Evaluation of Prognostic Factors in 198Buccal Mucosa Cancer Patients: Univariate and Multivariate Analysis

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Abstract

Background: Buccal mucosa cancer is the most common oral subsitewhichis aggressive in nature, had high rate of locoregional recurrence and mortality in India. *Objective:* The aim of study was to evaluate prognostic factors for buccal mucosa cancer by univariate and multivariate analysis. *Materials and Methods:* A retrospective study was performed by reviewing medical records between 2013 and 2016. *Results*: A total 198 buccal mucosa cancer were selected within the study criteria which includes125 (63.1%) male and 73 (36.9%) femaleparticipant with mean age of 54 years. Of 198 patients, 24 (12%) recurrence and 7 (3.5%) disease-specific death was reported during follow-up period of 34 months (Median, 24 months).The Kaplan-Meier analysis shows 1st, 2nd and 3rd year overall survivals were 90%, 72% and 48%, respectively. In univariate analysis,patients age, socioeconomic status, risk habits, clinicalTNM stage, tumor depth and cell differentiation were significant at 95% confidence interval (CI), $p<0.05$ and further validated by multivariate analysis.The multivariate cox-regressionhazard risk (HR) revealed, age [HR, 0.593 (0.974 0.361), p=0.039], socioeconomic status [HR, 1.82 (1.43-2.55), p=0.048], risk habits [HR, 2.08 (2.168-4.39), p=0.027], TNM stage [1.27 (1.18-3.15), p=0.037], tumor depth [HR, 4.08 (1.22-13.58); p=0.021] and cell differentiation [HR, 2.45 (1.27-4.73); p=0.007]astrue independent prognostic factor at 95CI, $p<0.05$. *Conclusion*: Although several factors related to disease, the present study revealed that age, socioeconomic status, risk habits and clinical characteristics of TNM stage, tumor depth and cell differentiation may influence the survival outcome of patients.

Keywords: Clinical Stage; Multimodality Treatment; Oral Cancer; Prognostic Factor; Risk Habits.

Introduction

Oral squamous cell carcinoma (OSCC) is a significant global health problem; it has been rankedas sixth most common cancer worldwide [1].Of all oral subsites, buccal mucosa carcinoma is the most common cancer which behaves aggressively that easily invades adjacent tissue and has a tendency to occur locoregional recurrence of 26-80% [2-3]. Indian Council of Medical Research (ICMR) data suggests that 70-80% of oral cavity cancers present with advanced stage which isunresectable/ incurable [4]. In India, chewing, smoking and consumption of alcoholic beverages have become common social habits and highly prevalent among the rural population those with no formal education [5].

Surgery or radiotherapy as a single modality is currently considered a suitable method for the treatment of early stage buccal mucosa cancer, whereas postoperative radiation combined with surgical excision is recommended for advanced tumors [6]. However, treatment failures remain high, despite evolution in clinical diagnosis and treatment modalities, the prognosis for oral cancer remainsunstatisfied past 20 decades [7]. According to various studies, the 5-yearoverall survival of oral cancer varies from 50% to 60% [4]. Thus, further analysis of risk factors for tumor diagnosis and treatment are highly recommendable.

Although, several studies reported the influence of clinicopathological parameters, the significance of treatment strategies of oral squamous cell carcinoma, are still debatable [8]. Although several studies were

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conducted on buccal mucosa cancer, there were limited data on survival outcome and prognosis in India [9].

Particularly, there is a sparse prognostic significance of buccal mucosa cancer in this region, Tamilnadu. According to our knowledge, this retrospective analysis study is the first study to aim to analyse prognostic factors of 198 buccal mucosa cancer patients using univariate and multivariate risk analysis.

Materials and Methods

Patients Selection

The present retrospective study was carried out in Arignar Anna Memorial Cancer Hospital and Research Centre, Kanchipuram, Tamilnadu, which is one of the regional cancer centre in India according to Helsinki Declaration guidelines. The institutional review board (IRB) and directorate of medical education (DME), Tamilnadu clearance was obtained to conduct the study (Ref No.24984/2013).

Clinically and histopathologically confirmed primary buccal mucosa cancer were includedfor the study after obtaining patient's consent. Pre-malignant lesions / conditions and other oral sub-sites as alveolus, tongue, palate, retromolartrigone, tongue and floor of mouth were excluded from the study.

Data Collection

A total of 198 buccal mucosa cancer patients were reviewed from medical records between 2013 and 2016. Demographic details with respect to gender, age, risk habits, eastern cooperative oncology group performance status (ECOG-PS)and clinical details of tumor nodal metastasis (TNM) stageaccording to international union on cancer council (UICC) method and histopathological analysis followed by world health organization (WHO)guidelines [10-12]. Further, treatment details were also collected for all the patients.

Survival Outcomes

The patients were followed-up for three years after treatment. The follow-up outcome measure was set as overall survival which was calculated as the time from the first date of treatment to the date of death or last known date of patient was alive [13].

Statistical Analysis

Commercial software SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Survival rate was calculated using the Kaplan-Meier method, with the log-rank test. Univariate and multivariate cox-regression analysis were used to determine independent risk factors. All the statistics were considered at p<0.05 level of significance.

Results

Overview of Patients Characteristics

Demographic data of the patients were presented in Table 1. In the present study, a total of 198 patients with confirmed diagnosis of buccal cancer were included. There were 125 (63.1%) male and 73 (36.9%) female participants withratio of 1.7:1, respectively.The mean age of all participants was 55.72±16.82 years (range, 21-88 years). Of 198 patients, 124 (62.6%) were from lower socioeconomic class. Moreover, the patients had diagnosed with high frequency ofunderweight 89 (44.9%), tobacco habitual 87(44%) and poor physical performance using ECOG-PS 167 (84.3%). Patients clinical characteristics were analysed, 147 (64.5%) patients with advanced TNM stage III, 153 (77.3%) patients with ≥ 5 cm tumor size and ≥ 6 mm of tumor depth and 98 (49.5%) patients with well differentiated carcinoma were more frequently encountered. Further, among all the patients, 60 (30.3%) underwent multimodality post operative radiotherapy/ chemoradiotherapy treatment.

Survival Analysis

The median overall survival rate was 24 months(range, 3-34 months). At last follow-up, 24 (12.1%) patients were identified with recurrence and 7 (3.5%) had disease-specific death. The Kaplan-Meier overall survival curves are shown in Fig. 1. The 1-year, 2-year and 3-year overall survival rates for all patientswere 90%, 72% and 48%, respectively.

Univariate and Multivariate Analysis between Factors and Survival

Univariateand multivariate analysis of the prognostic factors for overall survival outline is given in Table 2. Of all demographic and clinical characteristics,the study showed with a hazard ratio (HR) ofdemographic characteristics. Hazard ratio for age 3.414 (95CI, 0.32-6.257), socioeconomic status 3.42 (95CI, 2.52-5.24), risk habits 6.20 (95CI, 2.12-12.76) and clinical features like TNM stage 2.35 (95CI, 2.02-4.20), tumor depth 3.31 (95CI, 2.33-4.72), and cell differentiation 1.31 (95CI, 1.08-1.59) were identified

as significant hazard risk factors that affect the survival probability.

The multivariate Cox-regression model was designed with a forward selection in which analysis of patient's demographic and clinical characteristics were done to assess their effect on fit of the model. Finally patient's age, socioeconomic status, risk habits, clinical TNM stage, tumor depth and cell differentiation wereconsidered to have independent association with recurrence and death at 95CI, p<0.05.

Patient'sage failed to show the hazard risk by fold difference. Patients from lower socioeconomic status and who were exposed with risk habits had a 1.82 and 2.08 fold greater risk of recurrence/death when compared with those from other socioeconomic background (95CI, 1.43-2.55) and non-habitual (2.168-4.39), respectively. Similarly, advanced TNM stage III&IV, tumor depth ≥ 6mm and cell differentiation

Table 1: Baseline demographic characteristics of study patients

Characteristics		No. of patients (n)	Frequency (%)
Gender			
	Male	125	63.1
	Female	73	36.9
Age (yrs)			
	<40 yrs	71	35.9
	≥ 40 yrs	127	64.1
Bodymass Index (BMI)			
	Underweight (<18.5 kg/m²)	89	44.9
	Healthy weight (18.5-24.9 kg/m²)	50	25.3
	Overweight (25-29.9 kg/m²)	39	19.7
	Obese (30-35 kg/m²)	20	10.1
Socioeconomic status (SES)			
	Upper	5	2.5
	Upper middle	16	8.1
	Lower middle	21	10.6
	Lower upper	32	16.2
	Lower	124	62.6
Risk Habits			
	Tobacco	87	44
	Non-Tobacco	30	15.1
	Multihabits	78	39.4
	No Habits	3	1.5
ECOG Status			
	Good performance	31	15.7
	Poor performance	167	84.3
Clinical stage			
	Stage I	13	6.6
	Stage II	17	8.6
	Stage III	13	6.6
	Stage IV	155	78.3
Tumor size			
	5 cm	45	22.7
	≥5 cm	153	77.3
Tumor depth			
	< 6 mm	60	30.3
	≥ 6 mm	138	69.7
Cell differentiation			
	Well differentiated	98	49.5
	Moderately differentiated	68	34.3
	poorly differentiated	32	16.2
Treatment strategies			
	Radiotherapy only	59	29.8
	Radio and chemotherapy	79	39.9
	Post operative radiotherapy	25	12.6
	PORT and chemotherapy	35	17.7

Table 2: Univariate and multivariate analysis of patient's characteristics by overall survivalusing Cox-proportional hazard analysis

| Characteristics		Univariate		Multivariate	
		Hazard risk (95%CI)	p-value	Hazard risk (95%CI)	p-value
Gender	Male Vs Female	1.29 (0.96-1.74)	0.733	0.83 (0.40-1.72)	0.623
Age	<40yrs Vs ≥40yrs	3.414 (0.32-6.257)	0.046*	0.593 (0.974 0.361)	0.039*
Bodymass Index (BMI)	Under Vs Healthy, Over and Obese	1.61 (1.19-2.19)	0.528	1.99 (1.04-3.89)	0.718
Socioeconomic status	Upper, Upper middle Vs Lower middle, Lower upper and Lower	3.42 (2.52-5.24)	0.000*	1.82 (1.43-2.55)	0.048*
Risk habits	Tobacco, Non-tobacco, Multihabits Vs No habits	6.20 (2.12-12.76)	0.032*	2.08 (2.168-4.39)	0.027*
ECOG Status	Good PS Vs Poor PS	1.13 (0.98-1.31)	0.087	1.32 (0.93-1.87)	0.118
Clinical TNM stage	Stage I, II Vs III and IV	2.35 (2.02-4.20)	0.049*	1.27 (1.18-3.15)	0.037*
Tumor size	5cm Vs ≥5 cm	0.97 (0.65-1.43)	0.089	0.99 (0.52-1.91)	0.996
Tumor depth	< 6 mm Vs ≥ 6 mm	3.31 (2.33-4.72)	0.025*	4.08 (1.22-13.58)	0.021*
Cell differentiation	Well Vs Moderate and Poorly differentiated	1.31 (1.08-1.59)	0.05*	2.45 (1.27-4.73)	0.007*
Treatment strategies	Radio chemo & radiotherapy alone Vs PORT & PORT chemotherapy	1.91 (1.65-2.29)	0.63	0.92 (0.58-1.48)	0.754

*significance at p<0.05 level
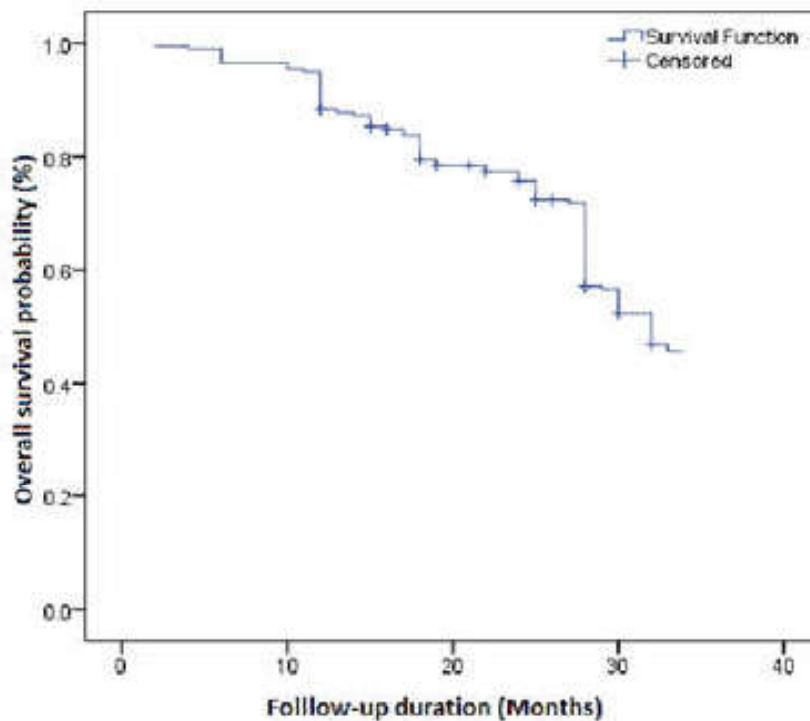
Fig. 1: Overall survival estimation of buccal mucosa carcinoma by Kaplan-Merier analysis

had a 1.27, 4.08 and 2.45 fold risk of recurrence/death than early stage of diagnosis I & II (95CI, 1.18-3.15), tumor depth < 6mm (95CI, 1.22-13.58) and moderate and poorly differentiated buccal squamous cell carcinoma, respectively.

Discussion

There were numerous demographic, clinical, pathologic and molecular markers have been implicated in predicting prognosis of oral cancer [7].

ICMR guidelines reported that prognostic factors for specific oral-subsites might improve the outcome [4]. As per previous studies and guidelines, the present study reveals the prognostic markers for buccal mucosa cancer.

Generally, the treatment fails due to recurrence of buccal mucosa cancer. The high rate of recurrence could be attributable to the absence of anatomic barriers that prevent the disease from spreading into buccal space [3,4]. Ghoshal et al. concluded that most locoregional recurrence occurred within the first 2 years of buccal mucosa cancer [15]. Diaz et al., reported that 54 (45%) out of 119 patients with buccal mucosa cancer presented with recurrences in 5-years follow-up [3]. In accordance to previous studies, the present study shows relatively high recurrence rate 24 (12%) within 3-years of follow-up of buccal mucosa cancer.

Past several decades, the 5-years survival of oral squamous cell carcinoma does not improve from 50% to 75% [1]. Dissanayaka et al., reported the 5- years survival rate of patients with buccal mucosa cancer was 65.9% [16]. Niu et al., found from a retrospective study that 3-years survival of buccal mucosa cancer was 74.6% from china [17]. Another south Indian study reported 3-years and 5-years disease-free survival of buccal mucosa cancer were 72% and 61%, respectively [2]. The finding of present study confirms the observation reported earlier that 3-years overall survival of buccal mucosa cancer was 48%, which is very poor. Thus, although there were progress in diagnostic and prognostic techniques; the survival was not improved.

Oral cancer is well known to affect more males than females with ratio of 2:1 [2]. In accordance to previous results, the male: female ratio of participants in our study was 1.7:1. The oral canceroccurs utmost in elderly may be due to long exposure of risk habits consumption [16]. A recent studies reported that elder patients more than 40 years showed worseprognosis in oral and oropharyngeal squamous cell carcinoma whereas gender did not affect survival [18-19]. The present study also supports the previous reports that majority of participants in the study weremale and elder'swho were ≥ 40yearsof age, prognostic significance was identified in age but not with gender.

Socioeconomic status plays an important role in predicting survival in head and neck squamous cell carcinoma [20]. In a meta-analysis study, 41 case-control studies across the globe had demonstrated that lower socioeconomic condition as an independent risk factor for development of oral squamous cell carcinoma [21]. People doing manual occupations such as agriculture, labouring and working in industries highly exposed with risk habits of tobacco, pan masala chewing habits and had increased risk for developing oral cancer [22].

In the present study, most of patients presented from lower socioeconomic statusthatwho have lower education and labouring occupation.In accordance to previous reports, our study revealed that socioeconomic statusand risk habits are an independedrisk factor for buccal mucosa cancer.

Past two decades, TNM stage of oral squamous cell carcinoma proved to be the most important clinical prognostic factor as well as treatment determinant.This has also proved to be a reliable indicator of prognosis along with tumor size, depth and nodal status being most significant factors affecting survival [16].

O'Brien et al., reported that tumor thickness influences the prognosis of early oral cancer and greater than 4 mm imparts a worse prognosis [23]. As previous reports, the present study revealedthat clinical characteristics of TNM stage and tumor depth as an independent risk factor for recurrence/ death of buccal mucosa cancer using multivariate cox-regression analysis.

Cell proliferation is considered one of the most important mechanisms in oncogenesis [7]. Lin et al., conducted a retrospective study including 145 patients diagnosed with buccal mucosa cancer and demonstrated that tumor differentiation was the most signifi-cant prognostic factorand reported that poorly differentiated carcinoma required an effective systemic treatment to achieve a better outcome [24]. There was consistent evidence of the value of tumor grade in determining prognosis: Higher grades equate to a poorer prognosis [25-26]. In contrary, Fang et al.,reported that histological grading does not have prognostic value on buccal mucosa cancer [27]. However, the present study revealed that cell differentiation isan independent hazard risk factor for buccal mucosa carcinoma in univariate and multivariate analysis which affect survival outcome.

Conclusion

The buccal mucosa cancer has a poor overall survival rate with a high tendency for recurrence within three years at the primary site and extends to involve the cervical lymph nodes. Further, the study also revealed that age, socioeconomic status, risk habits, TNM stage, tumor depth and cell differentiationare an independent prognostic factors for buccal mucosa carcinoma. Hence, this evaluation of prognostic factors might give "clinical clue" to

develop treatment strategies and to improve survival outcome.

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