

# Assessment of factors associated with early and late stage diagnosis of buccal mucosa carcinoma

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## ABSTRACT

**Background/Objectives:** Delayed reporting at advanced stage of oral cancer is a common problem in India. Hence, the purpose of study was to determine factors associated with early and delay diagnosis of buccal mucosa carcinoma. **Materials and Methods:** The questionnaire based cross-sectional study was conducted with 198 buccal mucosa carcinoma subjects. Sociodemographic, socioeconomic, clinical-histopathology characteristic, clinical symptoms and their habits were recorded. **Results and discussion:** In our study, 169(85.3%) had diagnosed with advanced stage, whereas 29(14.7%) diagnosed at early stage. Among all the factors, socioeconomic status, degree of differentiation and regional lymph nodes were found to be associated with stage of diagnosis, whereas sociodemographic, depth of tumor and tumor size were not associated ( $P < 0.05$ ). Multivariate logistic regression analyses exists independent associations with clinical and histopathological factors ( $P < 0.05$ ). Moderately differentiated (OR 13.32), poorly differentiated (OR 16.124) and presence of regional lymph node (OR 1.914) had risk of developing cancer in advanced stage than early stage of diagnosis. Hence, early diagnosis was best prevention of diseases. **Conclusion:** The study suggested that rising public awareness could reduce the burden of this disease and improves early diagnosis in India.

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## INTRODUCTION

In the present scenario world is heading towards various types of non-communicable diseases, among these cancer is one of the most common causes of morbidity and mortality (Krishna *et al.*, 2014). Worldwide, approx >10 million new cases and >6 million deaths occur each year due to cancer (WHO, 2004). Oral cancer is estimated to be the sixth most common cancer (Warnakulasuriya, 2008). Despite several diagnostic and therapeutic advances, the overall incidence and mortality associated with oral cancer is rising in worldwide, with current estimate of age-standardized incidence and mortality being  $6.6 \times 10^5$  and  $3.1 \times 10^5$  population for males and  $2.9 \times 10^5$  and  $1.4 \times 10^5$  in females respectively (Carvalho *et al.*, 2004). Drinking alcohol and smoking tobacco can synergistically cause cancer of the oral cavity, pharynx, larynx, and oesophagus (Krishna

*et al.*, 2014). Incidence and survival rates of cancer are clearly linked to socioeconomic factors, low-income and disadvantaged groups. Low socio-economic status was as well significantly associated with increased oral cancer risk in high and lower income-countries, across the world (Conway *et al.*, 2007). Previous studies reported that tumor stage related to diagnostic delay because the fact that certain cancers remain silent during the initial stages and induce symptoms only when they reach and advanced phase (Scott *et al.*, 2005), and also Pires reported that biological behaviour of tumor (poorly differentiated) was independent risk factor for late diagnosis (Pires *et al.*, 2013). Dikshit represented that metastasis to the regional lymph nodes is the single most important prognostic factor in predicting local and distant failure as well as survival (Dikshit *et al.*, 2012). However, tumor characteristic were important prognostic factor for oral cancer morbidity and mortality. Survival rates are considerably low in developing countries, due to delayed diagnosis and presentation of the tumor in advanced stage. Although the majority of oral cancers are readily visible, as a first visit almost 70% of the subjects were present with advanced stage III and IV disease.

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Similarly, many studies also reported that 50% of cases of oral cancer were diagnosed with advanced condition of stage III and IV which had higher morbidity and mortality rates (Das Neves *et al.*, 2015 and Forastiere *et al.*, 2001). Though many epidemiological studies about oral cancer have been done in different parts of India, buccal squamous cell carcinoma was leading subsite in south India but only few studies were carried out in specific subsite of oral cancer. Hence, this study conducted to assess the sociodemographic, socioeconomic, clinical and histopathological factors association with early and late stage of diagnosis in buccal mucosa carcinoma.

## MATERIALS AND METHODS

The cross-sectional questionnaire based study was carried out at Regional Cancer Centre, Arignar Anna Memorial Cancer Hospital and Research Centre, Kanchipuram during the year of 2013-2015. The institutional ethical committee permission from directorate of medical education (DME), Tamil nadu was obtained to conduct the study (No.24984). All the study subjects were included with their written and informed consent.

The study included 198 buccal mucosa carcinoma subjects among both sexes. All the patients underwent a clinical staging in accordance with the TNM system of the International union against cancer (Sobin *et al.*, 2002), at the time of presentation. On the basis of staging, patients were divided into 2 groups: Group 1 with early stage disease at presentation (i.e. stage I and II) and group 2 with late stage disease at presentation (i.e. stage III and IV). The questionnaire consisted of demographic, socioeconomic, clinical and histopathological variables and their habits. The relevant clinical data, stage of buccal mucosa carcinoma and histopathology reports was retrieved from hospital files. Histopathology confirmed pre-malignant lesions / conditions and other oral sub-sites were excluded.

## Statistics

Statistical analysis was carried out by using SPSS 16.0 version. Chi-square test was employed with level of significance at  $p < 0.05$ . Odds ratios (OR) and their respective 95% confidence intervals were obtained from multivariate analysis using binominal logistic regression analysis. The  $p$  value  $< 0.05$  was considered statistical significant.

## RESULTS

The study comprised 198 buccal mucosa carcinoma subjects, which constitute 125(63.1%) male and 73(36.9%) female subjects in 1:2 ratios, among this 76 (39%) were either single, divorced and widows. The mean age of all participants was  $55.72 \pm 16.82$  (mean  $\pm$  SD) years in the range from 23 to 88 years. Among all the subjects, 89 (45%) had poor body mass index (BMI) whereas 50 (25.3%) had healthy weight, 39 (20%) had over weight and 20 (10.1%) had obese. However, sociodemographic factors gender, age, BMI was not associated for diagnosis of buccal mucosa carcinoma based on stage of tumor by chi-square

method at  $p < 0.05$  (Table 1). According to KUPPUSAMY'S modified scale (Ravikumar, 2013), education, occupation and total family income together was prepared socioeconomic class. In our study, 169 (85.4%) were diagnosed with advanced stage of tumor whereas others 20 (10.1%) were diagnosed with early stage and also most of subjects 124 (63%) were in lower socioeconomic class. However, socioeconomic status was associated for stage of buccal cancer diagnosis by chi-square method at  $p < 0.05$  (Table 1).

**Table 1:** Relationship of sociodemographic and socioeconomic factors with early and late stage of buccal mucosa carcinoma (n-198).

Factors	Early stage n(%)	Advanced stage n(%)	P-value
No. of subjects (n-198)	29 (14.7%)	169(85.3%)	
<b>Sociodemographic factors</b>			
<b>Age (yrs)</b>			
<50	15 (7.5)	64 (32.3)	0.457
$\geq 50$	14 (7.1)	105 (53.1)	
<b>Gender</b>			
Male	22 (11.11)	103 (52.02)	0.124
Female	07 (3.53)	66 (33.3)	
<b>Marital status</b>			
Married	17 (8.58)	105 (53.03)	0.72
Single/divorced/widow	12 (6.06)	64 (32.32)	
<b>Body mass index (BMI)</b>			
underweight (<19)	10 (5.05)	79 (39.9)	0.273
Healthy weight (19-24)	06 (3.03)	44 (22.2)	
Over weight (25-29)	08 (4.04)	31 (15.67)	
Obese (30-35)	05 (2.52)	15 (7.60)	
<b>Socioeconomic status (Kuppusamy's modified scale)</b>			
Upper	01 (0.5)	04 (2.02)	0.026*
Upper middle	4 (2.02)	12 (6.06)	
Lower middle	7 (3.53)	14 (7.07)	
Lower upper	01 (0.5)	31 (15.66)	
Lower	16 (8.08)	108 (54.5)	

\* The  $p$  value  $< 0.05$  was considered statistical significant by chi-square analysis

**Table 2:** Clinical and histopathological factors association with early and late stage of buccal mucosa carcinoma.

Factors	Early Stage n(%)	Advanced Stage n(%)	p-value
<b>Histopathology</b>			
Well differentiated	27 (13.6)	71 (36)	0.000*
Moderately differentiated	2 (1.01)	66 (33.3)	
Poorly differentiated	0	32 (16.2)	
<b>Regional lymph node</b>			
Negative	27 (13.6)	15 (7.6)	0.039*
Positive	33 (16.6)	123 (62.1)	
<b>Depth of tumor</b>			
<2mm	11 (5.5)	07 (3.5)	0.782
2-4mm	21 (10.6)	21 (10.6)	
>4mm-6mm	24 (12.1)	62 (31.3)	
>6mm	04 (2.02)	48 (24.2)	
<b>Size of tumor</b>			
<2cm	11 (5.5)	07 (3.5)	0.511
2-4cm	25 (12.6)	32 (16.2)	
>4cm	24 (12.1)	99 (71.7)	

\* The  $p$  value  $< 0.05$  was considered statistical significant by chi-square analysis.

Distribution of clinical and histopathological factors among stage of diagnosis was illustrated in Table 2. In accordance to UICC, TNM classification of our subjects well distributed as follows by grouping the clinical stages I/II as early stage totally 29 (14.7%) of subjects and III/IV as advanced stage 169 (85.3%)

subjects were diagnosed. Degree of differentiation, regional lymph node, depth of tumor and size of tumor was an important clinical prognostic factor for diagnosis of tumor. However, degree of differentiation (p=0.000), regional lymph node exists significant (p=0.039) among stage of diagnosis whereas rest of the factors were not associated by chi-square analysis at p<0.05.

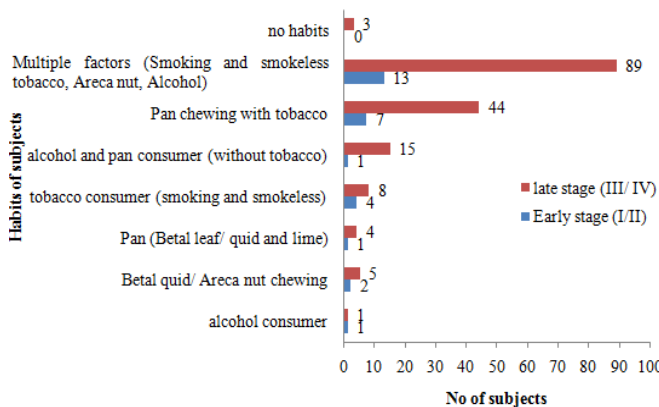
We used multivariate analysis using binominal logistic regression analysis to estimate odds ratios of delayed diagnosis and to identify length of delay. The biological behaviour of the tumour moderately differentiated squamous cell carcinoma had 13.132 and poorly differentiated had 16.124 times greater risk of late diagnosis than early diagnosis tumor. Regional lymph nodes presence had 1.914 times greater risk of late diagnosis than early stage diagnosis of buccal mucosa carcinoma (Table 3).

**Table 3:** Multivariate analysis using binominal regression analysis for factors association for stage of diagnosis.

Characteristic	S.E	Odds ratio	P value
<b>Histopathology</b>			
Well differentiated		Reference	
Moderately differentiated	0.756	13.132	.001*
Poorly differentiated	0.857	16.124	.020*
<b>Regional lymph node</b>			
Absent		Reference	
present	0.437	1.914	0.003*

\*The p value <0.05 was considered statistical significant.

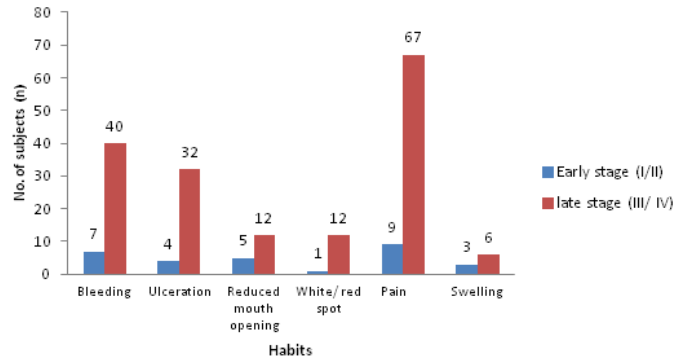
Figure 1 shows the distribution of habits among buccal mucosa carcinoma subjects. Most of the patients were aware of the potential harmful effects of smoking, tobacco chewing and alcohol intake. Still, multihabitual subjects were higher than rest of all other habitual, 166 (83.8%) had diagnosed with advanced stage of tumor whereas 32 (16.2%) had diagnosed with early stage of tumor.



**Fig. 2:** Description of clinical symptoms of buccal mucosa carcinoma subjects.

Figure 2 present clinical symptoms of buccal mucosa carcinoma. 76 (38.4%) most of the subjects had presented with pain and second most symptom was bleeding at the condition of infiltration, 47 (23.7%) subjects were diagnosed. 36 (18%) had ulceration, 17 (8.6%) had reduced mouth opening, 13 (6.6%) had red or white patch and 9 (4.6%) had swelling symptoms at the time diagnosis. Among the symptoms of buccal mucosa carcinoma, 169

(85.4%) had diagnosed at advanced stage of disease and rest of the subjects with early stage of diagnosis.



**Fig. 2:** Description of clinical symptoms of buccal mucosa carcinoma subjects.

**DISCUSSION**

The present study was undertaken to identify risk factors for diagnostic delay in early and advanced stage of buccal mucosa carcinoma. Despite recent advances in the management of oral cancer, the five-year survival rate of patients remains relatively unchanged at around 50% due to late diagnosis (Silverman, 2001). Subjects with advanced stage of the disease have a higher mortality rate than those at the initial stages and also various studies reported that screening of oral cancer might improve the survival by early diagnosis (Iamaroon *et al.*, 2004).

Many studies reported that sociodemographic variables (age, gender, marital status, religion) had non-association with patient delay. Similarly, our study also shown that most of the subjects were diagnosed in >50yrs of age group and male subjects were predominance than female (Iamaroon *et al.*, 2004). However, age, gender and marital status were not found to be significantly associated with delay.

In developing countries, a high proportion of subjects with oral cancer are from lower socioeconomic classes (Ganesh *et al.*, 2014). In India, previous studies reported that socioeconomic status was an independent risk factor for late stage of diagnosis (Kumar *et al.*, 2001), and another study reported that socioeconomic factors associated for late diagnosis of oral cancer and also low literacy rate and ignorance on the part of the patients are considered as additional factors for seeking late medical attention (Byakodi *et al.*, 2012). Our study socioeconomic status was associated with stage of diagnosis of buccal mucosa carcinoma. However, this high proportion of delay diagnosis was clearly associated with difficulties in accessing the health care system.

Noonan mention that many factors have been reported to be associated with the delay in the diagnosis of oral cancer, including site of lesion, size, degree of differentiation, involvement of regional lymph node, presence of metastases, tobacco, alcohol consumption, diet and dental factors from varies studies (Noonan, 2014). However, tumour characteristics are important in determining the oral cancer mortality. Well differentiated, low-grade oral squamous cell carcinoma usually

metastasizes to regional lymphnode only after invading connective tissue, muscle or bone. On the other hand, poorly differentiated, high grade oral cancer was biologically more aggressive and tends to metastasize to regional lymphnode early in the course of the disease (Pires *et al.*, 2013). Yeole revealed in his study that regional lymph node spread experience a threefold increase in mortality while those with distant metastasis have a sixfold excess risk (Yeole *et al.*, 2004). Similarly, in our study also reported that regional lymph nodes and histopathology of tumor had greater risk in advanced stage of diagnosis than early stage diagnosis of buccal mucosa carcinoma. Depth of tumor, size of tumor and subjects habits was not associated with the stage of diagnosis.

Survival rates were considerably low in developing countries; most of the subjects in rural population may not seek the medical care until the lesions become symptomatic and attend a reasonably large size. In our study, most of the subjects with pain and bleeding condition at advanced stage were diagnosed. Similarly, previous studies also reported that eighty-nine percent of patients in this study presented with pain and bleeding symptomatic and in more advanced stages may be associated with changes in articulation, difficulty swallowing or a neck mass. Over 20% of the patients in this study presented only when symptoms became severe and a further 53% delayed investigation of previously recognized symptoms (Groome *et al.*, 2011).

In summary, our study reported that diagnosing buccal mucosa carcinoma at an early stage when lesions were small and localised without regional lymph nodes and well differentiated tumor was believed to be the most effective means to reduce death, morbidity and disfigurement from this disease, along with reducing hospital cost, duration of treatment and professional fees than advanced stage of diagnosis. Hence, the study suggested that education campaigns to alert subjects about the warning signs and symptoms of oral cancer are needed to reduce the burden of disease.

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