



Predictors of Locoregional Recurrence in Oral Squamous Cell Carcinoma

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ABSTRACT:

Introduction: Lip and oral cavity cancer is the third and fifth most frequent cancer for men & women respectively in Bangladesh. Locoregional recurrence after primary surgery is common for oral cancer due to aggressive local invasion and metastasis. The objective of this study was to analyze the predictors of locoregional failure in a tertiary center hospital.

Materials and Methods: A prospective cohort study was designed to analyze the presence of recurrences of OSCC patients after surgery. The purposive sampling technique was used to include patients in the study. Excision of the primary tumor was done with neck dissection followed by reconstruction with local or regional flap. The variables considered were demographic information, site, TNM stage at diagnosis, margin status, lymph node metastasis, perineural invasion, recurrence, and the adjuvant therapy used for disease control. Patients were followed up by hospital revisits or phone calls and necessary information was collected through a standardized data collection sheet.

Results: A total of 39 patients were included for data analysis. The male to female ratio was 1:2 and the most common primary site was mandibular alveolar mucosa (31%). Nearly 90% of patients were admitted with stage III or IV lesions and tumor margin was positive in 21% of cases. Lymph node metastasis and perineural invasion were identified in 64% and 23% of cases respectively. Recurrence developed in 14 patients (36%) during the average follow-up of 13 months. Recurrences were more common in females (42%) and Postoperative histopathology showed a positive margin, perineural invasion, and N3 neck node. Univariate logistic regression analysis for locoregional recurrence showed no significant association between the variables and recurrence. Patients with clinically palpable lymph node, grade 2 lesion, presence of perineural invasion, presence of co-morbidity, patients who did not receive any adjuvant therapy, and patients who had metastatic neck node showed an increased odds ratio (OR>1).

Conclusion: The clinicopathologic and treatment-related factors of recurrence in OSCC were explored in this study. Although no significant association was identified between the variables and recurrence of lesions, a high recurrence rate was observed in a shorter span of the follow-up period.

KEY WORDS : Oral Squamous Cell Carcinoma.(OSCC), Oral Cancer, Cancer recurrence

INTRODUCTION:

The leading cause of death in developed countries is cancer and it is also the 2nd leading cause of death in developing countries.(1) The incidence rate of different types of cancer varies widely depending on geography, dietary habits, socioeconomic conditions & lifestyles. According to the International Association of Cancer Registries, the greatest burden of oral cancer in the world is in South Asian Countries. The incidence rate of lip & oral cavity cancer in 2020 in Bangladesh was 8.9% and it was the third and fifth most frequent cancer for men & women respectively.(2)

Treatment of Oral Squamous Cell Carcinoma (OSCC) includes surgical excision of the primary tumor with appropriate neck dissection, followed by adjuvant radiotherapy with or without chemotherapy in the presence of adverse features in the histopathology.(3) Even with great progress in the trimodality therapy in the last three decades, the prognosis of OSCC remains poor due to aggressive local invasion and metastasis, leading to recurrence.(4) Local recurrence, second primary tumors and regional or distant metastases may develop up to 47% of patients with OSCC.(5) Locoregional recurrence after primary surgery is considered to be a bad prognostic factor in terms of survival rate. Several clinicopathological factors may play a crucial role for the prediction of locoregional recurrence of OSCC.(6)

The primary objective of this study was to assess institutional outcomes of locally advanced OSCC patients. We collected clinicopathologic and follow-up data of patients with OSCC and analyzed the predictors of locoregional failure in a tertiary center hospital. This investigation may be helpful for the development of standardized treatment protocols for OSCC.

MATERIALS AND METHODS:

Patients: A prospective cohort study was designed to analyze the presence of recurrences of OSCC patients treated in Dhaka Dental College & Hospital from April 2014 to April 2016. Purposive sampling technique was used to include patients for the study. Patient inclusion criteria included the following: (1) Primary OSCC was confirmed by histopathological examination. (2) All patients were first treated with surgery. (3) Complete clinicopathologic data were available. (4) An absence of distant metastasis. Exclusion criteria includes: (1) Patients with synchronous lesions at other sites. (2) Patients received previous chemotherapy or radiotherapy. (3) Patients with early recurrence <6 weeks after treatment. All study patients underwent pretreatment evaluations, including complete blood cell count, chest X-ray, computed tomography (CT), and/or magnetic resonance imaging (MRI) of the oral and maxillofacial region and provided informed consent to participate in the study. Tumors were staged according to the TNM classification of the International Union against Cancer.

Treatment: Excision of primary tumor carried out with ≥ 1 cm healthy margin (both superficial and deep margin). Surgery included removal of primary tumor and supraomohyoid neck dissection (SOND) followed by reconstruction with local or regional flaps where indicated. All pathological assessments were performed by an expert oral histopathologist. Upon discharge from the hospital, all the patients were referred to attend the tumor board of another hospital for adjuvant therapy. The variables considered were demographic information, site, TNM stage at diagnosis, histologic grade, comorbidity, treatment, margin status, lymphnode metastasis, perineural invasion, recurrence, and the adjuvant therapy used for disease control.

Follow-up: Patients were followed up by hospital revisits or phone calls. The final date of follow-up was April 30, 2016. A standardized data collection sheet used to collect necessary information. The primary outcome of the study was local or regional recurrence. Local recurrence was defined as the reappearance of disease in original tumor bed beyond six weeks after treatment. Regional recurrence referred to cervical metastasis proven by aspiration.

Statistical analysis:

Data were analyzed with SPSS 20.0 (SPSS, Inc, Chicago, IL). The relationships between clinicopathologic factors for OSCC and recurrence were analyzed using Chi-Square or Fisher's exact test and odds ratio. P value < 0.05 were considered to be significant.

RESULT:

A total of 50 patients were initially enrolled in the study but 11 patients were lost during the follow up period. Data analysis carried out for the remaining 39 patients. Patient, tumor and treatment characteristics are summarized in table 1. Two-thirds of the patients were female and nearly same number of patient's age were below fifty years. The most common primary site was the mandibular alveolar mucosa (12/39 patients, 31%); followed by maxillary alveolar mucosa (28%), buccal mucosa (26%) and tongue (15%). More than two-third of patients (82%) had any sort of co-morbidity like

diabetes mellitus, hypertension, cardiac problem, bronchial asthma etc. Only 21% patients presented with early stage (Stage I and Stage II) lesions, whereas 89% patients were admitted with advanced stage lesion (12+19=31/39 patients). Eighty two percent patients (32/39 patients) had clinically palpable lymphnode but in the post-operative histopathological examination, lymphnode metastasis identified in 64% cases. Tumor margin was positive in 21% cases and perineural invasion was identified in 23% cases. Eighteen percent patients did not receive any sort of adjuvant therapy (chemotherapy or radiotherapy) after the surgery and only 39% patients could start adjuvant treatment within 8 weeks of surgery.

Table-1: Patient, tumor and treatment characteristics of cases.

	Total (cases)	Non-recurrence cases (n=25)		Recurrence cases (n=14)	
		Number	Percentage	Number	Percentage
Age					
< 50 years	24	14	58	10	42
> 50 years	15	11	73	4	27
Gender					
Male	13	10	77	3	23
Female	26	15	58	11	42
Size					
< 4 cm	22	14	64	8	36
> 4 cm	17	11	65	6	35
Site					
Cheek	10	7	70	3	30
Mandibular alveolar mucosa	12	7	58	5	42
Maxillary alveolar mucosa	11	8	73	3	27
Tongue	6	3	50	3	50
TNM stage					
Stage I	1	1	100	0	0%
Stage II	7	3	43	4	57
Stage III	12	8	67	4	33
Stage IV	19	13	68	6	32
Regional lymphnode					
Palpable	32	20	63	12	37
Not palpable	7	5	71	2	29
Histopathological grade					
Grade 1	25	18	72	7	28
Grade 2	14	7	50	7	50
Perineural invasion					
Absent	30	21	70	9	30
Present	9	4	44	5	56
Nodal metastasis					
N0	7	5	71	2	29
N1-N2	30	19	63	11	37
N3	2	1	50	1	50
Comorbidity					
Present	32	21	66	11	34

Absent	7	4	57	3	43
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Table-1 (continued)

	Total(cases)	Non-recurrence cases (n=25)		Recurrence cases (n=14)	
		Numb er	Percent age	Numb er	Percent age
Treatment					
Only surgery	7	4	57	3	43
Surgery with adjuvant therapy	32	21	66	11	34
Type of surgery					
Wide excision with SOND	34	22	65	12	35
Wide excision with RND	1	1	100	0	0%
Wide excision with RND with flap	4	2	50	2	50
Surgical delay from diagnosis					
< 2 weeks	4	2	50	2	50
> 2 weeks	35	23	66	12	34
Post operative margin clearance					
Negative	31	21	68	10	32
positive	8	4	50	4	50
Post operative lymphnode metastasis					
Metastasis	25	17	68	8	32
No metastasis	14	8	57	6	43
Types of adjuvant therapy					
Chemotherapy	6	3	50	3	50
radiotherapy	13	9	69	4	31
chemoradiotherapy	13	9	69	4	31
none	7	4	57	3	43
Time of adjuvant therapy					
< 8 weeks	15	12	80	3	20
> 8 weeks	16	9	56	7	44

Recurrence developed in 14 patients (36%) during the follow-up period. The mean follow-up period was 13 months for the whole series (range 8-25 months). Local recurrence developed in 6 patients, regional recurrence in 3 patients and locoregional recurrence developed in 5 patients. The average time to develop recurrence after surgery was 8.4 months (range 5-13 months). Recurrences were more common in females (42%) and below 50 years old patients (42%). Recurrence of lesion developed in the following situations- (1) Primary lesion involving tongue (2) Stage II and grade 2 lesion (3) Palpable cervical lymphadenopathy (4) Surgery requiring flap reconstruction (5) Post-operative histopathology showing positive margin, perineural invasion, and N3 neck node. Patients receiving only chemotherapy after surgery or did not receive any kind of adjuvant therapy showed higher percentage of recurrence (50% and 43% respectively). Interestingly, less recurrence observed in patients having any comorbid disease and post-operative no neck node metastasis (43% vs 34% and 43% vs 32% respectively).

Table-2: Univariate logistic analysis for the factors influencing locoregional recurrence

	Odd Ratio	95% Confidence interval		P-value
		Lower	upper	
Age				
< 50 years vs. > 50 years	1.964	.483	7.989	.571
Gender				
Female vs. Male	2.444	.542	11.028	.772
Size				
> 4 cm vs. < 4 cm	.955	.255	3.575	.284
TNM stage				
Stage III-IV vs stage I-II	.476	.098	2.306	.167
Regional lymphnode				
Palpable vs Not palpable	1.500	.251	8.977	.225
Histopathological grade				
Grade 2 and grade 1	2.571	.658	10.056	.303
Perineural invasion				
Present vs. absent	3.281	.699	15.406	.448
Neck stage				
N0 vs N1-N3	1.313	.375	4.599	.507
Comorbidity				
Present Vs absent	1.247	.271	7.570	.785
Treatment				
Only surgery vs Surgery with adjuvant therapy	1.432	.271	7.570	.439
Surgical delay from diagnosis				
<2 weeks vs >2 weeks	.686	.065	4.178	.999
Post operative margin clearance				
Negative vs positive	.476	.098	2.306	.084
Post operative lymphnode metastasis				
Metastasis vs No metastasis	1.594	.413	6.157	.343
Time of adjuvant therapy				
<8 weeks vs >8 weeks	.321	.065	1.600	.131

Univariable logistic regression analysis of the associated factors for locoregional recurrence are presented in Table 2. Patients of more than 50 years old and female gender were more likely to recur than patients of less than 50 years old and male gender respectively (odds ratio [OR]: 1.96; 95% confidence interval [CI]: 0.48-7.98; P= 0.57 and odds ratio [OR]: 2.44; 95% confidence interval [CI]: 0.54-11.03; P= 0.77 respectively). Although the results were not statistically significant in any cases (P>0.05), patients with clinically palpable lymph node (odds ratio [OR]: 1.50; 95% confidence interval [CI]: 0.25-8.98; P= 0.23), grade 2 lesion (odds ratio [OR]: 2.57; 95% confidence interval [CI]: 0.66-10.06; P= 0.30), presence of perineural invasion (odds ratio [OR]: 3.28; 95% confidence interval [CI]: 0.70-15.41; P= 0.45), presence of co-morbidity (odds ratio [OR]: 1.25; 95% confidence interval [CI]: 0.27-7.57; P= 0.79), patients who did not receive any adjuvant therapy (odds ratio [OR]: 1.4; 95% confidence interval [CI]: 0.27-7.57; P= 0.44), and patients who had metastatic neck node (odds ratio [OR]: 1.59; 95% confidence interval [CI]: 0.41-

6.16; $P = 0.34$) were more likely to recur than their counterpart. Patients with negative surgical margins were less likely to develop recurrence than patients with positive surgical margin (odds ratio [OR]: 0.48; 95% confidence interval [CI]: 0.10-2.31; $P = 0.08$)

DISCUSSION:

The prognosis of OSCC depends on diverse patient-, disease-, and treatment- related factors. Our data identified different demographic, disease characteristics and treatment related factors responsible for locoregional recurrence of OSCC. Sixty one percent of the patients were less than 50 years old but in an Indian study, nearly 80% patients were more than 50 years old.(7) This finding suggest that more young people are being affected by oral cancer. Female patients were predominant (66%) in our study which is contradictory to a study conducted in Taiwan where only 12% patients were female.(8) In a recent study conducted in the Tata Memorial Centre, India, found that nearly three-fourth of their patients presented in the advanced stage (Stage III & IV) (9). In a Korean research, Kimetel reported that 70% of their patients presented in the late stage of disease. (10) We found nearly 90% advanced cases in our study. This is due to lack of knowledge & awareness about oral cancer among general population, low socioeconomic status, inadequate health-care facilities, and severe scarcity of trained manpower.(9)

Locoregional recurrence of OSCC patients after surgery and adjuvant therapy remains a problem and can affect their survival.(8) Recurrence rate of OSCC varies depending on the anatomical site, quality of surgery, adjuvant therapy and mean follow-up period. Matthias Troelt et al. observed 21.6% recurrence (local, regional and locoregional) in their research at a median follow-up of 46 months.(11) Weilan Wang et al. found that 33.4% patients developed recurrence within a mean time of 31 months.(12) It is also observed that most of the recurrences developed within 2 years after treatment.(6) The recurrence rate of current study was 36% with a mean follow-up of 13 months only. It is assumed that the recurrence rate will be higher if the follow-up duration is increased.

Predictors for the locoregional recurrence of OSCC have been extensively studied in last two decades. Using the univariate Chi-square or Fisher's exact test analysis, Bo Wang et al. found that T stage, degree of tumour differentiation, pN stage and skin flap repair were significantly associated with tumour recurrence.(4) Yasmin Ghantous and her co-workers found that primary tumour site, pathological T stage and surgical margin status were significantly associated with recurrence ($P < 0.05$). (13) Ding Ding et al identified in a recent study on 149 oral cancer patients that poorer locoregional control was associated with race and positive surgical margins.(3) Various clinicopathological variables such as site, TNM stage, co-morbidity, depth of invasion, pattern of invasion and surgical margin were considered as reliable parameters for the prediction of locoregional recurrence in different studies.(6) We did not find any significant association between recurrence and the above mentioned variable, but got high odds ratio for perineural invasion, histopathological grade, female gender, clinically palpable neck node, co-morbidity and lymphnode metastasis. Having these features indicate that they have more chance to develop recurrence from their counterpart.

Today's standard best practice for the management of oral cancer is the surgical excision of the primary lesion with neck dissection followed by adjuvant radiotherapy and/or chemotherapy depending

upon the clinicopathological features.(14) Incomplete treatment may cause early relapse of the disease. We observed higher recurrence rate in those patients who had positive surgical margin (50%) and did not receive any adjuvant therapy (43%). The recurrence was very high for stage 2 lesion (57%) in compare to stage III & IV lesions (33% and 32% respectively). One possible explanation for such a finding is that, these patients may be undertreated at the original surgery.

The present research work had some limitations. The small sample size of the study population may be the intervening factor for the non-significant results. Multiple center study with larger sample size will provide more precise outcome. Furthermore, the follow-up period of this research was minimum in compare to other studies. Longtime follow-up is desirable to obtain better clinical outcome of the study.

CONCLUSION:

The clinicopathologic and treatment related factors of recurrence in OSCC were explored in this study. Although no significant association was identified among the variables and recurrence of lesions, a high recurrence rate was observed in a shorter span of follow-up period. Therefore, more judicious utilization of available expertise and resources are mandatory during oral cancer patient evaluation, planning, surgery, adjuvant therapy and finally follow-up to reduce the recurrence of lesion which in turn will increase the survival of the patients.

CONFLICT OF INTEREST: None.

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