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Original Research Article

Analysis of epidemiological and clinicopathological risk factors for locoregional recurrence of oral cavity squamous cell carcinoma: retrospective analysis of 150 patients with buccal mucosal carcinoma in a tertiary care centre

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ABSTRACT

Background: Oral cavity cancers, the second most common type in India, are responsible for 10% of the overall cancer burden. With a recurrence rate of 30% to 40% and a 5-year survival rate of 50%, these malignancies account for substantial morbidity and mortality. Despite advances in treatment modalities, survival rates following treatment completion have not improved significantly. The present study aimed to establish specific epidemiological and pathological factors which are responsible for recurrence after treatment completion in buccal mucosa cancers.
Methods: A retrospective analysis of the data of 150 patients treated for biopsy-proven cancers of the buccal mucosa was undertaken 2 years after treatment completion. Factors such as age, sex, education, lymphovascular invasion, extranodal extension (ENE), perineural invasion, depth of invasion, and pathological margin status were compared between patients who presented with recurrence and those who did not. Statistical significance was set at $p<0.05$.
Results: Of the 150 patients, 52 (34.6%) developed a recurrent disease within 2 years. The mean age of the study population was 45.6 years, and males constituted 84% of the included patients. Ipsilateral buccal mucosa was the commonest site of disease recurrence. Neck node metastasis, ENE, and margins of resection <5 mm, lymphovascular invasion, perineural invasion, and depth of invasion >10 mm, tobacco consumption, smoking were significantly related to the recurrence of disease.
Conclusions: Neck node metastasis, ENE, and margins of resection <5 mm, lymphovascular invasion, perineural invasion, depth of invasion >10 mm were the histopathological factors associated with recurrence in cancers of the buccal mucosa.

Keywords: Squamous cell carcinoma, Recurrece, Buccal mucosa, Extra nodal extension, Depth of invasion

INTRODUCTION

Oral cavity cancers pose an enormous burden on the Indian healthcare system, accounting for 10.3% of the overall cancer cases in India. Oral cavity cancers are the second most common cancers diagnosed after breast malignancies and the third most common cause of cancer-related mortality after cancers of the breast and cervix.[1] With a cumulative 5-year survival rate of around 50%, which decreases to 30% in advanced presentations, these cancers are responsible for substantial morbidity and mortality.[2] Advances in treatment modalities, including the use of adjuvant chemoradiotherapy have not led to a significant improvement in survival in oral squamous cell carcinoma (OSCC).[3]

Locoregional recurrence (LRR) is seen in 10% to 30% of patients following treatment completion and is generally considered to be a predictor of an unfavorable prognosis regarding survival.[4,5] Despite the massive impact of recurrence on OSCC prognosis, we have only a limited understanding of the patterns and factors responsible for recurrence.[3,6] This can be attributed to the diverse nature of studies done previously, varying treatment strategies, and the fact that squamous cell carcinomas (SCCs) arising in different subsites of the oral cavity are distinct entities. The absence of specific biomarkers to predict each patient's disease burden not only hinders our provision of effective treatment plans, but also leads to deficiencies in monitoring for recurrence.[7]

The present retrospective observational study aimed to analyze the epidemiological and clinicopathological features associated with LRR in OSCC of the buccal mucosa (BM).

METHODS

Study design and place

The present retrospective study was conducted in the Department of Surgical Oncology, Madras Medical College, Chennai, India. Reports of 150 biopsy-proven cases of OSCC of BM diagnosed and treated between January 2019 and July 2022 were analyzed retrospectively. Data was collected and analyzed from the medical records department and outpatient documentation 2 year after completion of treatment.

Inclusion criteria

The inclusion criteria for this study were as follows: patients with biopsy-proven OSCC of BM (extension into upper and lower gingivobuccal sulcus also included); patients aged >18 years; or patients who completed treatment according to institutional protocols.

Exclusion criteria

Exclusion criteria for patients were as follows: patients with SCC of other subsites of the oral cavity, such as the tongue, hard/soft palate, alveolus; patients presenting with a recurrence or distant metastasis; patients who received a form of anti-cancer therapy previously, including surgery, chemotherapy, or radiotherapy; those with positive surgical margins or; those who were lost to follow-up or who did not complete treatment according to institutional protocols.

Treatment

All patients with biopsy-proven OSCC of BM were staged using contrast-enhanced computed tomography (CECT) scans of the face and neck, as well as a CECT chest scan to detect lung metastasis. All patients underwent a wide local excision/ Composite resection of the primary carcinoma, including a marginal/hemimandibulectomy (if needed) with neck dissection either selective or comprehensive neck dissection according to institutional protocols. Reconstruction was done using a uni/bipaddle pectoralis major myocutaneous flap, nasolabial flap, free flap or SSG. The pathological stage was assigned postoperatively according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM classification.[8] Patients with positive neck node metastasis, T3/T4 stage disease and closest margin of resection <5 mm received adjuvant treatment in the form of postoperative radiotherapy at a dose of 60 Gy to the tumor bed and ipsilateral neck. Those with extranodal extension (ENE) received additional chemotherapy in the form of weekly cisplatin. Patients with positive margins were excluded from the study.

Follow-up

Follow-up done at monthly intervals. A thorough physical examination was conducted along with a chest X-ray. Patients presenting with suspicion of recurrence underwent a CECT scan of local part along with a CECT scan of the chest and PET CT if needed inequivocal cases. Suspicious lesions were biopsied.

Statistical analysis

We investigated the following factors: age, sex, pathological stage, tumor (T) stage, nodal (N) stage, DOI, PNI, lymphovascular invasion (LVI), ENE, and closest margin of resection. The relationship of these factors with the recurrence of OSCC was established by comparing the data of those who had recurrences and those who did not. Statistical analysis was undertaken using statistical package for the social sciences (SPSS) version 25. The prognostic significance of DOI and pathological margins was calculated at various cutoff values. Univariate and multivariate analyses were used to identify the independent risk factors for LRR. The Chi-square test was used for the univariate analysis, and multivariate analysis of the prognostic factors was performed using the cox logistic regression method. In all analyses, $p<0.05$ was considered significant.

RESULTS

The study included 150 patients who underwent wide local excision and neck dissection, followed by reconstruction using a pedicled flap or a free flap, to manage OSCC of BM between January 2019 and July 2022. Adjuvant therapy in the form of radiotherapy or chemoradiotherapy was administered if indicated. Analyses took place 2 year after the completion of treatment.

Fifty-two patients (34.6%) exhibited recurrence and 98 patients (65.4%) were disease-free at 2 years after treatment completion. Among the 52 patients who

developed recurrence, 32 (61.5%) were diagnosed within the first 12 months of treatment completion, and the other 20 cases (38.5%) were detected at the 2-year follow-up. Males constituted 84% of the study population, with 126 cases, whereas females were affected in 24 cases (16%). Of the 150 patients, 100 (66.6%) were younger than 50 years, and 50 patients (33.4%) were aged 50 years or older at the time of primary presentation. Compared to the 115 patients (76.6%) who admitted to a regular pan chewing habit, only 70 patients (46.6%) admitted to a regular habit of smoking cigarettes or bidis. A small number of patients (n=21, 14%) had not received any formal education, we found a relationship (p=0.07) between the absence of formal education and development of LRR but not statistically significant (Table 1).

The most common site of disease recurrence was the ipsilateral BM with 29 cases (55.8%). The ipsilateral neck was affected in 15 (28.8%) cases (12 patients had skin and soft tissue recurrence, 3 patients had nodal recurrence). In four patients (7.6%), recurrences developed at the margins of pectoralis major myocutaneous flap which was used to reconstruct the defect. Contralateral neck nodes were affected in four cases (7.6%). On histopathological analysis, 116 patients (77.3%) presented with a moderately differentiated carcinoma, the commonest variety found in both the recurrence and non-recurrence groups.

Interestingly, most patients in the recurrence group presented with a T3 disease (28 cases, 53.8%), followed by a T2 disease (13 cases, 25%). T4 disease was seen in only eight patients (15.4%) in the recurrence group. In the Non recurrence group, T2 was the commonest presentation (37 patients, 37.8%), followed by T3 disease with 33 patients (33.6%) and T4 disease was seen in 18 patients (18.4%) (Table 2). There exists a greater statistical significance between T3 of cases with recurrence and without recurrence (p=0.02, Chi square=5.7). N1 disease in 19 patients (36.5%) formed the commonest nodal presentation in the recurrence group; it is important to note that 15 patients (28.8%) in the recurrence group presented with ENE. In the group without recurrence, a pathologically uninvolved neck (N0) was the commonest presentation, with 57 cases (58.2%). Only nine patients (9.2%) in N3b group.

The present study found that there is a statistically significant difference which occurs in N3b cases with recurrence and without recurrence (p=0.002, Chi square=9.7) (Table 2). Among the 150 cases included in our study, PNI and LVI were seen in 19 cases (12.6%) and 29 cases (19.3%), respectively. Higher rates of PNI and LVI were reported in the recurrence group, a statistically significant association between LRR and PNI /LVI was present (p). Out of 150 patients, 70 patients had depth of invasion >10 mm and 80 patients had DOI <10 mm. In the recurrence group Out of 52 patients, 31 patients (59.6%) had a DOI >10 mm and 21 (40.4%) patients had DOI <10 mm. The present study established a statistically significant relationship between a larger DOI and LRR.

A significant association was seen between development of LRR and margins of resection that were less than 5 mm. Of the 52 patients presenting with recurrence, 32 patients (61.5%) had close margin of resection less than or equal to 5 mm (1-5 mm) and 20 patients (38.5%) had margin of resection >5 mm. The relationship between recurrence and the closest margin of resection being less than 5 mm was statistically significant (p=0.002) (Table 2).

Table 1: Epidemiological risk factors.

Epidemiological risk factors	Cases with recurrence n=52 (%)	Cases without recurrence n=98 (%)	P value	χ^2
Sex				
Male	46 (88.5)	80 (81.6)	0.3	1.1
Female	6 (11.5)	18 (18.4)		
Age (years)				
<50	39 (75.0)	61 (62.2)	0.19	2.5
>50	13 (25.0)	37 (37.8)		
Smoker				
Yes	32 (61.5)	38 (38.8)	0.008*	16.99
No	20 (38.5)	60 (61.2)		
Pan chewing				
Yes	46 (88.5)	69 (70.4)	0.01*	6.2
No	6 (11.5)	29 (29.6)		
Education				
No formal	11 (21.2)	10 (10.2)	0.07	3.39
School and above	41 (78.8)	88 (89.8)		

$\chi 2$ denotes Chi-square value, *represents significant statistical value

Table 2: Histopathological variables.

Histopathological variable	Cases with recurrence (n=52) (%)	Cases without recurrence (n=98) (%)	P value	χ^2
Grade of tumor				
WD	9 (17.3)	17 (17.4)		
MD	41 (78.9)	75 (76.5)	0.77	0.15
PD	2 (3.9)	6 (6.1)		
Pathological tumor stage				
T1	3 (5.8)	10 (10.2)		
T2	13 (25.0)	37 (37.8)	0.30	2.3
T3	28 (53.8)	33 (33.6)		
T4A	8 (15.4)	18 (18.4)		
Pathological node stage				
N0	13 (25.0)	57 (58.2)		
N1	19 (36.5)	23 (23.5)		
N2A	2 (3.9)	4 (4.1)	0.38	5.5
N2B	3 (5.8)	5 (5.1)		
N3B	15 (28.8)	9 (9.2)		
Extra nodal extension				
Yes	15 (28.8)	9 (9.2)	0.002*	9.72
No	37 (71.2)	89 (90.8)		
Perineural invasion				
Yes	14 (26.9)	5 (5.1)	0.0001*	14.5
No	38 (73.1)	93 (94.9)		
Lymphobvascular invasion				
Yes	20 (38.5)	9 (9.2)	<0 .0001**	18.6
No	32 (61.5)	89 (90.8)		
Depth of invasion (mm)				
≤10	21 (40.4)	59 (60.2)	0.02	5.3
>10	31 (59.6)	39 (39.8)		
Closest margin of resection (mm)				
≤5	32 (61.5)	34 (34.7)	0.002*	9.9
>5	20 (38.5)	64 (65.3)		

χ2 denotes Chi-square value, *represents significant statistical value, **indicates highly significant data

DISCUSSION

Tumour recurrence is associated with a mortality rate of approximately 90% and therefore represents one of the major problems in diagnosis and treatment of patients with oral cavity squamous cell cancers.[29] Although 2 year of follow-up is a relatively short time to comment on recurrences in oral cavity cancers, as a tertiary care center in India, we mainly dealt with advanced cases. Most of our patients who experience recurrence present within 2 years of treatment completion. Therefore, this analysis was performed at 2 years. Men were predominantly affected in our study, accounting for 84% (126 cases) of the study population. Other reports from our region and other areas in the Indian subcontinent supported this trend of higher prevalence of OSCC in males.[9-11]

Although the majority of patients in the Western world with oral cavity cancers present at an older age.[12,13] The mean age of patients in our study was 45.6 years. Overall, 66.6% of our study population was younger than 50 years of age. Other studies from in and around India also reported a trend of younger patients presenting with oral cavity cancers.[9,10] Although two studies from Iran found a statistically significant relationship among a younger age of disease presentation, LRR, and survival, the present study could not establish such a correlation.[14,15]

Younger age of disease presentation and higher prevalence of OSCC in males in our study can be attributed to the rampant pan chewing behavior of young males in our region and a possibility of continuation of the habit even after undergoing treatment for OSCC, which might contribute to recurrence.[16]

Many studies from around the world have concluded that the risk of LRR increases with age.[12,13] Increased duration of exposure to pan and other carcinogens may support more presentations and an increased incidence of recurrence in older age.[17] We found a relationship (p=0.07) between the absence of formal education and the incidence of recurrence in our population but not statistically significant. Although only 21 patients (14%) in our study had not received formal education, a significantly higher

proportion of patients in the group with recurrence had not received formal education compared to the group without recurrence (21.2% versus 10.2%, respectively). The educated patients may have been more concerned about their ailment and attended their follow-up visits consistently. They probably avoided pan in any form post treatment. We could not find any other previous literature to corroborate or dispute this finding.

In our study there exists a greater statistical significance between T3 of cases with recurrence and without recurrence (p=0.02, Chi square=5.7). In a meta-analysis on margin size and disease recurrence, Anderson et al asserted that the recurrence rates were similar between T1/T2 and T3/T4 groups.[18] Other studies failed to demonstrate the importance of an advanced T-stage for LRR.[11,19,20] We found a significant association between neck node metastasis and the development of recurrence whose significance was maintained in the multivariate analysis. The impact of pathologically involved nodes on recurrence have been documented by several studies from around the world.[19,21,22]

Kartini et al reported that patients in Indonesia with N2 disease had a 1.4-fold higher risk of mortality than N0 patients.[15] Several researchers have also reported an association between LRR and ENE.[22,23] Other studies, including a 2015 study from the Memorial Sloan Kettering Cancer Center, stated that the spread of disease 1.7 mm beyond the nodal capsule was associated with lower odds of disease-free survival after treatment.[24,25]

We found ENE to be significantly associated with recurrence. While the impact of tumor differentiation on LRR has been documented by several researchers, neither our study nor several others have established a significant relationship between tumor differentiation and prognosis.[11,20,26,27] It is important to note that moderately differentiated tumors affected more than 77.3% of the patients in both the recurrence and non-recurrence groups in our study.

The inclusion of DOI in the new AJCC staging system for oral cavity malignancies demonstrates its significance in determining the prognosis of these tumors.[8] Many reports have documented a worst chance of disease-free survival as the DOI increases, especially to more than 10 mm.[21,22] The present study found a statistically significant impact of a DOI of more than 10 mm on LRR. 59.6% of the patients who developed recurrence had a DOI >10 mm, 39.8% of the patients who did not develop recurrence within 1 year of treatment completion had a DOI >10 mm.

Our study also established statistically significant impact of PNI and LVI on LRR. Several studies, including that of Abbas et al in Karachi, successfully established the significance of these factors for LRR.[11,19,22] Interestingly, Marinelli et al reported that PNI and LVI had an impact on overall survival but could not establish their role in LRR.[13] Marzouki et al determined that PNI had a significant impact on LRR, whereas LVI was not found to have a statistically significant relationship with LRR.[20]

Apart from pathologically proven neck node metastasis, the other factor identified in the multivariate analysis as having a statistically significant relationship with LRR was the closest margin of resection measuring less than 5 mm. The width of the margins is of importance because epithelial dysplasia has been found near the surgical margins and can be an important cause of recurrence in patients not receiving adjuvant therapy.[18]

Anderson et al and Carrillo et al also concluded that margins less than 5 mm had a greater risk of LRR.[18,19] A few studies have questioned the impact of margins on the overall prognosis.[5,20] Abbas et al observed that although a positive margin was not associated with a poorer outcome, close margins were associated with a higher incidence of recurrence.[11] These varying results could probably be explained by the uneven distribution of tumor sites and the impact of adjuvant therapy in patients with close or positive margins.

Limitations

The limitations of this study includes its retrospective design with a relatively short follow-up. We were not able to document the continued pan chewing and smoking habits of our patients post treatment. Another factor that could have impacted the results and was not assessed was the interval between surgery and the start of adjuvant treatment.

CONCLUSION

The present retrospective study found that the histopathological factors responsible for recurrence in patients presenting with OSCC were neck node metastasis, ENE, and close margins of resection, lymphatic invasion, perineural invasion, and depth of invasion >10 mm during the primary surgery. It is incumbent upon us to recognize factors responsible for and predictive of recurrence. Aggressive treatment with early recognition of locoregional failures will go a long way in increasing survival rates for OSCC. A multicentre study was needed to help us determine which factors are not only responsible for LRR but relevant to overall survival.

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