Indian Journal of Surgical Oncology (June 2019) 10(2):286–291
https://doi.org/10.1007/s13193-019-00896-8

ORIGINAL ARTICLE

Retrospective Outcome Analysis of Buccal Mucosal and Lower Alveolar Squamous Cell Carcinoma from a High-Volume Tertiary Cancer Centre

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Received: 26 November 2018 / Accepted: 14 February 2019 / Published online: 28 February 2019

Abstract
To evaluate treatment outcome and factors affecting locoregional control and distant metastasis in buccal mucosal and lower alveolar squamous cell carcinoma. A retrospective analysis of all diagnosed cases of buccal mucosal and lower alveolar squamous cell carcinoma in patients who underwent surgical treatment in 2011 was included from the data base. The patients were analysed for their habits, trismus, skin and bone involvement, neck nodes, type of surgery for primary and nodes, differentiation of tumour, pathological nodal status, recurrence site, and duration after completion of treatment and follow-up. A total of 114 patients were included in the study. The mean duration of follow-up was 23.8 months. On follow-up, 30 patients had recurrence (26.32%) either locoregional or distant metastasis. Age less than 45 years, nodal positivity, presence of perineural invasion, extracapsular spread, and degree of differentiation were found to be statistically significant by univariate analysis ($p < 0.05$). On multivariate analysis, node positivity and presence of perineural invasion emerged as independent predictors of recurrence. Cox regression analysis showed trismus, node positivity, and perineural invasion are significantly associated with recurrence. Aggressive multimodality treatment achieves good local control rates even in locally advanced disease, and the intent of treatment should be curative. Node positivity, presence of perineural invasion, and presence of trismus are found as independent predictors of recurrence. Clinically, presence of trismus is associated with poorer outcomes in view of higher stage.

Keywords Buccal mucosal and lower alveolar squamous cell carcinoma · High-volume tertiary cancer centre · Oral cancer · Trismus

Introduction

Oral cancer is a major problem in India where it ranks among the top three types of cancer in the country [1]. Age-adjusted rates of oral cancer in India are high, that is 20 per 100,000 population, and account for over 30% of all cancers in the country [2]. The gingivobuccal sulcus subsite cancer accounts for a sizeable number of oral cavity cancer in India and aptly called the "Indian cancer" [3]. It is the most common site for oral cancer in the Indian subcontinent due to the habit of chewing tobacco [4].There is a significant delay in presentation for definitive treatment among these patients with around 50% of the patients presenting in stages III and IV [5]. Despite presenting at later stages, the cancer is still amenable for curative multimodality treatment with reasonably good outcomes.

The aim of our study was to evaluate treatment outcome and factors affecting locoregional control and distant metastasis in buccal mucosal and lower alveolar squamous cell carcinoma. Our centre being the tertiary care for cancer, volume of oral cavity cancer is very high. We analysed the outcome and recurrence pattern in buccal mucosa and lower alveolus cancers in our centre to find out the factors affecting the tumour recurrence and overall survival. We retrospectively analysed the group of patients with buccal mucosal and lower alveolar squamous cell carcinoma presented to our centre in 2011.

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Table 1 Baseline characteristics of the patients analysed in our study

Variable	Number	Percent
Clinical characteristics		
Skin involvement	41	35.9
Bone involvement	71	62.3
Presence of trismus	43	37.7
Composite stage		
Stage I	9	7.9
Stage II	3	2.6
Stage III	6	5.3
Stage IV	96	84.2
Status at the time of surgery		
Primary surgery	69	60.5
Post-neoadjuvant chemotherapy	20	17.5
Salvage surgery	16	14.0
Surgery for recurrence	3	2.6
Surgery for second primary	6	5.3
Grade of the tumour		
Well differentiated	22	19.3
Moderately differentiated	79	69.3
Poorly differentiated	13	11.4
Other pathological features		
Perineural infiltration	20	17.5
Extracapsular extension	16	14.7
Lymphovascular emboli	2	1.8

Material and Methods

There were a total of 519 cases of oral cavity malignancies surgically treated at our centre in 2011. Of which, 114 patients were buccal mucosal and lower alveolar squamous cell carcinoma. All the patients were seen in the outpatient department. A detailed patient history regarding their habits of smoking, tobacco chewing, areca nut usage and alcohol intake was entered. The patients were examined for the presence of trismus and classified as none if inter-incisor distance was more than 3.5, mild between 2.5 and 3.5 cm, moderate between 1.5 and 2.4 cm, and severe less than 1.4 cm. The presence of ulcer or skin nodule or when the skin was not pinchable over the growth was taken as skin involvement. The presence of bone involvement was considered with presence of fracture or gross bone erosion or irregular thickening on palpation. In doubtful cases, an orthopantomogram was performed to look for erosion destruction. In patients with severe trismus limiting the clinical examination of the infratemporal fossa (ITF) extension and in patients were the orthopantomogram was inconclusive, CT scan of face and neck was performed. Clinically palpable nodes were recorded according to the level of nodes involved. All patients were staged according to AJCC staging seventh edition of head and neck cancers [6]. The treatment plan of all patients was decided in multi-disciplinary tumour board. Only patients who underwent surgical treatment were included in the study. Patients who were unfit for surgery and were in inoperable cases and those with disseminated metastasis were excluded from the study.

During surgery, the margins of the primary were always analysed with frozen section by the pathologist. The margins were considered negative if 5 mm or more, close if 2 to 4 mm, and positive if less than 2 mm. In case of close or positive margins, re-excision was done immediately until negative margins were achieved. All patients who were node positive and stage T4a received adjuvant radiotherapy. Those with extracapsular spread or margin positive on final pathology received adjuvant chemoradiotherapy. Data were recorded for the type of surgery for primary and nodes, type of reconstruction, differentiation of tumour, margin status, positive nodes by pathology, presence of extracapsular spread, pathological primary tumour characteristics like perineural involvement and lymphovascular extension, and prior treatment and adjuvant treatment received. Each variable was compared and correlated with recurrence pattern of the patient. The patients were followed up for recurrence in the outpatient department clinically. Punch biopsy was done in suspicious local recurrence and fine needle aspiration cytology (FNAC) in nodal recurrence. Patients with systemic symptoms underwent appropriate imaging to rule out distant metastasis.

The collected data were entered in Microsoft Excel and analysed using SPSS software. The effect of various variables on the tumour recurrence was analysed with univariate analysis. As well, the relationship among various variables was estimated using multiple logistic regression analysis and Cox regression analysis. Any p value less than 0.05 was considered statistically significant.

Table 2 Comparison of T and N status of the patients included in our study

N	T1	T2	T3	T4
N0	9	3	0	23
N1	1	3	2	25
N2	0	5	3	39
N3	0	0	0	1

Results

A total of 519 patients were diagnosed with oral malignancy in 2011, of which 114 patients with buccal mucosal and lower alveolar squamous cell carcinoma were included in our study. The age of the patients in our study ranged from 24 to 76 years with a mean of 58.4 years. Of the total patients, 76.3% ($n = 87$) of them were male. Male-to-female ratio was 3.2:1. Baseline characteristics of the patients analysed in the study were summarised in Table 1.

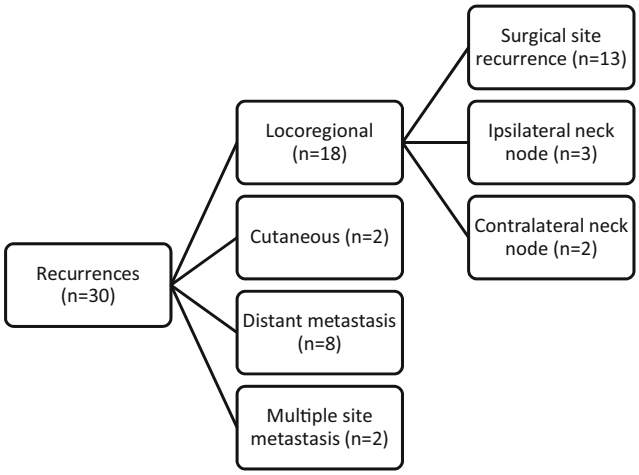

Fig. 1 Recurrence pattern of the patients on follow-up

The majority of the patients included in our study were locally advanced belonged to T4 disease ($n = 88$, 77.1%). Of the 114 patients, 106 patients underwent neck dissection as a part of their treatment. Eight patients did not undergo neck dissection either due to surgery for local recurrence or due to surgery for second primary. Comparison of T and N staging of our patients was summarised in Table 2.

After the surgery, 83 patients were planned to receive post-operative radiotherapy, of which only 77 received. The remaining 31 patients did not receive radiotherapy considering either their final pathological stage or their history of prior radiation. All patients were followed up once in every 3 months in the first year, once in every 4 months in the second year, and 6 monthly thereafter. Mean duration of follow-up was 23.8 months. Of these, 30 patients had recurrences. Recurrence patterns in these patients were summarised in Fig. 1. The Kaplan-Meier analysis showed disease-free survival was 71.87% at the end of 2-year duration.

Younger age, higher grade, presence of trismus, node positivity, presence of perineural invasion, and extracapsular spread were associated with higher recurrence by univariate analysis. Table 3 summarises the univariate analysis of several variables on recurrence. Multiple logistic regression analysis of the effect of several variables showed node positivity and

Table 3 Predictors of recurrence by univariate analysis

Variables	Total number of patients	Number of recurrences	Percent	X^2	p value
Age					
≤45	14	7	50	4.62	*0.032*
>45	100	23	23		
Skin involvement					
Present	73	22	30.1	1.53	0.271
Absent	41	8	19.5		
Bone involvement					
Present	71	9	20.9	1.03	0.383
Absent	43	21	29.6		
Trismus					
Present	43	13	18.3	6.22	*0.016*
Absent	71	17	39.5		
Node positivity					
Present	47	24	51.1	21.56	*0.000*
Absent	59	6	10.2		
Degree of differentiation					
Well differentiated	22	2	9.1	11.72	*0.003*
Moderately differentiated	79	20	25.3		
Poorly differentiated	13	8	61.5		
Perineural infiltration					
Present	20	10	50	7.017	*0.012*
Absent	94	20	21.3		
Extracapsular spread					
Present	16	9	56.2	9.85	*0.007*
Absent	90	21	23.3		
Lymphovascular extension					
Present	2	2	100	5.7	0.068
Absent	112	28	25		

Italic values are statistically significant

Table 4 Predictors of recurrence by multiple logistic regression analysis

		B	S.E.	*p*	Odds (95% CI)
Age (> 45 ®)	≤ 45	− 0.38	0.78	0.627	0.68 (0.15–3.17)
Trismus (No ®)	Yes	0.80	0.54	0.141	2.23 (0.77–6.49)
Positive nodes (absent ®)	Present	1.90	0.60	*0.001*	6.70 (2.07–21.68)
Differentiation histopathology (WD ®)	MD	− 0.19	0.93	0.835	0.82 (0.13–5.07)
	PD	1.34	1.05	0.204	3.81 (0.48–29.91)
Perineural infiltration	Yes	1.51	0.68	*0.027*	4.52 (1.19–17.16)
Extracapsular spread	Yes	0.53	0.68	0.442	1.69 (0.44–6.49)
	Constant	− 2.89	0.88	0.001	

Italic values are statistically significant

presence of perineural invasion as independent predictors of recurrence. Table 4 summarises the effect of variables on recurrence by multiple logistic regression analysis. Cox regression analysis of the effect of several variables showed presence of trismus, node positivity, and presence of perineural invasion are significantly associated with recurrence which is summarised in Table 5 and Fig. 2.

Discussion

Buccal mucosal and lower alveolar squamous cell carcinoma is most commonly seen in the fourth and fifth decades as seen in our study with mean age group being 58.4 years [7]. Cancers of the buccal mucosa are more aggressive as compared with cancers arising from other parts of the oral cavity [8]. The peak age frequency of occurrence in India is at least a decade earlier than that described in the western literature [9]. Gupta et al. observed an increase in the incidence of oral cancer in the younger (less than 50 years) age group [10]. The literature for overall outcome in younger patients is conflicting. Few studies have shown that the disease is aggressive in younger patients [11–13], and few others had showed better survival with these patients [14–18]. And there are few studies which showed no statistically significant difference in different age groups [19–23]. In our study, though univariate analysis showed significant recurrence (*p* 0.032) in less than 45-year age group, it was not significant by multivariate analysis, suggesting multiple confounding factors. As in our study, Chang et al. [24] also did not find poor prognosis in younger age patients. Both less than 45 years and more than 45 years seemed to have the same outcome for buccal mucosal and lower alveolar squamous cell carcinoma.

Trismus can occur due to a variety of causes in buccal mucosal and lower alveolar squamous cell carcinoma such as tumour growth, infection, surgery, or radiation [25]. In our study, it was mainly due to tumour involvement and these tumours fall into stage IV with poor prognosis and outcomes. There is not much of literature correlating presence of trismus to recurrence rates and overall survival. In our study, statistically significant correlation for recurrence was found with presence of trismus in univariate (*p* 0.016) and in Cox regression analysis (*p* 0.014). This might be due to presence of advanced disease, i.e. stage IV, and increased perineural invasion associated with these tumours involving the neural element-rich masticator space. Trivedi et al. had shown that patients resected with negative margins have favourable outcome with aggressive multimodal treatment [26].

The type of differentiation was significant for recurrence on univariate analysis in our study ($p = 0.003$) although it was not significant on multiple logistic regression and Cox regression analysis. Thomas et al. found histological grade is an independent prognostic indicator for poorer survival in early stage of oral cavity SCC [27].

Multiple investigations have shown that perineural invasion (PNI) is associated with disease recurrence, increased probability of regional and distant metastasis, and an overall decreased 5-year survival rate in head and neck squamous cell carcinoma

Table 5 Predictors of recurrence by Cox regression analysis

		B	S.E.	*p*	Odds (95% CI)
Age (> 45 ®)	≤ 45	0.07	0.54	0.896	1.07 (0.37–3.12)
Trismus (No ®)	Yes	1.02	0.42	*0.014*	2.77 (1.23–6.26)
Positive nodes (absent ®)	Present	2.05	0.53	*0.000*	7.80 (2.77–21.94)
Differentiation histopathology (WD ®)	MD	− 0.42	0.79	0.598	0.66 (0.14–3.11)
	PD	0.79	0.81	0.329	2.21 (0.45–10.79)
Perineural infiltration	Yes	1.12	0.51	*0.028*	3.05 (1.13–8.25)
Extracapsular spread	Yes	0.28	0.44	0.525	1.32 (0.56–3.15)

Italic values are statistically significant

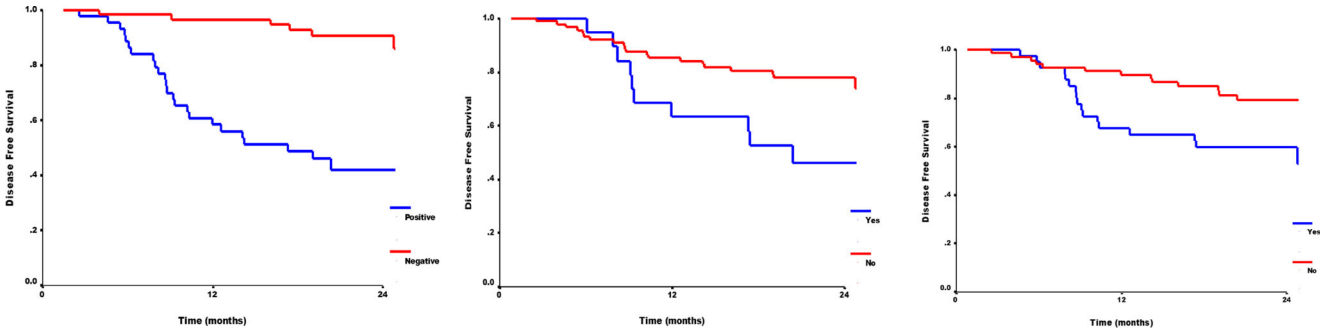

Fig. 2 Graphs showing the effect of variables on recurrence by Cox regression analysis

[28–32]. Liao et al. found PNI is an independent risk factor with 5-year overall survival in pT4 N0 patients [13]. Varsha et al. showed that the occurrence of PNI was as high as 40.5% [33]. In our study, only 17.5% of the patients had PNI. But, it turned out to be statistically significant and an independent predictor of recurrence. Bur et al. in a recent systematic review addressed the outcome for adjuvant radiotherapy in patients with only PNI and found it lacking [34]. In AJCC eighth edition, PNI did not qualify as one of the criteria for staging [35]. More studies are needed in future with larger cohort to evaluate the significance of PNI which may help to prognosticate and select patient for adjuvant treatment or targeted therapy.

Disease recurrence in the patients with lymphovascular spread of the tumour and bone involvement did not reveal any significant results in our study. In Jones et al., lymphovascular spread and mandibular involvement were found to be statistically significant and had an impact on the overall survival [36].

It is a well-known fact that nodal positivity is an adverse prognostic factor in oral squamous cell cancers [37, 38]. In our study too, it was found to be significant by all statistical models. The presence of nodal involvement showed a higher recurrence rate in spite of aggressive multimodal treatment. In latest edition of AJCC staging for oral cancers, depth of invasion and extracapsular spread were found to be an independent prognostic factor and had been incorporated into the staging system [35].

A number of studies had proven that extracapsular spread (ECS) in the lymph nodes has an adverse prognostic outcome [37, 39]. In these studies, the occurrence of ECS was high, of about 20–25%, while it was only 14% in our study. This variable was found to be statistically significant only on univariate analysis (p 0.007).

Conclusion

Aggressive multimodality treatment achieves good local control rates even in locally advanced buccal mucosal and lower alveolar squamous cell carcinoma, and the intent of treatment should be curative. Younger age of the patient, higher grade of the tumour, presence of trismus, node positivity, presence of perineural invasion, and extracapsular extension are associated with higher risks of recurrence. Node positivity, presence of perineural invasion, and presence of trismus are found as independent predictors of recurrence. Clinically, presence of trismus is associated with poorer outcomes in view of higher stage.

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