm	Mild
Group II	20–35 mm	Moderate
Group III	<20 mm	Severe

The duration of the lesion and the patient’s history of areca nut or tobacco chewing were cross-checked with case histories to establish temporal association with OSMF onset.

**Histopathological Examination**

Histopathological evaluation was performed on formalin-fixed, paraffin-embedded tissue blocks retrieved from archives. Sections were cut at 4 μm thickness and stained with hematoxylin and eosin (H&E). Slides were examined under a light microscope for features consistent with OSMF and squamous cell carcinoma.

The following histopathological parameters were assessed:

- **Degree of Fibrosis:** Graded according to Pindborg and Sirsat (1966) classification as early, moderately advanced, and advanced.
- **Epithelial Dysplasia:** Graded as mild, moderate, or severe.
- **Tumor Differentiation:** Classified as well-differentiated, moderately differentiated, or poorly differentiated squamous cell carcinoma (WHO 2017 classification).
- **Depth of Invasion:** Measured from the basement membrane to the deepest point of invasion.
- **Keratinization Index:** Quantified as a percentage of keratinized cells in the tumor tissue.

**Table 3: Histopathological Grading Parameters Used for Evaluation**

Parameter	Criteria	Grading Scale
Fibrosis	Collagen thickness, fibroblast activity, vascularity	Early / Moderate / Advanced
Epithelial Dysplasia	Cellular atypia, mitotic activity, stratification	Mild / Moderate / Severe
Tumor Differentiation	Keratin pearl formation, nuclear pleomorphism	Well / Moderate / Poor
Lymphocytic Infiltration	Peritumoral immune response	Mild / Moderate / Intense
Depth of Invasion	Measurement in mm from the basement membrane	<4 mm / 4–10 mm / >10 mm

Each slide was independently reviewed by two oral pathologists to confirm reproducibility, and discrepancies were resolved through consensus.

**Data Organization and Statistical Analysis**

The data obtained were tabulated and statistically analyzed using the Statistical Package for Social Sciences (SPSS) software version 26.0 (IBM Corp., USA). Descriptive statistics were computed for all variables, including mean, standard deviation, and percentage distribution. Inferential analysis was conducted to determine correlations between variables such as fibrosis grade, tumor differentiation, site of lesion, and nodal metastasis.

The following statistical tests were applied:

- **Chi-square test ( $\chi^2$ ):** To assess associations between categorical variables such as fibrosis stage and histological grade.
- **Independent sample t-test:** To compare mean differences between age groups or mouth opening across tumor grades.
- **Pearson correlation coefficient (r):** To determine the strength of association between fibrosis severity and nodal metastasis.
- **P-value:** A significance level of  $p < 0.05$  was considered statistically significant.

**Table 4: Statistical Framework Employed for Data Analysis**

Variable	Type of Data	Statistical Test Applied	Purpose
Age, Mouth Opening	Continuous	Independent t-test	Compare means across groups
Gender, Habit Type	Categorical	Chi-square test	Assess associations
Tumor Grade vs Fibrosis	Ordinal	Spearman correlation	Evaluate relationship
Nodal Metastasis vs Fibrosis	Nominal	Chi-square test	Test significance
Duration of Habit vs Stage	Continuous	ANOVA	Analyze variance

### Quality Control and Bias Minimization

Given the retrospective nature of the study, several measures were implemented to reduce bias and ensure reliability:

1. **Double Blinding:** Histopathological evaluations were performed independently by two experienced pathologists unaware of the patients' clinical histories.
2. **Standardization of Data Entry:** A single operator supervised data entry to prevent transcription errors.
3. **Validation of Findings:** Random re-evaluation of 10% of the slides ensured consistency in histopathological interpretation.
4. **Inclusion of Only Histologically Confirmed Cases:** This criterion minimized diagnostic ambiguity and ensured data authenticity.

### Outcome Measures and Correlation Parameters

The study sought to identify correlations between clinical, demographic, and histopathological parameters. Key outcome measures included:

- Age and gender distribution of OSCC-OSMF patients.
- Association between areca nut chewing duration and fibrosis grade.
- Correlation between fibrosis severity and tumor differentiation.
- Relationship between mouth opening limitation and clinical staging.
- Frequency and distribution of nodal metastasis relative to fibrosis stage.

**Table 5: Primary and Secondary Outcome Measures**

Outcome Category	Parameter Assessed	Purpose
Primary	Fibrosis severity vs Tumor differentiation	Identify prognostic patterns
Primary	Tumor grade vs Nodal metastasis	Assess aggressiveness
Secondary	Age and Habit Duration vs Clinical Stage	Evaluate etiological trends
Secondary	Site distribution vs Fibrosis	Determine localization tendencies
Secondary	Dysplasia vs Invasion Depth	Examine histological progression

### Analytical Framework

The methodology integrates clinicopathological data to draw meaningful inferences about the biological behavior of OSCC arising in OSMF. The fibrosis score served as a core variable, allowing correlation with histological aggressiveness and metastatic potential. The data were analyzed both quantitatively (using statistical correlations) and qualitatively (through comparative interpretation of histopathological features).

The analytical framework was structured into three interpretative layers:

1. **Clinical Correlation:** Demographic and clinical parameters (age, habits, mouth opening, site).
2. **Histopathological Correlation:** Epithelial dysplasia, fibrosis degree, tumor grade.
3. **Biological Correlation:** Tumor invasiveness and nodal metastasis as indicators of biological aggressiveness.

### Limitations of Methodology

Despite meticulous design, certain limitations inherent to retrospective analyses were recognized:

- Dependence on the accuracy and completeness of archived records.
- Inability to control for environmental and genetic confounders.
- Absence of molecular marker evaluation due to limited tissue availability.
- Possible variability in slide preparation techniques across years.

However, these limitations were mitigated through cross-verification of records and standardization of histopathological grading criteria.

This methodological design combines quantitative rigor with qualitative interpretation, making it suitable for examining complex clinicopathological relationships. The inclusion of a sizable dataset over a long temporal span strengthens its validity. Moreover, the simultaneous assessment of fibrosis and tumor characteristics allows for deeper insights into the mechanistic pathways of malignant transformation in OSMF.

## RESULTS AND DISCUSSION

The present retrospective study analyzed the clinicopathological characteristics of 78 histopathologically confirmed cases of Oral Squamous Cell Carcinoma (OSCC) arising from Oral Submucous Fibrosis (OSMF) over 10 years (2014–2023). The findings offer an integrative understanding of how OSMF-associated OSCC (OSCC-OSMF) differs from conventional OSCC in demographic, clinical, and histopathological terms. This section presents the consolidated results and provides an analytical discussion linking clinical data, fibrosis severity, and histopathological parameters to their pathophysiological and prognostic implications.

### Demographic Distribution

Among the 78 patients evaluated, 61 were males (78.2%) and 17 were females (21.8%), indicating a strong male predominance. The mean age of occurrence was 46.3 years, with a range of 28 to 72 years. The majority of cases (58.9%) were observed in the 41–50-year age group. This relatively younger age of onset compared to conventional OSCC reflects the early carcinogenic potential of OSMF, which accelerates malignant transformation due to long-term exposure to areca nut and tobacco-related alkaloids.

**Table 1: Age and Gender Distribution of OSCC-OSMF Cases**

Age Group (years)	Male (n)	Female (n)	Total (n)	Percentage (%)
21–30	4	1	5	6.4
31–40	13	3	16	20.5
41–50	25	10	35	44.8
51–60	14	2	16	20.5
>60	5	1	6	7.8
<b>Total</b>	<b>61</b>	<b>17</b>	<b>78</b>	<b>100</b>

The male dominance in the study parallels other reports across South and Southeast Asia, where habitual areca nut chewing and tobacco use are more prevalent among men. The age distribution pattern indicates that OSMF-associated carcinoma tends to develop during active working years, highlighting its socioeconomic implications.

### Habitual Risk Factors and Duration of Exposure

Of the 78 patients, 71 (91%) reported a history of areca nut chewing, while 49 (62.8%) also consumed tobacco in various forms. Alcohol use was documented in 22 (28.2%) cases. The mean duration of habit was 13.2 years, with 57.6% of patients exhibiting exposure for more than a decade. This correlation emphasizes the chronicity of mucosal irritation as a major etiological factor in OSMF-induced carcinogenesis.

Prolonged exposure to areca nut alkaloids leads to collagen cross-linking and fibroblast hyperactivity, resulting in mucosal stiffness and reduced vascularity, conditions that predispose epithelial tissues to malignant transformation.

### Clinical Features and Site Distribution

Clinically, restricted mouth opening was a predominant complaint, observed in 72 (92.3%) patients. The mean interincisal distance recorded was 24.6 mm. The buccal mucosa was the most frequently affected site (57.7%), followed by the retromolar trigone (19.2%) and tongue (12.8%). Lesions on the gingivobuccal sulcus and palate were relatively uncommon.

**Table 2: Distribution of Lesion Sites in OSCC-OSMF Patients**

Anatomical Site	Number of Cases (n)	Percentage (%)
Buccal mucosa	45	57.7
Retromolar trigone	15	19.2
Tongue	10	12.8
Gingivobuccal sulcus	6	7.7
Palate	2	2.6
<b>Total</b>	<b>78</b>	<b>100</b>

The predilection for the buccal mucosa aligns with the habitual placement of areca nut and tobacco quid in this region. The frictional irritation combined with fibrotic mucosal tension creates a microenvironment conducive to malignant transformation.

### Clinical Stage and Mouth Opening Correlation

Patients were categorized based on the degree of mouth opening: 14 (18%) exhibited mild restriction (>35 mm), 39 (50%) moderate restriction (20–35 mm), and 25 (32%) severe restriction (<20 mm). Interestingly, severe restriction correlated with more advanced histological grades and deeper tumor invasion. This finding indicates that progressive fibrosis in OSMF might restrict the invasive spread superficially but facilitates vertical infiltration due to submucosal stiffness and ischemia.

Statistical analysis revealed a significant correlation ( $p < 0.05$ ) between mouth opening and histopathological tumor differentiation, demonstrating that patients with more severe fibrosis often presented with poorly differentiated carcinomas.

### Histopathological Findings

Histopathological analysis of re-evaluated slides revealed distinct differences between OSCC arising in OSMF and conventional OSCC. Among the 78 OSCC-OSMF cases, 42 (53.8%) were well-differentiated, 26 (33.3%) moderately differentiated, and 10 (12.8%) poorly differentiated squamous cell carcinomas.

**Table 3: Histopathological Grading of Tumor Differentiation**

Grade	Number of Cases (n)	Percentage (%)
Well differentiated	42	53.8
Moderately differentiated	26	33.3
Poorly differentiated	10	12.8
<b>Total</b>	<b>78</b>	<b>100</b>

The predominance of well-differentiated carcinomas supports the hypothesis that OSMF-associated carcinomas tend to develop within a chronically fibrotic but immunologically active stroma, limiting rapid dedifferentiation. However, in advanced fibrosis stages, ischemic mucosal changes may promote cellular atypia, leading to more aggressive histological variants.

#### Fibrosis Grading and Tumor Association

Fibrosis severity was graded according to Pindborg and Sirsat (1966): early (20.5%), moderately advanced (44.9%), and advanced (34.6%). Notably, the severity of fibrosis correlated inversely with the degree of tumor differentiation. Advanced fibrosis was often associated with moderate to poorly differentiated carcinomas, suggesting that the progressive hypoxia of fibrotic tissue may act as a driving factor for tumor aggressiveness.

**Table 4: Correlation between Fibrosis Severity and Tumor Differentiation**

Fibrosis Grade	Well Differentiated (n)	Moderately Differentiated (n)	Poorly Differentiated (n)	Total (n)
Early	10	5	1	16
Moderate	21	11	3	35
Advanced	11	10	6	27
<b>Total</b>	<b>42</b>	<b>26</b>	<b>10</b>	<b>78</b>

The observed inverse trend (Spearman's correlation coefficient = -0.41,  $p = 0.003$ ) highlights that as fibrosis progresses, the stromal microenvironment becomes increasingly hypoxic and inflammatory, promoting genetic instability and epithelial dysplasia. This finding corroborates molecular studies indicating upregulation of hypoxia-inducible factor (HIF-1 $\alpha$ ) and vascular endothelial growth factor (VEGF) in OSMF-related carcinogenesis.

#### Nodal Metastasis and Depth of Invasion

Lymph node involvement was detected in 27 (34.6%) patients. The majority of cases with nodal metastasis corresponded to advanced fibrosis grades and poorly differentiated histology. The mean depth of invasion among metastatic cases was 7.2 mm compared to 4.1 mm in non-metastatic cases, indicating a statistically significant relationship ( $p = 0.01$ ).

This correlation suggests that while OSMF-induced fibrosis restricts lateral spread, it enhances vertical infiltration, facilitating deeper tissue invasion and early lymphatic dissemination. Moreover, perineural invasion was observed in 15.3% of the total cases, most commonly in those with severe fibrosis, further underscoring the role of fibrotic stiffness in altering invasion patterns.

#### Comparative Interpretation and Literature Correlation

The results of this study reaffirm that OSCC arising in the background of OSMF represents a distinct clinicopathological entity. While the male predominance and buccal mucosa predilection remain consistent with previous studies (e.g., Hazarey et al., 2015; Rajendran et al., 2020), the present findings emphasize that carcinogenesis in OSMF is characterized by unique histopathological and behavioral trends.

Earlier studies have reported that OSCC-OSMF tends to show a higher proportion of well-differentiated tumors and lower metastasis rates than conventional OSCC. However, this study indicates that with advancing fibrosis, the trend may reverse due to stromal ischemia and hypoxia, which induce epithelial transformation and enhance metastatic potential.

Furthermore, the relatively younger mean age of patients in this cohort highlights a growing concern regarding the early onset of oral malignancies in populations with increasing areca nut consumption. These findings underline the necessity of incorporating fibrosis severity as a prognostic parameter in OSCC staging systems.

#### Histopathological Patterns and Clinical Implications

The simultaneous presence of fibrosis and epithelial dysplasia introduces a complex interplay between epithelial atrophy and stromal remodeling. Fibrotic tissues exhibit reduced vascularity, thereby limiting the nutrient supply to the overlying epithelium. This ischemic stress induces genetic mutations, resulting in dysplastic transformation.

Microscopically, the presence of keratin pearls, epithelial stratification, and altered nuclear morphology confirmed the malignant potential of OSMF mucosa. Stromal inflammation and collagen densification observed in moderate and advanced stages further signify the role of chronic inflammatory mediators, including transforming growth factor-beta (TGF- $\beta$ ) and interleukin-6 (IL-6),

in promoting oncogenic signaling.

Clinically, restricted mouth opening not only poses diagnostic and therapeutic challenges but also delays early detection. Surgical resection in fibrotic tissues is often complicated by reduced mucosal elasticity and poor wound healing, emphasizing the importance of early diagnosis and multidisciplinary management.

#### Statistical Correlations and Prognostic Indicators

Statistical analysis confirmed significant correlations between fibrosis severity and both tumor grade ( $p = 0.003$ ) and nodal metastasis ( $p = 0.01$ ). Additionally, the duration of the areca nut habit demonstrated a positive association with fibrosis grade ( $r = 0.47$ ,  $p < 0.001$ ). Patients with longer durations of chewing habit ( $>10$  years) showed a higher prevalence of advanced fibrosis and poorly differentiated carcinomas.

These results align with the hypothesis that areca nut's alkaloid content, particularly arecoline, perpetuates fibroblast activation and collagen cross-linking, ultimately creating a microenvironment conducive to malignant transformation.

The prognostic outlook for OSCC-OSMF patients in this cohort appeared marginally better in early and moderate fibrosis stages due to the predominance of well-differentiated carcinomas. However, the subset with advanced fibrosis demonstrated reduced survival indicators, consistent with the hypothesis that increased tissue rigidity and vascular compromise enhance invasive behavior.

#### Integrative Discussion: Pathophysiological Insights

From a pathophysiological standpoint, the transition from OSMF to OSCC represents a continuum of mucosal injury, fibroblast hyperactivity, and epithelial adaptation. The results of this study illustrate that fibrotic remodeling of the submucosa alters mechanical and biochemical signaling pathways, influencing the direction of tumor growth.

In early fibrosis, epithelial atrophy predominates, but as fibrosis advances, chronic hypoxia leads to the selection of aggressive cellular clones capable of surviving under nutrient-deprived conditions. These adaptive mutations foster a more invasive phenotype. This observation reinforces the concept that OSMF acts as both a barrier and a facilitator, restricting lateral spread but promoting vertical invasion and metastasis in advanced stages.

Moreover, the high prevalence of well-differentiated carcinomas in the initial stages supports the notion that OSMF-induced carcinogenesis follows a slower progression compared to de novo OSCC. Nevertheless, once fibrosis reaches a critical threshold, tumor behavior becomes markedly aggressive due to the hypoxic and pro-fibrotic signaling cascade.

#### Clinical Relevance and Future Perspectives

The study highlights the necessity for clinicians and pathologists to recognize OSCC-OSMF as a separate diagnostic category requiring tailored management protocols. Given the fibrotic restriction and altered vascularity, surgical excision margins must be carefully determined, and adjunctive therapies such as antifibrotic agents and antioxidants should be considered in preventive strategies.

Furthermore, integrating fibrosis grading into prognostic indices may enhance the predictive accuracy for recurrence and metastasis. Future prospective studies incorporating molecular markers such as HIF-1 $\alpha$ , VEGF, and matrix metalloproteinases (MMP-2, MMP-9) could provide deeper insights into the molecular mechanisms underlying fibrosis-driven carcinogenesis.

#### Summary of Key Findings

1. **Demographics:** Male predominance (78.2%) and a mean age of 46.3 years.
2. **Habits:** Areca nut chewing (91%) is the predominant etiological factor.
3. **Site Distribution:** Buccal mucosa is most affected (57.7%).
4. **Histopathology:** Well-differentiated carcinomas constituted 53.8% of cases.
5. **Fibrosis Correlation:** Advanced fibrosis is linked to poorer differentiation and increased nodal metastasis.
6. **Prognostic Implications:** Early-stage fibrosis is associated with more favorable histological grades and outcomes.

**In conclusion**, the results of this retrospective analysis establish that OSCC arising in the background of OSMF exhibits unique clinicopathological behavior distinct from conventional OSCC. The severity of fibrosis significantly influences tumor differentiation, invasion depth, and metastatic potential. These findings advocate for integrating fibrosis assessment into diagnostic and prognostic frameworks to enhance the early detection, risk stratification, and management of OSMF-associated oral malignancies.

## CONCLUSION

The present retrospective investigation into the *clinicopathological characteristics of Oral Squamous Cell Carcinoma (OSCC) arising from Oral Submucous Fibrosis (OSMF)* provides a comprehensive understanding of this distinct oncopathological entity. The findings clearly demonstrate that OSCC developing in an OSMF background possesses unique epidemiological, clinical, and histopathological attributes that set it apart from conventional OSCC. The data underline that chronic exposure to areca nut and tobacco are key etiological factors in OSMF, not only initiating fibrotic transformation of the oral mucosa but also creating a

biological environment conducive to malignant conversion. The intricate interplay between fibrosis, epithelial atrophy, and hypoxia appears central to the pathogenesis and progression of carcinoma in these patients.

The demographic analysis reaffirmed a striking male predominance and early age of onset, reflecting both behavioral and sociocultural determinants of disease prevalence. The observation that the majority of affected individuals were in their fourth and fifth decades underscores the social and economic implications of the condition, particularly in regions where areca nut consumption remains culturally entrenched. The predominance of lesions in the buccal mucosa further supports the habitual placement of quid as a localized factor contributing to chronic mucosal trauma and carcinogenesis. From a histopathological standpoint, the study elucidated a higher frequency of well-differentiated carcinomas in OSMF-associated OSCC, indicating that the dense fibrotic stroma may initially restrain local tumor infiltration. However, the paradoxical association between advanced fibrosis and increased nodal metastasis highlights a dynamic shift in tumor biology as fibrosis progresses. The chronic hypoxia and altered extracellular matrix composition characteristic of advanced OSMF seem to foster genetic instability, angiogenesis, and epithelial-mesenchymal transition, collectively driving tumor aggressiveness. This dual behavior, superficial restriction yet deep invasion, marks OSMF-associated OSCC as a biologically distinct subset demanding specialized diagnostic and therapeutic attention. Clinically, the limitations imposed by trismus and mucosal rigidity complicate both early detection and surgical management. Many cases are diagnosed only after malignant transformation has occurred, reflecting the insidious nature of OSMF and the inadequacy of current surveillance mechanisms. The findings of this study strongly advocate for routine screening and long-term follow-up of all patients diagnosed with OSMF, irrespective of symptom severity. Early detection through cytological evaluation, biopsy of suspicious lesions, and fibrosis grading could play a pivotal role in reducing morbidity and mortality.

From a therapeutic perspective, understanding the fibrotic component is essential for surgical planning, as the reduced vascularity and stiffness of the tissues can influence wound healing, graft uptake, and postoperative recovery. Moreover, the inclusion of fibrosis grading as an adjunct parameter in staging systems could enhance prognostic accuracy and facilitate more individualized treatment protocols. The study also underscores the necessity of integrating antifibrotic agents and habit cessation strategies into the management of OSMF to reduce the likelihood of malignant transformation. In a broader public health context, these findings highlight the urgent need for awareness campaigns aimed at eliminating areca nut and tobacco consumption, especially among younger populations. Community-based interventions, early oral screening programs, and incorporation of oral cancer education into primary healthcare can serve as effective preventive measures. In summary, OSCC arising from OSMF embodies a complex biological phenomenon where chronic fibrosis evolves into a carcinogenic microenvironment through sustained epithelial stress and hypoxia. This study contributes significant evidence toward characterizing its clinicopathological spectrum and emphasizes the importance of early intervention, vigilant surveillance, and multidisciplinary management. By correlating the severity of fibrosis with tumor behavior, the research establishes a foundation for future studies exploring molecular mechanisms and targeted therapies. Ultimately, combating OSMF-related oral carcinoma demands a combined effort spanning clinical research, pathology, behavioral modification, and policy reform to alleviate the growing burden of this preventable malignancy.

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