

# Risk factors associated with the mortality rate of oral squamous cell carcinoma patients

## A 10-year retrospective study

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### Abstract

In Malaysia, oral cancer is very common and the reported 5-year survival of such patients is nearly 50% after treatment with surgery and radiotherapy, much lower than most of the developed countries. This study aimed to investigate the socio-demographic and clinicopathological parameters that influence the mortality rate of the patients suffering from oral squamous cell carcinoma (OSCC) in the Kelantan population.

In this retrospective study, data regarding socio-demographic, clinicopathological factors, and treatment outcome associated with OSCC were gathered from the archives of the medical records office of Hospital Universiti Sains Malaysia. For statistical analysis, simple and multiple logistic regression were performed. The significance level was set to  $P < .25$ .

A total of 211 OSCC cases were registered in Hospital Universiti Sains Malaysia from January 1, 2000 to December 31, 2018. Majority of them were male (57.82%), non-smoker (54.97%), non-alcohol consumer (91.94%), and non-betel quid chewer (93.83%) Malay (60.66%) patients. The tongue was the most commonly involved part of the oral cavity (41.52%). Histologically, the majority of the cases had moderately-differentiated OSCC (52.82%). Most of the patients were diagnosed at stage IV at the time of diagnosis (61.61%). When this study was performed, the survival status of the majority of the patients was alive (68.24%).

Within the analyzed socio-demographic and clinicopathological parameters, gender, alcohol consumption, T-classification, histological grading, and treatment status have been demonstrated as an independent risk factors for mortality rate in multivariate analysis. Hence, these parameters need to be taken into account for the individualized therapy management of OSCC patients.

**Abbreviations:** AOR = adjusted odds ratio, CI = confidence interval, HPV = human papillomavirus, HUSM = Hospital Universiti Sains Malaysia, OR = odds ratio; OSCC = oral squamous cell carcinoma, RT = radiotherapy, USM = Universiti Sains Malaysia.

**Keywords:** clinicopathological, mortality, oral cancer, oral squamous cell carcinoma, retrospective, treatment outcome

## 1. Introduction

Oral squamous cell carcinoma (OSCC) represents 90% of the total oral cancers.<sup>[1]</sup> Males and older individuals (>65 years) are more likely to be encountered with oral cancers.<sup>[2]</sup> A hike in the prevalence of OSCC among young adults has been a cause of particular concern. Over the past 30 years, the incidence of

tongue cancers has increased by up to 60% in adults who are aged under 40 years.<sup>[3]</sup> The tongue is considered as the most commonly involved intra-oral site for oral cancers.<sup>[4]</sup> Posterior-lateral border and ventral surfaces of the tongue are the most frequently involved sites in tongue cancers followed by the floor of the mouth. Relatively less common intra-oral sites are gingiva, hard palate, buccal, and labial mucosa.<sup>[5]</sup>

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The habits of alcohol consumption, betel quid chewing, and tobacco smoking are established cultural risk factors associated with pre-malignant oral lesions and OSCC.<sup>[6,7]</sup> In some regions of the world, variations are observed due to different types of ethnicities in a population. Such inter-ethnic differences might be due to the genetic pre-disposition of various ethnicities towards an escalated risk of pre-malignant oral lesions and OSCC.<sup>[8]</sup> Human papillomavirus (HPV) is known to be a risk factor for head and neck cancers. In the US, the percentage of HPV-associated OSCC has risen from 20% to more than 70%.<sup>[9]</sup>

In Malaysia, OSCC contributes to about 10.6% deaths in government hospitals<sup>[10]</sup> whereby relatively high percentage (67.1%) of cases were detected at advanced stage.<sup>[11]</sup> This fact is attributed by the lack of awareness and knowledge especially the sign and symptoms of OSCC.<sup>[12]</sup> Being multiracial in Malaysia, OSCC incidence varies by ethnic group whereby half of the OSCC cases in Malaysia were among the Indian population.<sup>[13]</sup> This could be due to the prevalent betel quid chewing habit among the Indians which also suggests that the occurrence of OSCC is pre-disposed by lifestyle and cultural practices.<sup>[14]</sup>

OSCC is treated mainly by surgery in stages I and II and by surgery with adjunctive therapy in stages III and IV.<sup>[15]</sup> Patients having positive margin and extra-capsular spread in the nodes are treated utilizing chemoradiation after surgery. Patients with nodal metastasis, perineural extension, and lymphovascular emboli or with advanced tumour stages are treated with adjunctive radiotherapy (RT) after surgery.<sup>[16]</sup> Despite the several treatment options available, the overall 5-year survival rate after treatment of OSCC is approximately 50%.<sup>[17]</sup> Loco-regional recurrence is the most common cause for treatment failure. Recurrence is known to occur in about 35% of patients treated for OSCC.<sup>[16]</sup> Recurrent cancer patients have lesser chances of survival.<sup>[18]</sup>

In recent years, the importance of biological markers for prognosis of patients with OSCC has been demonstrated.<sup>[19]</sup> However, the different biological growth patterns of malignancies mean that the identification of and socio-demographic and clinicopathological risk factors is still of utmost importance for predicting mortality.<sup>[20,21]</sup> However, data on socio-demographic and clinicopathological characteristics of patients with OSCC are still rare and therefore, for clarification, need to be obtained for a larger numbers of patients.<sup>[22]</sup> Therefore, the present retrospective, single-center study investigated the importance of socio-demographic and clinicopathological parameters that influence the mortality rate of the patients suffering from OSCC in the Kelantanese population.

## 2. Materials and methods

### 2.1. Study design and data collection

This cross-sectional retrospective study consisted of 211 OSCC patients collected from the archives of the medical record office of Hospital Universiti Sains Malaysia (HUSM) in the period 2000 to 2018. Socio-demographic (age, gender, ethnicity, smoking status, betel quid status, alcohol status, HPV pre-disposing factors including sexual activity with multiple partners, practicing oral sex, immunocompromised patients, and personal contact touching someone's warts without protection that have been exposed to HPV as well as the family history of the tumor), clinicopathological data (tumor anatomical site and size, TNM staging, recurrence or distant metastasis, and histological subtype

of the tumor), and treatment outcome (dead or alive) were retrieved from patients' files. The registration numbers of patients were retrieved from the computerized database search for all oral cancer patients in the School of Medical Sciences, Universiti Sains Malaysia (USM). Few records of patients diagnosed with oral cancer were retrieved from the archives of Oral Pathology Laboratory at the School of Dental Sciences, USM. Based on registration numbers, patients' files were retrieved from the medical record office of HUSM. A standardized data collection questionnaire was used for data collection. The information that was not available in the medical records was included in the exclusion criteria.

### 2.2. Statistical analysis

IBM SPSS Statistics, version 24.0 (SPSS Inc, Chicago, USA) was used for data analysis. To find out the prevalence of OSCC, descriptive, and bivariate analyses were performed, and the results were presented as frequency and percentages. Simple logistic analysis was performed for screening variables associated with risk factors including age, gender, ethnicity, alcohol consumption, tobacco smoking, betel quid chewing, the familial background of the tumor, HPV infection, TNM classification, TNM staging, tumor site, histological grading of tumor, metastasis, and treatment. The significance level was set to  $P < .25$ . In order, to determine the association between clinicopathological characteristics with treatment outcome, multiple logistic regression was used, with dead or alive being the dependent variable. Multiple logistic regression consists of several steps including; data exploration, simple logistic regression (univariate analysis), variable selection, checking multicollinearity and interaction, checking the overall fit of the model, establishing a final model and interpretation.

### 2.3. Ethical correlations

This study was submitted to and approved by the Human Ethics and Committee USM and was performed in conformity with the Jawatankuasa Etika Penyelidikan (Manusia), USM, Malaysia (JEPeM code – USM/JEPeM/18100613).

## 3. Results

A total of 268 OSCC cases were notified and registered in HUSM from January 1, 2000 to December 31, 2018. Of these, 211 cases could complete the inclusion criteria and were included in this study, whereas 57 OSCC cases were excluded due to missing and/or lost data in medical records.

### 3.1. Socio-demographic features

In this study, male patients (n=122, 57.82%) were more than female patients (n=89, 42.18%) with a mean age of 48 years. Majority of them were non-smoker (n=116, 54.97%), non-alcohol consumer (n=194, 91.94%), and non-betel quid chewer (n=198, 93.83%) Malay (n=128, 60.66%). The detailed socio-demographic data are shown in Table 1.

### 3.2. Clinicopathological features

The tongue was the most commonly involved part of the oral cavity with OSCC (n=98, 46.44%), followed by buccal mucosa

**Table 1**  
**Sociodemographic and clinicopathological features of oral squamous cell carcinoma patients.**

Variables	n (%)
Age (years)	No. of patients (%)
18–25	05 (2.36)
26–35	18 (8.53)
36–45	45 (21.32)
46–55	73 (34.59)
56–65	34 (16.11)
66–75	26 (12.32)
76–85	09 (4.26)
86–90	01 (0.47)
Gender	
Male	122 (57.82)
Female	89 (42.18)
Ethnicity	
Malay	128 (60.66)
Indian	61 (28.90)
Chinese	19 (9.00)
Others	Nil
Tobacco consumption	
Smoker	95 (45.02)
Non-smoker	116 (54.97)
Alcohol intake	
User	17 (8.05)
Non-user	194 (91.94)
Betel quid use	
User	13 (6.16)
Non-user	198 (93.83)
Mixed habits (tobacco, alcohol, and betel quid):	07 (3.331)
Past family history of tumor	
Yes	48 (22.74)
No	163 (77.26)
HPV pre-disposing factors	
Yes	55 (26.06)
No	156 (73.94)
TNM staging	
Stage I	14 (6.63)
Stage II	18 (8.53)
Stage III	49 (23.22)
Stage IV	130 (61.61)
Histological grade	
Well differentiated	130 (61.61)
Moderately differentiated	51 (24.17)
Poorly differentiated	31 (14.69)
Survival status	
Alive	144 (68.24)
Dead	67 (31.75)

HPV = human papillomavirus.

(n = 33, 15.63%) (Fig. 1). Histologically, the majority of the cases had well-differentiated OSCC (n = 130, 61.61%). Most of the patients were diagnosed at stage IV at the time of diagnosis (n = 130, 61.61%). When this study was performed, the survival status of the majority of the patients was alive (n = 144, 68.24%). Stage III comprised of 49 cases (23.22%). The detailed clinicopathological features are shown in Table 1 and Figure 1.

### 3.3. Treatment outcome status

In the 19-year period (2000–2018), 84.83% (n = 179) patients had received treatment, while 15.16% (n = 32) patients did not receive any treatment. Around 77.65% (n = 139) of patients who had undergone treatment lived, while 84.37% (n = 27) who did not receive any treatment died (Table 2).

### 3.4. Univariable analysis of socio-demographic and clinicopathological factors with treatment outcome status of OSCC

To analyze the individual association between independent variables of socio-demographic as well as clinicopathological factors and dependent variables of treatment outcome status of OSCC, univariable analysis was performed. Table 3 depicts the factors having  $P < .25$  which are associated with the treatment outcome status of OSCC in univariable analysis.

### 3.5. The established final model for variables/factors associated with treatment outcome status

After performing all the statistical analyses, a final model for the clinicopathological factors associated with treatment outcome status of OSCC was established. The results of multiple logistic regression analyses for these variables are shown in Table 4. According to multivariable analysis, the significant variables/factors to be included in the final model are as follows.

**3.5.1. Gender.** Gender plays a crucial role in the treatment outcome as the  $P$  value was statistically significant ( $P = .005$ ). According to multivariable analysis, in Kelantan, females suffering from OSCC are at 10% lower risk to die than males (Adjusted odds ratio [AOR] = 0.90; 95% confidence interval (CI): 0.02, 0.49;  $P = .005$ ).

**3.5.2. Alcohol intake.** Based on the multivariable analysis of this study, the alcohol consumption variable was statistically significant ( $P = .020$ ) for the mortality rates of OSCC patients. It shows that the patients who consume alcohol are about 17 times more likely to die from OSCC than non-alcoholics (AOR = 16.81; 95% CI: 1.86, 197.15;  $P = .020$ ).

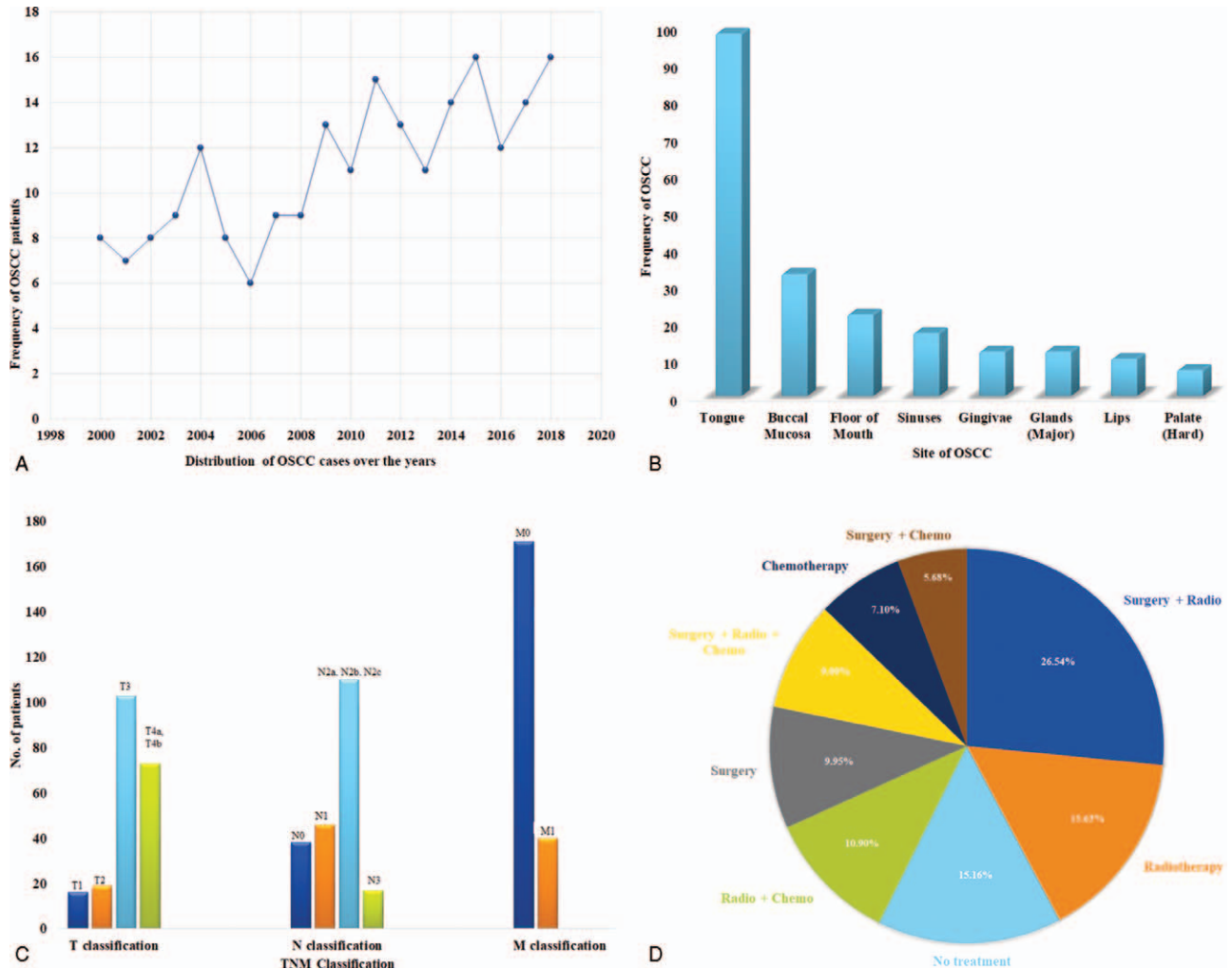
**3.5.3. T-classification.** Based on the multivariable analysis of this study, the T-classification factor was statistically significant ( $P = .036$ ) for the mortality rates of OSCC patients. It shows that the patients who had increasing tumor size of OSCC are almost 5 times more likely to die than others (AOR = 4.58; 95% CI: 1.14, 22.02;  $P = .036$ ).

**3.5.4. Tumor histological grade.** According to the multivariable analysis of this study, tumor histological grade was statistically significant ( $P = .028$ ) for the mortality rates of OSCC patients. It shows that the patients having poorly-differentiated histological grade of OSCC are approximately 8 times more likely to die than patients having another histological grading of OSCC, that is, well-differentiated or moderately differentiated (AOR = 7.88; 95% CI: 1.55, 45.38;  $P = .028$ ).

**3.5.5. Treatment status.** Based on the multivariable analysis of this study, treatment (received or not) factor was statistically significant ( $P = .048$ ) for the mortality rates of OSCC patients. It shows that the patients who received treatment for OSCC are around 6 times less likely to die than the patients who did not receive any treatment (AOR = 5.67; 95% CI: 1.22, 32.16;  $P = .048$ ).

## 4. Discussion

Usually, oral cancer begins as an inconspicuous red or white spot or sore somewhere in the oral cavity. An area of the mouth including the tongue, lips, buccal mucosa, floor of the mouth,



**Figure 1.** (A) Distribution of OSCC cases over the years. (B) Site distribution of OSCC. (C) Frequency of OSCC cases presenting with TNM classification. (D) Type of treatment modalities used for OSCC patients. OSCC = oral squamous cell carcinoma.

gingiva, or palate can be affected by it.<sup>[23]</sup> Globally, it has been well reported that the incidence of OSCC escalates with increasing age. Individuals above 40 years of age are at peak risk for developing OSCC.<sup>[24]</sup> Men are more prone to developing them than women.<sup>[25]</sup> In this study, the mean age of OSCC cases was 48 years  $\pm$  11.4 and the prevalence of OSCC was more in men than women (1.4:1). These findings are in accordance with multiple studies conducted to associate the age<sup>[26–29]</sup> and gender factors<sup>[25,28,30–31]</sup> with the increasing risk of developing OSCC.

According to Ng et al,<sup>[32]</sup> the prevalence of OSCC was reported highest in Indian ethnic people (63.8%) followed by Malays (19.6%) and Chinese (16.6%). Similarly, Hirayama<sup>[33]</sup> reported that the incidence of oral cancer was highest among the Indian ethnic group. Zain and Ghazali<sup>[34]</sup> reported a variation in the prevalence of OSCC among individual provinces of Peninsular Malaysia. The state with the highest rate of oral cancer incidence was Selangor (8.2 per 100,000), whereas the states with the lowest rate were Kelantan, Kedah, and Terengganu (1.9 per 100,000). According to Ghazali et al,<sup>[35]</sup> individuals belonging to Indian ethnicity had the highest incidence of mouth cancer, whereas Malays had the highest incidence of lip and tongue cancers. Moreover, the incidence of mouth cancer among Indians

residing in Kelantan was higher than Indians living in the Indian subcontinent and other migrant Indian populations. In the present study, individuals belonging to Malay ethnicity were more prone to develop OSCC when compared to Indians and Chinese. One explanation to this finding might be the higher proportion of Malays and lower proportion of Indians and Chinese residing in the Kelantan province when compared to the Selangor province which has higher rates of oral cancer among Indians.

Globally, alcohol consumption accounts for approximately 75% of oral cancers.<sup>[36]</sup> A combination of alcohol intake and tobacco smoking is just like double trouble that augments the effect and may escalate the risk for oral cancer.<sup>[37]</sup> Polymorphism in aldehyde dehydrogenase-2 gene is more prevalent in Asian countries as compared with Western countries. Light alcohol consumption was associated with the risk of OSCC in Asian countries which is suggestive of the possible role of pre-disposing genetic factors.<sup>[36]</sup> In Malaysia, beer and stout are consumed by several ethnic groups. There is limited data regarding the consumption of alcohol among Malaysians probably due to religious and ethnic sensitivity.<sup>[38]</sup> The Malays, being Muslim, do not consume alcohol as alcohol consumption in any form is

**Table 2**  
Treatment outcome status of oral squamous cell carcinoma patients.

Treatment outcome status	Alive (n)	Dead (n)
Treatment (n)		
Yes 179 (84.83%)	144 (68.24%)	67 (31.75%)
No 32 (15.17%)	5 (15.62%)	27 (84.37%)

prohibited in their religion. This might be a potential reason why there is only a minute proportion of drinkers in this study (8.05%). Despite the lower percentage of alcohol consumers in this study, a statistically significant association was observed between alcohol consumption and risk for developing oral cancer as well as mortality due to OSCC. This finding is in agreement with several prospective studies as well as systematic reviews and meta-analyses performed to assess the association of alcohol intake with risk of OSCC.<sup>[38–42]</sup>

Tumor size and extent, nodal involvement as well as presence or absence of loco regional metastasis hold a vital role in the prognosis of OSCC patients.<sup>[43]</sup> In this study, a statistically significant association was observed between T classification and mortality related to OSCC. T3 and T4 stage tumors were associated with higher chances of mortality than tumors at stage T1 and T2. This finding is in agreement with other several studies that reported the poor prognosis of oral cancer patients who presented with T3 or T4 stage.<sup>[43–46]</sup> Furthermore, a significant association was evident in this study between nodal involvement (N1, N2, N3) as well as distant metastasis (M1) and prognosis of the OSCC patients. These findings have been in accordance with several other studies that reported that these variables were responsible for the poor prognosis of OSCC patients.<sup>[45,47,48]</sup> A possible explanation might be the association between increased tumor size with nodal metastasis along with local recurrence which eventually may lead to poor prognosis.

Moderate to poorly differentiated tumors are responsible for the poor prognosis of OSCC patients when compared with well-differentiated ones.<sup>[49]</sup> In this study, the most commonly seen type of histological differentiation of tumor was well-differentiated (61.61%), followed by moderately-differentiated (24.17%) and poorly-differentiated (14.69%) tumors. The findings of this study are in agreement with several other reports stating that the patients having a well differentiated histological grade of OSCC were less likely to die than patients having another histological grading of OSCC, that is, moderately-differentiated or poorly differentiated.<sup>[48–52]</sup>

In this study, approximately 85% of OSCC patients had undergone treatment, either in the form of surgery or any other treatment modalities. Out of this 85%, 77.65% of patients survived and 22.35% died. According to a study, an essential clinical prognostic indicator involves complete tumor excision with sufficient margins. It has been reported that with each 1 mm of clear margin, the chances of survival were improved by 8%.<sup>[53]</sup> Another study reported that surgical margin involvement was associated with a high recurrence rate and poor prognosis.<sup>[54]</sup>

In this study, the majority of the patients received a combination of surgery and RT. This finding coincides with the guidelines of the National Comprehensive Cancer Network. According to National Comprehensive Cancer Network, the standard of care for early-stage resectable (T1/T2) OSCC is

**Table 3**  
Simple logistic regression analysis of the factors associated with the mortality rate of oral squamous cell carcinoma.

Variables	Crude OR (95% CI)	Wald	P value
Age	0.88 (0.94, 1.05)	0.33	.842
Gender			.078*
Male	1		
Female	0.37 (0.12, 1.12)	2.82	
Ethnicity			.660
Malay	1		
Non-Malay	1.27 (0.17, 1.18)	0.08	
Alcohol			.135*
Non-user	1		
User	0.18 (0.02, 1.65)	2.43	
Smoking			.136*
Non-smoker	1		
Smoker	2.19 (0.77, 6.54)	2.14	
Betel quid			.282
Non-user	1		
User	0.53 (0.13, 1.67)	1.16	
Family history of tumor			.810
No	1		
Yes	1.08 (0.33, 3.73)	0.07	
HPV infection			.234
No	1		
Yes	1.34 (0.56, 4.35)		
T classification			.046*
T1, T2	1		
T3, T4	2.88 (1.12, 7.76)	3.88	
N classification			.234*
N0	1		
N1, N2, N3	2.38 (0.58, 8.68)	1.45	
M classification			.120*
M0	1		
M1	6.06 (0.64, 54.72)	2.65	
TNM staging			.678
Stage I, II	1		
Stage III, IV	2.68 (1.24, 6.86)	0.32	
Tumor site			.434
Locations except tongue	1		
Tongue	1.45 (0.56, 4.63)	0.88	
Poorly differentiated oral cancer			.048*
Yes	1		
No	0.23 (0.06, 0.88)	4.34	
Moderately differentiated oral cancer			.120*
Yes	1		
No	13.36 (0.66, 9.12)	2.42	
Metastasis			.058*
No	1		
Yes	5.18 (1.10, 26.42)	3.94	
Treatment			.038*
Yes	1		
No	4.67 (1.28, 14.72)	4.22	

HPV = human papillomavirus.

\*Represents a statistically significant difference

surgery and RT; the majority of surgeons give preference to primary resection with or without elective neck dissection.<sup>[55]</sup> For early-stage disease, equivalent locoregional control rates can be obtained in comparison to surgery; however, RT requires both external beam and brachytherapy to be used together.<sup>[56]</sup> There is no robust prospective study comparing the 2 modalities against one another, but a single case series by<sup>[57]</sup> demonstrated superior locoregional control with definitive surgical resection compared

**Table 4**  
Multiple logistic regression analysis of the factors associated with mortality rate of oral squamous cell carcinoma.

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Gender			.005
Male	1		
Female	0.37 (0.12, 1.12)	10.10 (0.02, 0.49)	
T classification			.036
T1, T2	1		
T3, T4	2.88 (1.12, 7.76)	4.58 (1.14, 22.02)	
Alcohol intake			.020
Non-drinker	1		
Drinker	0.18 (0.02, 1.65)	16.81 (1.86, 197.15)	
Tumor histological grade			.028
Well/moderately-differentiated tumor	1		
Poorly differentiated tumor	0.23 (0.06, 0.88)	7.88 (1.55, 45.38)	
Treatment			.048
Yes	1		
No	4.67 (1.28, 14.72)	5.67 (1.22, 32.16)	

to definitive RT for early-stage OSCC<sup>[58]</sup> pointed out, however, that these patients received less intense treatment protocols than those recommended today<sup>[59]</sup> then performed a retrospective study of 148 patients with T1/T2, N0 disease and documented clear margins after definitive surgical resection with >90% locoregional control. In general, oral cavity cancers are best treated with surgery, whereas definitive RT should only be used if surgery is unable to be performed or is refused by the patient.

The limitations of this study are essential to recognize. The limited sample size due to the confinement of this study to 1 hospital and less proportion of Indian and Chinese ethnic groups may have restricted the generalizability of the findings to the Malaysian population. The results of this study might not be generalized to other ethnic groups because this study was conducted in Kelantan, which is a dominant Malay state. As this was a retrospective study, the patients with lost/missing/incomplete data had to be excluded, which might have underestimated the findings.

## 5. Conclusion

Within the analyzed socio-demographic and clinicopathological parameters, gender, alcohol consumption, T-classification, histological grading, and treatment status have been demonstrated as an independent risk factors for mortality rate in multivariate analysis. Hence, these parameters need to be taken into account for the individualized therapy management of OSCC patients.

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