Research Paper

Nodal involvement in Oral Squamous Cell Carcinoma (SCC) patients with and without Oral Sub Mucous Fibrosis (OSMF): A Comparative Study

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ABSTRACT

Aim: The aim of the study is to compare and evaluate neck node status of oral cancer patients with and without Oral Sub Mucous Fibrosis (OSMF) treated surgically.

Methodology: A total of 50 patients of Indian origin who were diagnosed with Squamous Cell Carcinoma (SCC) of oral cavity and had not taken any prior treatment were included in the study. Clinical examination and metastatic workup was done for all patients. Patients diagnosed with resectable primary and without distant metastasis were taken up for surgery. For all patients, resected specimens were sent for radical histopathological examination.

Result: The differences in nodal involvement in T₁, T₂ & T₃ sized lesions were non-significant, while in T₄ sized lesions, a statistically significant lower incidence of nodal involvement in patients with-OSMF as compared to patients without OSMF was observed.

Conclusion: Presence of N₀ neck in T₄ lesions in oral SCC patients with OSMF has potential implications on the present pattern of spread and treatment protocols, leading to need for further research with OSMF as independent risk factor for nodal involvement

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1. Introduction

Squamous cell carcinoma (SCC) is the most common form of oral cancer in the Indian subcontinent. The annual mortality rate from head & neck SCC is over 11,000 which corresponds to 2% of all deaths due to cancer.¹ In the Indian subcontinent, the main cause of HNSCC are chewing tobacco, betel nut, betel leaf, and smoking. In western population this is due to the smoking cigarette and alcoholism. Due to these habits a large percentage of oral cancer patients have associated Oral Sub Mucous Fibrosis (OSMF).

Oral Sub Mucous Fibrosis is a condition first described by Sushruta (2500–3000 BC) as Vidari. Pindborg (1966) defined

OSMF as, “an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat”.² Various components are seen like sunken or stiff cheeks, pseudo proptosis, multiple perioral skin folds, whitening of the oral mucosa, poor oral hygiene, bald tongue, chronic non healing ulcers, lacking in mobility of tongue, dysphagia etc.³

Cancers of the oral cavity may involve any single one of these specialized types of tissue or more than one tissue. As noted, tissues includes bone, muscle, nerves, a rich supply blood vessels, numerous salivary glands and the specialized lining called mucosa. Although tumors may arise in any of these types of tissues they are most commonly related to changes in the lining of the oral cavity and is called squamous cell carcinoma (SCC) (Fig. 1).¹

Metastasis is the development of secondary malignant growths at a distant site from a primary site of cancer due to spread of

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Fig. 1. Pre Op.

Fig. 2. Intra Op.

treating cancers of oral cavity are surgery, radiation therapy and chemotherapy. In general, stage I and stage II cancer require one type of treatment, either surgery or radiation therapy, to successfully control the cancer. Advanced stage III and stage IV cancers will often require combinations of surgery, radiation therapy and chemotherapy or even the use of all three. Overall survival rates for any cancer of the oral cavity are about 70% in 5 year survival for stage I or II, 50% for stage III and roughly 35% for stage IV disease.¹

This study aims to compare and evaluate neck node involvement in oral SCC patients with and without OSMF treated surgically.

cancerous cells via lymphatic channels or blood. More than half the oral cancer patients present with lymph node metastases and histological confirmation of metastatic disease is the most important prognostic factor.¹ The main routes of the cervical lymph node spreading go through the first station nodes (Level I and II) and second station nodes including the Level III, IV, and V. Predicting the lymphatic spread can help in choosing the appropriate surgical procedure and may also help in predicting the outcome.⁴

The most significant prognostic factors are the site of the positive node in or out of the sentinel node and the number of positive nodes; and a more accurate approach can be obtained by combining both factors. Node location in the upper or lower neck remains a substitute prognostic factor for the site of the positive node in or out of the sentinel node.⁵ The three main tools for

Fig. 3. Resected Specimen.

Fig. 4. Post Op.

Table 1

Table showing relative site involvement in oral SCC.

SITE	FREQUENCY	PERCENT
Alveolus	8	16.0%
Buccal mucosa	22	44.0%
Buccal mucosa/alveolus	2	4.0%
Buccal mucosa/lip	1	2.0%
Lip	1	2.0%
Palate	1	2.0%
Retro Molar Triangle	1	2.0%
Tongue	14	28.0%
TOTAL	50	100.0%

Table 2

Table showing habits associated with oral SCC.

HABITS	FREQUENCY	PERCENT
No habits	10	20.0%
Alcohol	1	2.0%
Chewing	12	24.0%
Chewing and Alcohol	3	6.0%
Chewing and Smoking	11	22.0%
Chewing, Smoking and Alcohol	11	22.0%
Smoking	2	4.0%
TOTAL	50	100.0%

2. Methodology

The study was conducted in the Department of Oral & Maxillofacial Surgery at Shree Bankey Bihari Dental College, Masuri, Ghaziabad, Dharamshila Cancer Hospital, Delhi-96 & C3 Healthcare, Vasundhra Enclave, Delhi-96. The criteria for selection of patients in the study are enumerated below:

Inclusion Criteria

1. Biopsy proven cases of SCC of oral cavity.

Table 3

Table describing staging of SCC patients with and without OSMF.

STAGE	OSMF		TOTAL
	Absent	Present	
T ₁	2	4	6
T ₂	4	15	19
T ₃	4	3	7
T ₄	7	11	18
TOTAL	17	33	50

Table 4Table showing non-significant differences in nodal involvement in T₁ lesions with and without OSMF.

T ₁ Neck node status	OSMF		TOTAL
	Absent	Present	
Negative	1 50.0%	4 100.0%	5 83.3%
Positive	1 50.0%	0 0.0%	1 16.7%
TOTAL	2 100.0%	4 100.0%	6 100.0%

Chi-square value = 2.400, p-value = 0.121.

Chi-square test.

Non-significant difference.

2. Patients who have not been previously treated for oral cancer

Exclusion Criteria

1. Post Radiotherapy, Chemotherapy & Surgery patients
2. Patients with T_x primary lesion

Fig. 5. Neck node status in T₁ patients with and without OSMF.

Table 5

Table showing non-significant differences in nodal involvement in T₂ lesions with and without OSMF.

T ₂	OSMF		TOTAL
	Absent	Present	
Neck node status			
Negative	1 25.0%	6 40.0%	7 36.8%
Positive	3 75.0%	9 60.0%	12 63.2%
TOTAL	4 100.0%	15 100.0%	19 100.0%

Chi-square value = 0.305, p-value = 0.581.

Chi-square test.

#Non-significant difference.

3. Patients with unknown primary tumor

4. Patients not willing to provide informed consent for treatment of oral cancer.

A total of 50 patients fulfilling the above criteria were included in the study and were further subdivided on the presence/absence of OSMF. Clinical and functional criteria for the diagnosis of OSMF included restricted mouth opening with palpable fibrous bands.⁶ Clinical examination included the size of the tumor, site of the tumor, neck node involvement status. For all patients, metastatic work up was done via Computerized Tomography/MRI (Face & Neck), Chest X-ray/CECT Thorax, USG Abdomen or PET-CT as per standard protocol.

The patients who were diagnosed with SCC with no evidence of distant metastasis were taken up for primary surgical resection

with neck dissection and reconstruction under GA Figs. 2–4. For all operated patients, excised tissue was subjected to radical histopathological examination which consists of gross sampling, pathological tumor size, pathological lymph node status, extra capsular spread, perineural invasion, lymphovascular invasion and histopathological variant or grade.

3. Result

The study population consisted of 44 (88%) males and 6 (12%) females. The most common sites involved in decreasing order were buccal mucosa (44%), Tongue (28%) and alveolus (16%) and has been tabulated in Table 1. The associated habits in these patients have been tabulated in Table 2. Table 3 describes staging of SCC patients with and without OSMF.

The neck node status was compared between OSMF and Non-OSMF patients in each of the stages using Chi-Square Test. Non-significant differences in the neck node status between OSMF and non-OSMF patients was observed in T₁ (Table 4, Fig. 5), T₂ (Table 5, Fig. 6) & T₃ (Table 6, Fig. 7) lesions.

However, negative neck node was significantly more in OSMF patients with T₄ lesions. Also, positive neck node was significantly more among non-OSMF patients exhibiting T-4 lesions (Table 7, Fig. 8)

4. Discussion

Squamous cell carcinoma (SCC) is the most common malignant neoplasm of the oral cavity, accounting for more than 90% of all oral malignancies.¹ Early diagnosis is the key to success in the management of oral squamous cell carcinoma. In the past, squamous cell carcinoma of the oral cavity was primarily found

Fig. 6. Neck node status in T2 patients with and without OSMF.

Table 6

Table showing non-significant differences in nodal involvement in T₃ lesions with and without OSMF.

T ₃ Neck node status	OSMF		TOTAL
	Absent	Present	
Negative	3 75.0%	2 66.7%	5 71.4%
Positive	1 25.0%	1 33.3%	2 28.6%
TOTAL	4 100.0%	3 100.0%	7 100.0%

Chi-square value = 0.058, p-value = 0.809.

Chi-square test.

Non-significant difference.

in elderly men with the risk factors being tobacco and excessive alcohol use.⁷ Squamous cell carcinoma most commonly develops in the sixth or seventh decade of life, usually in patients who have significant risk factors from smoking or alcohol use. A subgroup of patients less than 45 years old, however, develops squamous cell carcinoma of the head and neck in whom the role of tobacco or alcohol use is less clear in the etiology of their cancer.⁸

Most oral cancers are epithelial squamous cell carcinomas because most of the risk factors injure the most superficial layers of the mucosa and gingiva. These areas experience a constant turnover and prolonged exposure to risk factors, including tobacco, alcohol, viruses, drugs, and betel nut (alone or in combination), which cause genetic mutations that ultimately result in an increase in incidence and prevalence of the disease.⁹ The oral cancer ranks number one among all cancers in male patients and number three among cancers in female patients. Causal association between oral

Table 7

Table showing significant differences in nodal involvement in T₄ lesions with and without OSMF.

T ₄ Neck node status	OSMF		TOTAL
	Absent	Present	
Negative	2 28.6%	9 81.8%	11 61.1%
Positive	5 71.4%	2 18.2%	7 38.9%
TOTAL	7 100.0%	11 100.0%	18 100.0%

Chi-square value = 5.103, p-value = 0.024*.

Chi-square test.

*Significant difference.

cancer and the chewing of betel quid containing tobacco leaves or stem and other tobacco habits has been extensively studied.¹⁰ In India the peak age frequency of occurrence is at least a decade earlier than that described in Western literature. Sex ratio reveals a 2: 1 preponderance of male patients. Only 10%–15% of cases present in localized stages.¹⁰ Carcinoma of the oral cavity has a great potential for metastatic spread to neck lymph nodes with incidence reported to be 34%–50%.⁴

The course of oral SCC is unpredictable, but the TNM stage (T-tumour size, N-nodal metastasis, M-distant metastasis) of the primary tumour correlates well with the survival rate.¹¹ The most significant prognostic factors for SCC are the site of the positive node in or out of the sentinel node and the number of positive nodes; and a more accurate approach can be obtained by combining both factors. Node location in the upper or lower neck remains a substitute prognostic factor for the site of the positive

T 3

Fig. 7. Neck node status in T₃ patients with and without OSMF.

Fig. 8. Neck node status in T4 patients with and without OSMF.

node in or out of the sentinel node.⁵ While the importance of treatment of the neck in clinically detected lymph nodes is beyond doubt, elective treatment of the clinically negative neck continues to bring controversy.⁴ The prognosis is best when the primary tumour is small and there is no evidence of regional lymphnode involvement or distant metastasis. In fact, the 5-year survival rate of persons with early-stage oral SCC according to the TNM staging system may reach 80%–90%, whereas the five-year survival rate for advanced-stage oral SCC is about 40%.¹²

The presence of extracapsular lymphnode spread is associated with a high-rate of local and regional recurrence, distant metastasis and mortality.¹³ About 8% of patients with oral SCC will have distant metastases at the time of diagnosis,¹³ most frequently to the lungs.¹⁴ Important factors at the time of diagnosis of oral squamous cell carcinoma- determining survival are the presence of regional lymphnode metastases, the size (surface dimension) and depth (extent of local infiltration) of the carcinoma, the oral anatomical site affected and the histopathological grade of the carcinoma. After treatment, factors correlating with survival will be whether or not the margins of the resected carcinoma were free of invading carcinomatous cells, because this will determine whether or not there will be local recurrence; and whether or not a second tumour will develop in the same or in a contiguous epithelialized precancerized field.¹¹

Sentinel Node Biopsy (SNB) is now routinely used in clinical practice in order to avoid unnecessary lymph node removal in breast cancer and malignant melanoma, considering the high morbidity of axillary and groin dissection. In these patients, SNB is mainly a staging procedure for selecting those patients that could benefit from adjuvant treatments. On the contrary, neck dissection is a key part of the treatment of oral SCC, because patients die on account of regional recurrences. SNB, in oral SCC, is applied in

many Institutions, in clinical trials, mainly to guide the decision-making on neck management in N_0 cases treated with a trans-oral approach.^{15,16} Dynamic lympho-scintigraphy is under study in order to identify all the levels reached by the lymphatic stream from the primary tumour: this information could allow a personalised selective neck dissection to be carried out.¹⁶

In 1952, Schwartz described five Indian women from Kenya with a condition of the oral mucosa including the palate and pillars of the fauces, which he called “atrophiadiopathica (tropica) mucosaeoris”. Later it was termed oral submucous fibrosis (OSMF); other names are “diffuse oral submucous fibrosis”, “idiopathic scleroderma of the mouth”, “idiopathic palatal fibrosis”, “sclerosing stomatitis” and “juxta-epithelial fibrosis”.¹⁷ In spite of intensive research over the years into the etiologic factors of oral submucous fibrosis, a single etiologic factor cannot be pointed out with certainty rather several causative factors have been proposed. Patients suffering with oral submucous fibrosis initially present with a blanched or marble-like pale mucosa, vesiculations, and also intolerance to hot and spicy food.³ Studies from Pakistan, India and China consistently showed that chewing of areca nut was the major aetiologic factor for oral leukoplakia and oral submucous fibrosis.¹⁸ Dr. V K Hazarey found that the male-to-female ratio of oral submucous fibrosis was 4.9:1. Occurrence of oral submucous fibrosis was at a significant younger age group (<30 years) among men when compared with women.¹⁹

The present study reveals negative neck node in T₄ lesions with and without OSMF being 81.1% and 28.6% respectively. Dysregulation of collagen metabolism has an important role in the pathogenesis of OSMF. Wang et al (2007) reported that areca nut extract induces oxidative stress²⁰ which in turn could possibly cause lymphatic occlusion²¹. This could explain the decreased nodal involvement in T₄ lesion in OSMF patients as reported in the

present study. Chaturvedi et al (2013) in a similar study reported that patients of oral cancer with OSMF had lesser incidences of nodal metastasis.²²

This study has provided new facts about the nature of oral SCC and its nodal spread in OSMF patients. There was no significant difference in the distribution of neck node status between OSMF and Non-OSMF patients, for T₁, T₂ and T₃ lesions. However, in T₄ sized lesion, nodal involvement was significantly less in OSMF patients. The presence of N₀ status in T₄ lesions has potential implications on the present theories and patterns of spread of oral SCC, leading to need of further research with OSMF as an independent risk factor influencing nodal involvement and subsequent modifications in treatment protocols for OSMF patients to reduce morbidity.

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