

Original Research Article

A correlation of depth of tumour invasion and pattern of cervical metastasis in Oral Squamous Cell Carcinoma (OSCC) in the background of Oral Submucous fibrosis (OSMF)

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Abstract: The aim of this study to determine the depth of tumor invasion and pattern of cervical metastasis in patients of OSCC with OSMF. Methods: The authors prospectively investigated 40 patients of OSCC with OSMF who underwent surgery for OSCC with curative intent over a 2 year period. OSCC with OSMF was more commonly seen in males (87.5%) compared to females (12.5%). Buccal mucosa was the most frequently involved site, accounting for 40% cases. Broader's grading showed 65% moderately differentiated, the overall incidence of cervical lymph node metastasis was found to be 37.5% (n=15) out of 40 cases level Ib node was found to be frequently involved (23.26%). Mean depth of tumour invasion was 4.46mm. A cut-off predictive value of ≥ 4 mm of depth of tumour invasion (DTI) was found to be reliable indicator of cervical node metastasis. Relationship of histopathological depth of tumor invasion and cervical metastasis was found to be statistically significant ($p = 0.006$). The correlation between tumor size and cervical lymph node metastasis was found to be insignificant. Conclusion: OSCC with OSMF affects younger population showing better grade of tumor differentiation, predominantly involving buccal mucosa, GB sulcus and tongue with lesser DTI, superficial and more predictable nodal metastases, most commonly involving level I lymph nodes. These factors together may act as guide line to form a strategy for management of OSCC with OSMF which could be more conservative than the established protocol.

Keywords: Oral submucous fibrosis, Oral squamous cell carcinoma, Depth of tumor invasion, Cervical metastasis

INTRODUCTION

Areca nut chewing leads to a ubiquitous potentially malignant disorder called oral submucous fibrosis (OSMF), characterized by progressive fibrosis of the oral mucosa. Areca nut is an independent group I human carcinogen in accord with the International Agency for Research on Cancer (IARC), World Health Organization (WHO) [1]. WHO defined OSMF as "a slowly progressive disease in which the fibrous bands form in the oral mucosa, ultimately leading to severe restriction of movement of the mouth, including the tongue." [1] OSMF has a worldwide diverse prevalence with the disease being pandemic in countries of south Asia such as India, Pakistan, Bangladesh and Sri Lanka. This can be attributed largely to the rampant use of betel/areca nut consumption in various forms in these regions. There are many regional variations in areca nut

use Viz combination of use of areca nut + slaked lime + betel leaf \pm tobacco, pan masala (powdered areca nut with additives, flavoring agents, and tobacco), and raw areca nut. Recently, the estimated prevalence of OSMF in India was reported to range from 0.2% to 1.2% [3].

Apart from the morbidity associated with fibrosis, OSMF is now an acknowledged potentially malignant disorder [4]. A positive dose dependent relationship between frequency and duration of betel quid chewing and risk of development of OSMF and oral carcinoma exists. The combined use of betel quid with tobacco increases the risk of carcinogenesis in a dose-dependent manner. The prevalence, incidence, mortality and morbidity associated with although variable across the world, are high in areas where betel nut/betel leaf/tobacco use is high [3]. Last four decades

have witnessed growing body of evidence in the literature reporting varied malignant transformation of OSMF to oral squamous cell carcinoma (OSCC).

Malignant transformation rate of OSMF was found to be in the range of 7-13% [5]. The cause of it is multifactorial. The most common reason is the reduced elasticity of the oral mucosa which subjects the mucosa to trauma mainly due to malposed teeth, a sharp edge, and special to mention an impacted third molar. More dangerous to mention is habit of betel-nut mixed with tobacco in which apart from development of condition, carries a high risk for developing a lesion. Oral cancer is the most common cancer in Indian males (13% of all malignancies) and is the third most common cancer in Indian females [6]. OSCC has loco-regional ramifications. It has a greater tendency to metastasize to regional lymphnodes in a predictable manner. The overall 5-year survival of patients with OSCC is less than 50% [6].

Concomitant association of OSMF with OSCC is remarkable in that the dense fibrosis and less vascularity of the corium, in the presence of an altered cytokine activity creates a unique environment for carcinogens from both tobacco and areca nut to act on the epithelium. Less vascularity may impair the quick absorption of carcinogens into the systemic circulation and this reduced and blocked submucosal vascularity may have a beneficial effect on overall prognosis [5]. In his seminal work, Chaturvedi P *et al.* [8] exemplified the impervious nature of OSCC associated with OSMF. The authors concluded that OSCC in the background of OSMF behaves in a distinct clinicopathological manner in which the subset of disease was found to be common in younger males with better prognostic factors such as better grade of tumor differentiation, lesser incidence of nodal metastases, and extracapsular spread.

The fibrotic environment in OSMF entails lesser depth of tumour invasion; this complimented with blockage of submucosal lymphatics as a result of fibrosis resulting in lesser incidence of nodal metastasis led the investigators to hypothesize that OSCC associated with OSMF may behave differently than OSCC which occurs alone. Hence, a prospective observational study was designed and deliberated to validate the above hypothesis.

SUBJECTS AND METHODOLOGY

The present prospective, observational audit was designed and implemented between April 2013 and June 2016 at our center. This study was a prospective audit without any special/ different interventions, for which the necessary institutional ethics committee waiver/exemption was obtained. All the patients with a non-healing ulcer of oral cavity with features of OSMF (intolerance to hot and spicy foods, pale looking oral mucosa, palpable fibrous bands, and chronic progressive trismus) were subjected to biopsy

for conformation of OSCC. If found positive, these were histologically graded into Well / Moderate / Poorly differentiated (by Broder's classification). Patients with non-epithelial malignancy, multiple index tumours, history of chemotherapy, radiotherapy \pm surgery and Second primary tumours were excluded. A total of 40 consecutive patients fulfilling the above criteria were included in the study

The following clinical and pathologic findings were recorded: age, sex; habit history, primary site of disease according to various subsites (oral tongue, buccal mucosa, lower and upper alveolus, hard palate, lip, floor of mouth, retromolar trigone [RMT]); clinical and pathologic tumor classification (cT and pT); clinical and pathologic nodal status (cN and pN); and histopathology parameters, such as cut margin status and depth of tumour invasion. All patients underwent comprehensive pre-surgical evaluation, which included a medical history and complete physical examination, complete blood count, routine blood biochemistry, magnetic resonance imaging (MRI) scans of the head and neck, chest radiographs. The staging of OSCC was assigned according to pathological status at presentation for primary surgical treatment. In this study we resorted to patient staging according to the staging criteria from the 1997 American Joint Committee on Cancer (AJCC), 5th edition [9], as the correct staging of pT4b disease according to the AJCC 2002 criteria might be confounding for OSCC analysis.

All patients underwent standard treatment i.e. Wide local excision of lesion, Neck dissection supraomohyoid neck dissection for N0 neck and modified neck dissection for N+ neck followed by appropriate adjuvant treatment based on histopathologic parameters. Fibrotomy, coronoidectomy ipsilateral \pm contralateral side and reconstruction with suitable flap. Resected specimen (index tumour) and resected levels of lymph nodes were assessed, grossed, labeled and subjected to intra operative frozen section, Step serial sectioning and Immuno-histochemical (IHC) evaluation with Pancytokeratin.

OBSERVATIONS AND RESULTS

A total of 40 patients with OSCC with OSMF were examined. Among the patients included for the study, males were predominantly affected i.e. 87.50 % (n=35) than females which were 12.50% (n=5) only. Most commonly affected age group was of 41-50 years (32.5%), followed by 31 – 40 years (27.5%) and 21 – 30 years (17.5 %). Buccal mucosa was the most frequently involved site, accounting for 40% cases, followed by lower gingivo-buccal sulcus in 22.5% case and tongue in 17.5% cases.

Histopathologically, Broder's grading showed 65% moderately differentiated, 30% well differentiated and 5% poorly differentiated OSCC with OSMF. Cervical lymph node metastasis was found in 15

(37.5%) out of 40 cases with the frequent involvement of level Ib (23.26%) lymph nodes. Depth of tumor invasion was found to be statistically significant ($p = 0.006$) with cervical lymph node metastasis. A cut-off

for predicting nodal metastasis was found at an infiltration depth of 4mm. The correlation between tumor size and cervical lymph node metastasis was found to be non-significant [Table 1].

Table-1: The correlation between tumor size and cervical lymph node metastasis

Gender				
	No of patient (n=40)	(%)		
Male	35	87.5		
Female	5	12.5		
Age wise distribution				
21-30	7	17.5		
31-40	11	27.5		
41-50	13	32.5		
51-60	4	10		
61-70	5	12.5		
Mean	43.67±12.96 years			
Primary site of tumour with cervical metastasis				
Site	No of patient, n=40 (%)	N+ (%)		
Buccal Mucosa	16 (40%)	8 (50%)		
Tongue	7 (17.5%)	2 (28.57%)		
Retromolar	1 (2.5%)	1 (100%)		
Upper GB sulcus	2 (5%)	0 (0%)		
Lower GB sulcus	9 (22.5%)	3 (33.33%)		
Alveolus	4 (10%)	1 (25%)		
Maxilla	1 (2.5%)	0 (0%)		
Total	40 (100%)	15 (37.5%)		
Degree of differentiation with cervical metastasis				
Broader's grading	No of patients, n=40 (%)	N + (%)		
Well differentiated	12 (30%)	1 (8.33%)		
Moderately differentiated	26 (65%)	12 (46.15%)		
Poorly differentiated	2 (5%)	2 (100%)		
Pathological pT classification				
Staging	No of patients, n=40 (%)	N + (%)		
I	1 (2.5%)	1 (100%)		
II	3 (7.5%)	1 (33.33%)		
III	10 (25%)	5 (50%)		
IVa	26 (65%)	8 (30.76%)		
Correlation in size of tumor and cervical metastasis				
	Correlation coefficient (r)	95% confidence interval	p-value	Significance
Size	0.185	0.14-3.40	0.253	Not significant
OSMF grading				
OSMF grading	No of patients, n=40 (%)	N + (%)		
I	3 (7.50%)	2 (66.66%)		
II	9 (22.50%)	5 (55.55%)		
III	13 (32.50%)	4 (30.76%)		
IV	15 (37.50%)	4 (26.66%)		
Level of cervical node metastasis				
Level of cervical nodes	Frequency	(%)		
Not involved	25	58.14		
Level Ia	1	2.33		
Level Ib	10	23.26		
Level IIa	3	6.98		
Level IIb	2	4.65		
Level III	1	2.33		
Level IV	1	2.33		
Level V	0	0.00		
Correlation in Depth of tumor invasion and cervical metastasis				
	Correlation coefficient (r)	95% confidence interval	p-value	Significance
Histopathological	0.42	0.0113-0.456	0.006	Significant

DISCUSSION

Areca nut is the fourth most common psychoactive substance in the world. It has been estimated that betel quid (with Areca nut) is used by approximately 10–20% of the world's population and that globally up to 600 million users chew areca nut [10]. The Indian subcontinent has one of the highest incidences of oral cancer in the world, chiefly due to the high prevalence of chewing a combination of smokeless tobacco and areca nut [7, 8]. In India, Areca nut and its various forms such as gutka, khaini, mawa, and paan that contain smokeless tobacco and areca nut consumption is widespread. Consequently, analyses of habit history in the present study population make a noteworthy revelation that all patients of OSMF with OSCC had habit of consumption of dried and cut areca and its various preparations for a variable duration.

OSMF is a chronic, insidious disease that affects oral cavity and sometimes pharynx and predisposes it to malignant changes. It has been reported that about 2% to 10% of these may transform into malignancy [3]. Areca nut trails distinct molecular pathway for carcinogenesis and this may attribute to an altered clinical and biological behavior led the investigators to deliberate the present study.

A distinctive male gender predilection was seen 87.50% (n=35) as compared to females 12.50% (n=5). This can be explained by the fact that the incidence of chewing tobacco and betel nut is higher among males. This finding is in accordance with the study of Chaturvedi *et al.* [8]. However, conflicting evidence on the sex distribution of oral cancer in the young have been reported [11, 12].

In patients with OSCC with OSMF, the most commonly involved age group in decreasing order was in the group of 41 – 50 years accounting for 32.50%, followed by 31 – 40 years (27.50%) and 21 – 30 years (17.50%). Interesting to note is that 7 cases out of 40 were in between age group 21 – 30 years, youngest being 24 year old. Hashmi GS *et al.* [13] reported similar observations for disease predilections showing greater incidence of age within 4th – 5th decade of life. Recently Chaturvedi *et al.* [8] also reiterated similar observation, in that the author found that mean age of 45.11 years for disease occurrence in patients with OSCC with OSMF.

Regarding the site predilection in oral cavity, it was observed that the most common site involve was buccal mucosa (40%) followed by lower gingiva-buccal sulcus (22.5%). 7 (17.5%) cases out of 40 showed involvement of tongue. Similarly, Chaturvedi *et al.* [8] found buccal mucosa & gingivo buccal complex as the most commonly affected site in 66 (59%) followed by tongue 43 (38.39%) in OSMF OSCC group. The tongue typically shows atrophy of keratinized structures such as papilla, giving it a bald appearance; rendering it

vulnerable to malignant changes. Apart from the presence of etiological factor like tobacco chewing; trauma from wisdom teeth and sharp teeth does play role in OSMF with OSCC. Continuous betel-nut chewing habit leads to attrition of teeth and leading to sharp edges which constantly irritate the non-resilient mucosa and tongue during mastication and speech. This inflicts injury to the mucosa and tongue paring way for malignant transformation.

One of the determinant factors for survival in patients of oral cancers is metastasis and recurrence. Metastasis unequivocally signifies that tumour is malignant. The presence or absence of metastatic disease in cervical lymph nodes of oral cancer patients is the single most important determinant of therapy as well as the prognosis of the patient. Cancer of the head and neck metastasize to the cervical lymph node in a predictable fashion based on the primary sites and sub-sites.

In the present study, we found that 15 (37.5%) out of 40 patients showed lymph node metastasis to various levels. Out of these 15 patients, 8 (53.33%) cases were positive for lymph node metastasis had their primary lesion over buccal mucosa, followed by lower GB sulcus 3 (20%), followed by tongue 2 (13.33%) cases. Chaturvedi *et al.* [8] mentioned lesser incidence of nodal metastases in cases of OSCC with OSMF while Zhou *et al.* [14] showed that patients with OSCC with OSMF had no neck node metastases. Opposing observations were made by Hashmi GS *et al.* [13] wherein the author perceived, that initial stage of nodal metastasis was predominant in cases of OSCC with OSMF.

Literature reveals that of all the prognostic parameters that have been evaluated, tumor thickness and depth of invasion have emerged as the best predictors for cervical nodal metastasis. Moore *et al.* [15] elucidated the conceptual difference between depth of invasion and tumor thickness. According to him, “Depth of invasion” entails the extent of cancer growth into the tissue beneath an epithelial surface while, tumour thickness concerns the entire tumor mass; in the present study, we implemented the evaluation of depth of tumour invasion and its influence on nodal metastasis. Infiltration depth is considered a better predictor for nodal status, because it compensates for exophytic growth or tissue destruction by the tumour. We found that depth of invasion ranged from 2.8 to 6.5 mm complementing and in agreement with results of Hashmi GS *et al.* [13], Chaturvedi *et al.* [8] and Zhou *et al.* [14]. They stated that patients of OSCC with OSMF show thinner lesions.

Better degree of differentiation of tumours was observed in the present study. Moderately differentiated tumour accounted 65% (n=26), with high incidence for neck node metastasis 46.15% (n=12), while 2 cases of

poorly differentiated tumours showed 100% incidence for regional metastasis. This disparity in the observation is attributable to smaller sample size. High proliferative activity and basal cell hyperplasia in combination with rapid exfoliation of superficial cells and epithelial atrophy suggest rapid epithelial turnover rate is in OSMF. Presence of surface keratinized layer in this situation suggests faster maturation or differentiation of epithelium in OSMF. Thus, the epithelial cells are genetically programmed for high turnover rate and faster differentiation or maturation to form keratin. During malignant transformation of OSMF, the transformed epithelial cells may retain the genetic memory of faster differentiation and maturation resulting in better grade of tumor differentiation [16].

All the tumours in the present study group were in advanced stage (pT3 and pT4). We did not encounter any significant nodal involvement (pN+), clinical lymphovascular invasion or cervical node enlargement enough to anticipate any extra capsular spread. Accurate prediction of histological tumour thickness may influence management regarding surgical margins, use of reconstruction and elective neck dissection. Currently there are no proven methods to assess tumour invasion pre-operatively, although it is common practice to attempt evaluation in order to determine the requirement for elective neck dissection. The mean depth of tumour invasion was 4.46 mm and the predictor cut off value for cervical metastasis was 4 mm. This can be attributed to better degree of tumour differentiation and less depth of tumour invasion.

CONCLUSION

OSCC with OSMF affects younger population showing better grade of tumor differentiation, predominantly involving buccal mucosa, GB sulcus and tongue with lesser depth of tumor invasion, superficial and more predicable nodal metastases, most commonly involving level I lymph nodes. It is important to rehabilitate and treat the submucous fibrosis on other side by performing fibrotomy, coronoidectomy and reconstruction with a suitable flap so as to have a satisfactory mouth opening postoperatively. These factors together may act as a guide line to form a strategy for management of OSCC with OSMF which could be more conservative than the established protocol. However a study with larger sample size is required to arrive at a logical conclusion.

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