

Squamous cell carcinoma of buccal mucosa: An analysis of prognostic factors

Saurabh Bobdey, Jignasa Sathwara, Aanchal Jain, Sushma Saoba, Ganesh Balasubramaniam

Abstract

Introduction: Carcinoma of the buccal mucosa is the most common oral cavity cancer in the Indian subcontinent. The aim of this study was to analyze the outcome and evaluate prognostic factors in surgically treated buccal mucosa squamous cell carcinoma (BMSCC) patients. **Materials and Methods:** A retrospective study was performed by reviewing the medical records of 409 pathologically proven buccal mucosa cancer patients, who were diagnosed and surgically treated in Tata Memorial Hospital between January 1, 2006, and December 31, 2008. **Results:** The overall 5-year survival of the cohort was found to be 54.1%. The stage-wise survival rate for tumor, node, metastasis (TNM) Stage I, II, III, and IV patients was found to be 85.2%, 82.9%, 56.3%, and 42.6% ($P < 0.00$), respectively. On multivariate Cox proportional hazard analysis, the presence of comorbidity, histological tumor size, pathological lymph node status, tumor differentiation, perineural invasion, and extracapsular spread were found to be independently associated with overall survival. **Conclusion:** BMSCC is an aggressive malignant tumor. In addition to TNM classification, other clinical and pathological factors also have a significant role in BMSCC prognostication. Hence, there is a need to move beyond TNM and develop a more inclusive, flexible, and easy to use prognostic system.

Key words: Buccal mucosa cancer, survival, prognostic factor

Introduction

Oral cancer is one of the most fatal public health problems in the Indian subcontinent. In India, oral cavity cancer is the second leading cancer as compared eleventh globally. India alone accounts for a quarter (77,000 cases) of total number of oral cancer cases across the globe.^[1,2] Carcinoma of the buccal mucosa is the most common oral cavity cancer in India. As per the data available from the National Cancer Registry Programme (Population-Based Cancer Registries), the males of Ahmedabad urban showed highest age-adjusted rate for mouth cancer (18.11) followed by Bhopal (14.2).^[3] In the Hospital-Based Cancer Registry report, cancer of the mouth is also ranked as the leading site in Mumbai in males and was within the first five leading sites in all registries in males.^[4] In the developed countries, carcinoma buccal mucosa is relatively uncommon as compared to the Indian subcontinent.^[5] The relatively high incidence of oral cancer in India is mainly because of extremely popular use of the smokeless tobacco product called gutkha and betel quid chewing (with or without tobacco), which renders its population and especially its youth to a greater risk of developing oral submucous fibrosis, a premalignant disease resulting in increased incidence of oral cancer in younger patients.^[6]

Long-term survival reflects cure and is a positive measure that can be used by planners and health professionals to discuss the outcome of cancer diagnosis and treatment. Literature on management and survival of cancers in the west is widely available, but data in the Indian context is sparse. The few studies conducted in India have reported a 5-year survival rates for buccal mucosa cancers ranging from 80% for Stage I disease to 5%–15% for locally advanced disease.^[5] Therefore, the present study was conducted to provide a holistic picture of buccal mucosa cancer survival and to evaluate and validate the predictors of survival in the Indian population.

Material and Methods

The medical records of 409 pathologically proven buccal mucosa cancer patients, who were residents of Mumbai, diagnosed and surgically treated in Tata Memorial Hospital

between January 1, 2006, and December 31, 2008, were analyzed retrospectively. Data on details of demography, clinical status (tumor, node, metastasis [TNM]) of the tumor, treatment, histopathological tumor characteristics, and status of the patient (Alive/Dead) at the end of 5 years from the date of diagnosis were retrieved from the medical records. The study had the approval of the Research Ethics Committee of the hospital.

Patients' overall survival (OS) duration was defined as the time interval between the date of diagnosis and the date of death or the date of the last follow-up, whichever was earlier. The closing date for recording the last follow-up was taken as December 31, 2015. Kaplan–Meier methods were used to estimate the OS by patient groups, and the log-rank test was used to compare survival curves. Factors which were found to be significantly related to survival on univariate analysis were considered in multivariate modeling. Cox regression method was used to investigate the independent predictors of survival. All statistical analyses were performed using the Statistical Package for Social Science program (SPSS for Windows, version 20, SPSS, Chicago, IL, USA). $P < 0.05$ was considered to be statistically significant.

Results

The patients' characteristics are summarized in Table 1. As shown, the median age was 52 years (range: 24–85 years), and the percentage of males and females were 70.9% and 29.9%, respectively. Out of the 409 patients, 319 (77.9%) were diagnosed at late Stages (III and IV), and only 90 patients (22.1%) were diagnosed at early Stages (I and II). The median follow-up period was 41 months (range, 1–103 months). The 5-year OS of the cohort was 54.1%, and stage-wise survival rate for TNM Stage I, II, III, and IV patients was found to be 85.2%, 82.9%, 56.3%, and 42.6% ($P < 0.00$), respectively.

Univariate analysis of prognostic factors

Five-year survival as per various demographic and clinicopathological factors is presented in Table 1. The OS curves according to gender, age group, education and marital

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Department of Medical Records, Biostatistics and Epidemiology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Correspondence to: Dr. Saurabh Bobdey,
E-mail: sbobdey@yahoo.com

Table 1: Patient's characteristics and factor-wise five-year survival

Parameter	Number of patients (%)	5-year overall survival (%)	P
Age (median: 52 years, range: 24-85 years)			
<40	61 (14.9)	58.6	0.35
≥40	348 (85.1)	53.2	
Sex			
Male	128 (70.9)	53.2	0.41
Female	44 (29.1)	56.3	
Education			
Illiterate	113 (27.6)	52.5	0.86
Schooling	249 (60.9)	54.4	
College and above	47 (11.5)	58.0	
Marital status			
Unmarried	19 (4.6)	54.8	0.85
Married	343 (83.9)	53.6	
Widow/widower	47 (11.5)	58.2	
Comorbidity			
Absent	268 (65.5)	58.6	0.04
Present	141 (34.5)	47.0	
Clinical T Classification			
T1	46 (11.2)	75.6	0.00
T2	97 (23.7)	66.0	
T3	35 (8.5)	60.5	
T4	231 (56.4)	43.3	
Clinical N Classification			
N0	172 (42.1)	74.8	0.00
N+	237 (57.9)	41.1	
Tumor stage, AJCC			
I	31 (7.6)	85.2	0.00
II	59 (14.4)	82.9	
III	65 (15.9)	56.3	
IV	254 (62.1)	42.6	
Differentiation			
Well differentiated	51 (12.5)	84.8	0.00
Moderately differentiated	286 (69.9)	57.1	
Poorly differentiated	72 (17.6)	20.6	
Tumor size (histopathological) (cm)			
<2	95 (73.8)	67.8	0.00
2-4	225 (46.4)	52.7	
>4	89 (24.8)	42.9	
Histopathological lymph node involvement			
Absent	202 (54.3)	66.9	0.00
Present	170 (45.7)	31.1	
Bone involvement			
Absent	246 (60.1)	63.5	0.00
Present	163 (39.9)	41.3	
Skin involvement			
Absent	362 (88.5)	56.4	0.07
Present	47 (11.5)	44.7	
Perineural invasion			
Absent	341 (60.4)	61.9	0.00
Present	68 (27.8)	28.0	
ECS			
Negative	243 (59.4)	63.7	0.00
Positive	129 (31.5)	28.0	
Treatment			
Surgery only	157 (38.4)	63.3	0.06
Surgery + radiotherapy	171 (41.8)	49.7	
Surgery + radiotherapy + chemotherapy	81 (19.8)	44.1	

ECS=Extracapsular spread

status and treatment demonstrated no statistical differences by univariate analysis ($P > 0.05$). Cases having concomitant

hypertension, diabetes mellitus, heart disease, asthma, or human immunodeficiency virus (HIV) either alone or in combination

were considered as having comorbidity. The OS rates of 5 years were 58.6% for patients with comorbidity as compared to 47% for patients without comorbidity ($P = 0.04$). Similarly, overall TNM stage, T classification and N classification significantly with OS. On consideration of histopathological factors, tumor size, histological lymph node involvement, bone involvement, perineural invasion, and extracapsular spread (ECS) were found to be significantly ($P < 0.05$) associated with OS on univariate analysis [Figure 1]. Patients showing histological evidence of skin involvement were found to have 5-year survival of 56.4% as compared to 44.7% in patients without skin involvement; however, this difference in survival failed to achieve statistical significance ($P = 0.07$).

Multivariate analysis of prognostic factors

All the factors which were found to significantly influence survival on univariate analysis were included in the multivariate analysis. In addition, to adjust for age and treatment, these factors were included in the multivariate model even though they did not significantly affect survival in univariate analysis. By multivariate cox regression analysis using the stepdown model reduction method, the presence of comorbidity, histological tumor size, pathological lymph node status, tumor differentiation, perineural invasion, and ECS were found to be independently associated with OS ($P < 0.05$) [Table 2].

Discussion

The median age of our patients was 52 years (range 24–85), which is similar to age distribution reported by other studies from India.^[7,8] This validates the fact that prolonged contact

of the quid with the mucosal site is suggested as an important etiological factor in terms of high incidence at specific sites and high frequency and longer duration of habit among older individuals.^[7,9] Out of the 409 patients, only 29.1% were females. This is similar to the 25%–30% that has been reported previously from India^[8,10] but is <38%–87% in America^[11] and >4%–7% reported from Taiwan.^[12,13] This discrepancy in sex seems to reflect the fact that the prevalence of betel quid chewing, which is known to have cause-effect relationship with oral cavity cancer, is much higher among men than women in India.^[14,15] Majority of patients in our study presented with locally advanced buccal mucosa cancer (79%). The high percentage (60%–80%) of advanced stage at diagnosis in India has been documented by a number of studies^[16] and has been largely attributed to lack of screening and early detection programs in India.^[17]

The overall 5-year survival in our study was found to be 54%, and with stage, it declined from 85.2% for Stage I to 42.6% for Stage IV. Yeole *et al.*^[18] in their study of 1808 oral cancer cases (including 492 buccal mucosa cancer) in Mumbai reported a 5-year observed survival rates of 34.6% for buccal mucosa cancer, which is much lower than our study. This difference can be because Yeole's study is based on Mumbai cancer registry data which included both treated and untreated cases. In contrast, our study comprised of only those patients who were diagnosed and had undergone primary surgical treatment at our institute. International and national studies reporting survival statistics specifically on buccal mucosa cancer are sparse. Few Indian authors who have studied exclusively buccal mucosa cancer have focused on one or more specific variable which was of interest to their study rather than providing holistic picture of buccal mucosa cancer survival. Iyer *et al.*^[19] studied 147 consecutive patients of buccal mucosa cancer and found 3-year OS rate of 91%, but their data included only N0 neck cases. Similarly, Badakh and Grover^[20] studied role of radiotherapy (RT) in only positive surgical margins patients. In international studies, Lubek *et al.*^[21] in their small study of 30 cases reported 53% 5-year survival rate which is comparable to survival observed in our study (54%). However, Huang *et al.*^[22] in their study of 172 squamous cell buccal mucosa cancer cases reported a 5-year survival of 64% which is higher than our study (54%). This difference could be because their study had only 42% advanced stage cases as compared to 79% in our study.

In our study, age and gender were not found to influence survival. Similar results of nonassociation of age and gender with buccal mucosal cancer survival has also been reported by other national and international studies.^[19,22] Educational inequalities in mortality have been documented across a wide range of countries. Several investigators have also found the statistically significant effect of income and education on cancer survival.^[18,23] This relation is based on the hypothesis that highly educated individuals may have better understanding of the relationship between health inputs and health outcomes, thus enabling them to choose treatment options better.^[24] However, in the present study, we did not find any significant relationship between education status and cancer survival; this may be because it was a single institution study and all the patients were treated as per same protocol regardless of caste, education, or socioeconomic status. Comorbidity is common among cancer patients;^[25] in our study, 34.5% patients had one or more comorbidities (hypertension, diabetes mellitus, heart disease, asthma, and HIV). Comorbidity

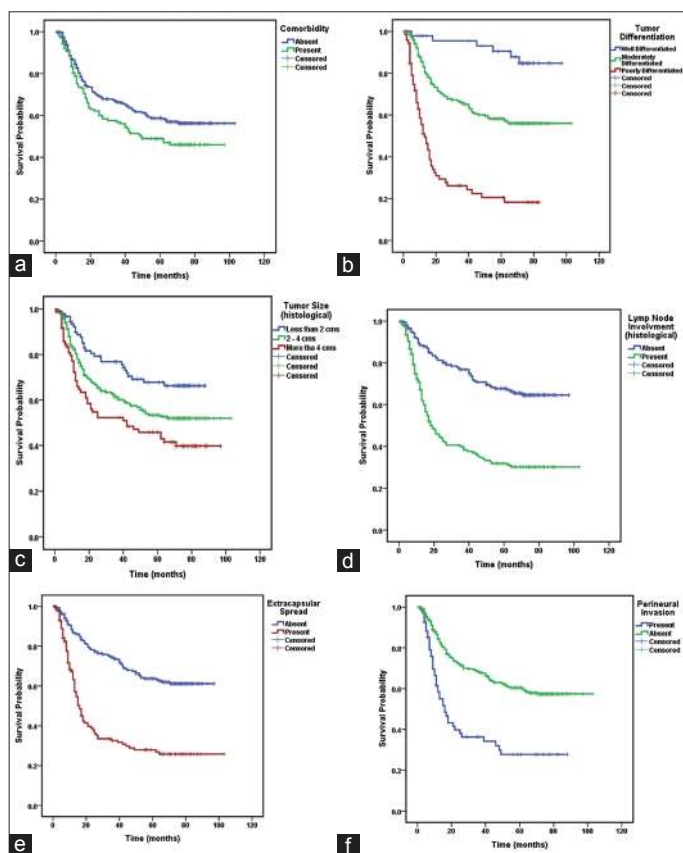


Figure 1: Kaplan–Meier survival curves for different prognostic factors. (a) Comorbidity (b) tumor differentiation (c) histological tumor size (d) histological lymph node involvement (e) extracapsular spread (f) perineural invasion

Table 2: Univariate and multivariate analysis of prognostic factors for overall survival in patients with buccal mucosa cancer

Parameter	Number of cases	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Age (years)					
<40	61	1			0.09
≥40	348	1.22 (0.79-1.90)	0.34		
Comorbidity					
Absent	268	1		1	
Present	41	1.35 (1.03-1.84)	0.02	1.23 (1.02-1.68)	0.03**
Differentiation					
Well differentiated	51	1		1	
Moderately differentiated	286	3.96 (1.74-9.03)	0.00	2.79 (1.21-6.44)	0.01**
Poorly differentiated	72	13.28 (5.69-30.99)	0.00	7.25 (3.04-17.26)	0.00**
Tumor size (cm)					
<2	95	1		1	
2-4	225	1.64 (1.08-2.50)	0.02	1.24 (0.80-1.92)	0.33
>4	89	2.33 (1.46-3.71)	0.00	1.69 (1.04-2.76)	0.03**
Lymph node, histological (absent)	202	1		1	
Lymph node, histological (present)	170	2.99 (2.18-4.11)	0.00	1.54 (1.50-2.57)	0.00**
Bone infiltration (absent)	246	1		-	
Bone infiltration (present)	163	1.85 (1.37-2.50)	0.00	-	0.24
Perineural invasion (absent)	341	1		1	
Perineural invasion (present)	68	2.59 (1.83-3.66)	0.00	1.51 (1.04-2.18)	0.02**
Extracapsular spread (absent)	243	1		1	
Extra capsular spread (present)	129	3.08 (2.27-4.18)	0.00	2.25 (1.60-3.08)	0.00**
Treatment				-	0.16
Surgery only	157	1			
Surgery + radiotherapy	171	1.00 (0.70-1.43)	0.96		
Surgery + radiotherapy + chemotherapy	81	1.70 (1.16-2.49)	0.00		

**Significant ($P < 0.05$). HR=Hazard ratio, CI=Confidence interval

has consistently been found to have an adverse impact on oral cancer survival,^[26,27] and we also found presence of comorbidity to be an independent marker of poor OS. There is reliable evidence that those with comorbidity receive less active treatment than those without, and this impacts their survival probabilities. In addition, those with comorbidity may also suffer higher levels of toxicity from cancer treatments, which may also detrimentally impact their cancer-specific survival.^[28]

Pathologists have long recognized the potential prognostic significance of cellular morphology in squamous cell carcinoma.^[29,30] Patients with moderately/poorly differentiated cancer in our study had a poor survival rate. Liao *et al.*^[31] also found that poor differentiation of cancer (hazard ratio [HR], 1.050; 95% confidence interval [CI], 1.016–1.084; $P = 0.034$) was a significant factor for disease-specific survival in multivariate analysis. In our series, the mortality rate in patients with moderately and poorly differentiated cancer was 2.79 and 7.25, respectively, times higher compared with that in patients with well-differentiated cancer. Similar adverse outcome has been reported by Iyer *et al.*^[19] In the present study, we also found perineural invasion to be an independent prognostic factor for patients with buccal mucosa cancer (HR, 1.051; 95% CI, 1.04–2.81; $P = 0.02$). Perineural invasion is an established predictor of poor prognosis in squamous cell carcinoma of head and neck region, and numerous clinical studies have documented its significance.^[32,33]

In this study, tumor size was taken as the pathologically measured maximum cross-sectional diameter of a resected tumor.^[34] We found that tumor size significantly influenced oral cancer survival. Tumor size of more than 4 cm was observed

to be independent predictor of poor OS (HR = 1.69, 95% CI = 1.04–2.76; $P < 0.01$). Maximum tumor diameter has traditionally been considered an important risk factor for the presence of concomitant nodal metastases, local recurrence, and poor survival.^[35,36] The presence of regional metastasis is an important factor for the prognosis of buccal mucosa cancer. Diaz *et al.*^[37] demonstrated that the 5-year survival rate for patients with N0 and N+ neck were 70% and 49%, respectively ($P = 0.01$). Our study results are comparable (N0, 74.8% vs. N+, 41.1%, $P < 0.00$) with the results of Diaz *et al.* In addition to clinical node involvement, we also examined the role of histological nodal metastasis, which too was found to be independent predictor of poor survival (HR = 1.54, 95% CI = 1.50–2.57; $P < 0.01$). These findings are in line with many other studies who have reported histologically positive cervical lymph nodes for squamous cell carcinoma as one of the simplest and perhaps the most important prognostic markers in oral cancer.^[38-41] Furthermore, ECS was also found to significantly influence survival and was an independent predictor of poor prognosis (HR = 2.25, 95% CI = 1.60–3.08; $P = 0.00$) [Table 2]. Woolgar *et al.* in their study of 173 positive neck dissections found ECS as the best prognosticator in the stepwise regression model of Cox.^[42] The prognostic importance of ECS has also been emphasized by several recent studies.^[37,43]

Surgery is the frontline treatment for buccal mucosa cancer.^[44] In our study, all the patients were treated with surgery either alone or in combination with RT or radiochemotherapy (RT + CT). Patients with surgery (63.3%) alone were found to have the best 5-year survival as compared to with surgery + RT (49.7%) or

surgery + RT + CT (44.1%); however, in multivariate analysis, treatment was not found to be an independent prognostic factor. Selection of treatment modalities is not only according to primary carcinoma extension but also might be decided by many other important clinical indices (i.e., tumor size, clinical stage, distant metastasis, histological differentiation, and lymph node involvement). Individuals who accepted surgery alone are often at an earlier clinical stage (75% cases of Stage I in our study were treated with surgery alone). Therefore, the better survival rates seen in only surgically treated patients might have been due to differences in disease stage and presence of other tumor-related prognostic factors, rather than differences in effectiveness of treatment methods.^[45] Furthermore, the purpose of the present study was to evaluate the various prognostic factors adjusted for treatment rather than to assess the efficacy of different treatment modalities.

There were several limitations of our study which need to be acknowledged. The study was conducted at a single institution, was of retrospective nature, and relies on data not primarily meant for research. Therefore, our study might be limited by biases, such as lack of random assignment, patient selection, and incomplete data acquisition, particularly in case of comorbidities, as only those conditions that were recorded in the medical case sheets were taken into consideration. A prospectively collected data will identify more detailed prognostic factors that can better account for the outcomes. Second, the single-institutional nature of our dataset may again be interpreted as a limitation, as demographic characteristics of the study cohort may be unique and may not be relevant in risk prediction of other patient populations. However, the study cohort being from a single institution had the advantage of having a uniform treatment policy, including postsurgical adjuvant therapy.

Conclusion

Buccal mucosa squamous cell carcinoma is the most common oral cavity carcinoma in the Indian subcontinent. Our study presents a comprehensive evaluation of prognostic factors and demonstrates that apart from conventional TNM system, other factors, namely, comorbidity, tumor differentiation, ECS, and perineural invasion also play a major role in buccal mucosa cancer prognostication. Hence, there is need to develop a new easy to use and flexible modular prognostic system that will aid in patient stratification and provision of aggressive treatment to patients with adverse prognostic indicators.

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Conflict of interest

There are no conflict of interest.

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