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ORIGINAL ARTICLE

Association of Socio-Demographic and Clinicopathological Risk Factors with Oral Cancers: A 19-Year Retrospective Study

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ABSTRACT

Objective: To determine the association of socio-demographic and clinic-pathological risk factors with oral cancer in Kelantan, Malaysia. **Material and Methods:** A 19-year cross-sectional survey was performed in Hospital Universiti Sains Malaysia (HUSM), Malaysia. Medical record of 301 oral cancer patients was retrieved from the Medical Records office. **Results:** The majority of the oral cancer cases were male (62.8%), non-smokers (57.5%), non-alcohol consumers (83.4%), non-betel quid chewers (96.7%), and belonged to Malay ethnicity (68.8%). At the time of diagnosis, most of the patients were at stage II (38.9%). Approximately one-third (30.6%) of the total OC patients experienced loco-regional/distant metastasis, whereas no metastasis was detected in around two-thirds of cases (69.4%). A combination of surgery and radiotherapy was the most commonly employed treatment modality (27.2%). At the time of this study, the survival status of most of the patients was alive (69.1%). The most frequently encountered oral cancer in the Kelantanese population was oral squamous cell carcinoma (70.1%), with the tongue being the most frequently involved oral cavity site (35.5%). **Conclusion:** More than three-fourths of the cases were alive at follow-up, which included the cases that did not undergo any form of treatment.

Keywords: Mouth Neoplasms; Carcinoma, Squamous Cell; Tongue Neoplasms; Salivary Gland Neoplasms.

Introduction

Globally, cancer is a disease of great concern due to its incidence and mortality [1]. According to the World Health Organization (WHO), by 2030, approximately 75 million individuals will be having cancer [2]. Oral cancer (OC) is one of the ten most commonly occurring cancers worldwide and it is attributed as the leading cause of death in certain geographical regions such as South-Central Asia [3]. It was estimated that in 2018, 407,600 people were affected by OC globally; approximately half of whom (199,560) died of the disease. Unfortunately, around two-thirds of these cases were reported in developing countries [4].

There is a wide disparity in the prevalence of OC by geographical area and sex [5]. Variations have been recognized at the molecular level and the clinic-pathological behavior in alcohol-associated and tobacco-smoking OC in Japan, United States (US), France, United Kingdom, as well as tobacco-chewing oral carcinomas in Southeast Asia [6]. In Malaysia, the Indian race was detected to have a higher risk of OC than Malays and Chinese [7].

Studies report that men over 50 years of age are at an increased risk of developing OC [1,8]. 85% of OC in women and 93% of OC in men are determined by lifestyle factors such as tobacco smoking, betel quid chewing, alcohol intake, the presence of pre-malignant lesions, etc. [9].

Oral squamous cell carcinoma (OSCC) is the most commonly encountered histological type (90%) of OC [8]. Posterior-lateral border and ventral surfaces of the tongue are the most frequently involved sites in tongue cancers, followed by the mouth floor. Relatively less common intra-oral sites are gingiva, hard palate, buccal and labial mucosa [10]. The site of the primary tumor occurrence, the tumor size (T stage), nodal metastasis (N stage) and extra-capsular spread of the primary tumor dictates the treatment modality – chemotherapy (CT), radiotherapy (RT), surgery, or a combination [11]. The OC's successful treatment outcome depends on the appropriate management of both the loco-regional lymphatics and the primary site [11].

This study aimed to determine the association of socio-demographic and clinic-pathological risk factors with oral cancers in Kelantan, Malaysia.

Material and Methods

Study Design and Sample

This was a retrospective cross-sectional study that comprised a collection of 301 OC patients' socio-demographic data, clinicopathological feature data, type and treatment modalities. The study site was Hospital Universiti Sains Malaysia (HUSM), Kelantan, which is located in northeastern Peninsular Malaysia. The required data were obtained from the medical record office of HUSM between January 2000 and December 2018.

Data Collection

The registration numbers of patients were retrieved from a computerized database search for all OC patients in the Records Unit of HUSM, and the histopathology reports were cross-examined from the archives of Oral Pathology Laboratory of HUSM. Few records of patients diagnosed with OC were retrieved from Oral Pathology Laboratory archives at the School of Dental Sciences, USM. A standardized data collection proforma was used to collect the relevant data of the patients. Records with missing information were excluded.

Data Analysis

Statistical Package for the Social Sciences (SPSS version 24.0 IBM, Armonk, NY: IBM Corp, USA) was used for data analysis. To calculate the absolute and relative frequencies, descriptive statistics were used.

Ethical Aspects

Human Ethics and Committee Universiti Sains Malaysia (USM) granted ethical approval. This research was performed in conformity with the Jawatankuasa Etika Penyeldikan (Manusia), USM, Malaysia (JEPeM code – USM/JEPeM/18100613).

Results

A total of 368 OC cases were registered. Of these, 301 cases were included. Sixty-seven OC cases were excluded due to missing and/or lost data in medical records. The final analysis was done on the data of 301 patients.

Socio-Demographic Features

The mean age was 55 years. Most of the participants were male (62.8%), non-smoker (57.5%), non-alcohol consumer (83.4%) and non-betel quid chewer (96.7%) and Malay (68.8%) (Table 1).

Table 1. Socio-demographic features of oral cancer patients.

Variables	N (%)
Age (in Years)	55.0 (Mean)
Gender	
Male	189 (62.8)
Female	112 (37.2)
Ethnicity	
Malay	207 (68.8)
Indian	63 (20.9)
Chinese	31 (10.3)
Tobacco Consumption	
Smoker	128 (42.5)
Non-Smoker	173 (57.5)
Alcohol Intake	
User	50 (16.6)
Non-User	251 (83.4)
Betel Quid Use	
User	10 (3.3)
Non-User	291 (96.7)
Past Family History of Tumor	
Yes	69 (22.9)
No	232 (77.1)
HPV Predisposing Factors	
Yes	63 (20.9)
No	238 (79.1)

The majority of the cases were diagnosed as stage II at the time of diagnosis (38.9%). A total of 30.6% of patients experienced loco-regional/distant metastasis, whereas no metastasis was detected in 69.4%. The majority of the patients received a combination of surgery and RT as the mode of treatment (27.2%). When this study was performed, the survival status of the majority of the patients was alive (69.1%) (Table 2).

Oral squamous cell carcinoma was the most frequently encountered OC in the Kelantanese population (70.1%), followed by mucoepidermoid carcinoma (8.3%) and adenoid cystic carcinoma (5.6%) (Table 3).

Table 2. Clinicopathological features of oral cancer patients.

Variables	N (%)
T Classification	
T1	37 (12.3)
T2	117 (38.9)
T3	48 (15.9)
T4a, T4b, T4c	99 (32.9)
N Classification	
N0	42 (13.9)
N1	75 (24.9)
N2a, N2b, N2c	138 (45.8)
N3	46 (15.4)
M Classification	
M0	209 (69.4)
M1	92 (30.6)
TNM Staging	
Stage I	27 (9.0)
Stage II	38 (12.6)
Stage III	96 (31.9)
Stage IVa, IVb, IVc	140 (46.5)
Treatment	
Surgery	43 (14.3)
Surgery + Chemotherapy	20 (6.6)
Surgery + Radiotherapy	82 (27.2)
Surgery + Chemotherapy + Radiotherapy	28 (9.3)
Radiotherapy	50 (16.6)
Radiotherapy + Chemotherapy	22 (7.3)
Chemotherapy	16 (5.3)
No Treatment	40 (13.3)
Survival Status	
Alive	208 (69.1)
Dead	93 (30.9)

Table 3. Types of oral cancers of different histopathological origins.

Histopathological Origin	Site Distribution	N (%)
Epithelial Origin (N / %)		
Squamous Cell Carcinoma (211 / 70.1%)	Tongue	98 (46.4)
	Anterior Tongue	61
	Posterior Tongue	37
	Buccal Mucosa	33 (15.6)
	Floor of Mouth	22 (10.4)
	Sinus	17 (8.0)
	Nasal Sinus	8
	Maxillary Sinus	5
	Paranasal Sinus	2
	Sphenoidal Sinus	2
	Alveolus	12 (5.7)
	Upper Alveolus	3
	Lower Alveolus	9
	Gland	12 (5.7)
	Parotid Gland	8
	Submandibular Gland	4
	Lip	10 (4.7)
	Upper Lip	7
	Lower Lip	3
	Hard Palate	7 (3.3)
Basal Cell Carcinoma (6 / 2.0)	Lip	4 (66.7)
	Lower Lip	4

	Gland	2 (33.3)
	Parotid Gland	1
	Submandibular Gland	1
Basaloid Squamous Cell Carcinoma (4 / 1.3)	Floor of Mouth	2 (50.0)
	Tongue	1 (25.0)
	Anterior Tongue	1
	Gland	1 (25.0)
	Parotid Gland	1
Malignant Melanoma (3 /1.0)	Palate	2 (75.0)
	Hard Palate	2
	Alveolus	1 (25.0)
	Lower Alveolus	1
Glandular Origin		
Mucoepidermoid Carcinoma (25 / 8.3)	Gland	15 (60.0)
	Parotid Gland	14
	Submandibular Gland	1
	Palate	6 (24.0)
	Hard Palate	5
	Soft Palate	1
	Floor of Mouth	3 (12.0)
	Alveolus	1 (4.0)
	Upper Alveolus	1
Adenoid Cystic Carcinoma (17 / 5.6)	Gland	12 (70.6)
	Submandibular Gland	7
	Parotid Gland	5
	Buccal Mucosa	3 (17.6)
	Tongue	1 (5.9)
	Anterior Tongue	1
	Sinus	1 (5.9)
	Sphenoidal Sinus	1
Adenocarcinoma (7 / 2.3)	Gland	5 (71.4)
	Parotid Gland	3
	Submandibular Gland	2
	Lip	1 (14.3)
	Lower Lip	1
	Sinus	1 (14.3)
	Nasal Sinus	1
Acinic Cell Carcinoma (3 / 1.0)	Gland	3 (100.0)
	Parotid Gland	3
Mesenchymal Origin		
Rhabdomyosarcoma (6 / 2.0)	Buccal Mucosa	3 (50.0)
	Alveolus	1 (16.7)
	Lower Alveolus	1
	Lip	1 (16.66%)
	Lower Lip	1
	Gland	1 (16.7)
	Submandibular Gland	1
Leiomyosarcoma (4 / 1.3)	Tongue	2 (50.0)
	Anterior Tongue	2
	Lip	1 (25.0)
	Lower Lip	1
	Palate	1 (25.0)
	Hard Palate	1
Angiosarcoma (3 / 1.0)	Tongue	2 (66.7)
	Anterior Tongue	2
	Gland	1 (33.3)
	Parotid Gland	1
B-cell lymphoma (3 / 1.0)	Tongue	3 (100.0)
	Anterior Tongue	2
	Posterior Tongue	1

Osteosarcoma (3 / 1.0)	Palate	3 (100.0)
	Hard Palate	3
Pleomorphic sarcoma (2 / 0.7)	Palate	1 (50.0)
	Hard Palate	1
	Sinus	1 (50.0)
	Nasal Sinus	1
Mixed/Other Origins		
Lymphoepithelial Carcinoma (4 / 1.3)	Gland	3 (75.0)
	Parotid Gland	3
	Lip	1 (25.0)
	Upper Lip	1

The tongue was the most commonly involved part of the oral cavity with OC (35.5%), followed by major salivary glands, including the parotid gland and submandibular gland (18.3%) and buccal mucosa (13.0%) (Table 4).

Table 4. Data distribution based on site of oral cancer.

Cancer Site	N (%)
Tongue	107 (35.5)
Anterior	69
Posterior	38
Buccal Mucosa	39 (13.0)
Floor of Mouth	27 (9.0)
Gingiva	15 (5.0)
Upper Gingiva	4
Lower Gingiva	11
Lips	18 (6.0)
Upper Lip	8
Lower Lip	10
Glands	55 (18.3)
Parotid Gland	39
Submandibular Gland	16
Palate	20 (6.6)
Hard Palate	19
Soft Palate	1
Sinuses	20 (6.6)
Nasal Sinus	10
Paranasal Sinus	2
Sphenoid Sinus	3
Maxillary Sinus	5

In the 19-year period (2000-2018), 86.7% patients had received treatment, while 13.3% did not receive any treatment. A total of 74.7% of patients who had undergone treatment lived, while 67.5% who did not receive any treatment died (Table 5).

Table 5. Status of treatment outcome in oral cancer patients.

Treatment	Treatment Outcome Status		
	Alive (N / %)	Dead (N / %)	**Total** (N / %)
Yes	195 (74.7)	66 (25.3)	261 (86.7)
No	13 (32.5)	27 (67.5)	40 (13.3)
Total	208 (69.1)	93 (30.9)	301 (100.0)

Discussion

Improvement of disease control is largely dependent on identifying risk factors and the epidemiology of that specific disease. Provisions of symptomatic treatment to cancer patients fail to help the cancer control strategies. The current study determined the types of OCs reported since the year 2000 in Hospital Universiti Sains Malaysia, located in Kelantan, Malaysia. This study also explored the association of OC with socio-demographic and clinic-pathological risk factors.

Globally, it has been well reported that the incidence of OC escalates with increasing age. Individuals above forty years of age are at peak risk for developing OC [12]. The mean age of 55 years was determined in the present study, which is in accordance with the data from Yemen, Pakistan, and a multi-center study [5,12,13]. The occurrence of OSCC was commonly observed in the sixth decade of life, which has been reported in several studies [13-17]. Several histopathological origins, including epithelial, glandular, and mesenchymal, were reported to commonly occur at different times [17]. According to gender, male cases were common than females, with a male ratio of 1.68 to 1. Our data's gender distribution was comparable with the Pakistani and African population [13,17]; however, the male predilection was observed up to 4.3:1 in multi-center studies involving larger sample data [12,16]. These findings are in accordance with multiple studies conducted to associate the age [13-16] and gender factors [15,17-20] with the increasing risk of developing OC.

We found that 70.1% of cases in this study had OSCC. Oral squamous cell carcinoma has been identified as the most commonly occurring malignant tumor of the oral cavity [1,13-15,17]. Several studies described their results by dividing the malignancies into different regions such as oropharynx, oral cavity, pharynx, and larynx [5,12,13]. The present study presented the data distribution based on the site of the tumor; and that within the oral cavity, the tongue was the most common tumor site, which is in accordance with several other studies [5,12,13] and in agreement with global epidemiology data that reported tongue as the most "cancer-prone" intra-oral site in most populations [21]. The site distribution was different in this study as compared with other studies conducted in other Asian countries, whereby the most frequent site of OSCC was buccal mucosa. This might be due to the habitual practice of placing betel quid between teeth and buccal mucosa, as commonly observed in populations of India, Myanmar, Thailand, and Taiwan [22]. In Malaysia and Indonesia, betel quid chewing habit has been primarily replaced with smoking since early to mid-1990s [23]. The second most common tumor site within the oral cavity included parotid and submandibular glands, which was also found to be in opposition to several other studies [12,18-20].

The present study's findings are in accordance with the TNM classification recommended for classifying malignant tumors [22]. The highest number of subjects presented with the T2 stage closely followed by the T4 stage, whereas Mendez et al. [8] reported most cases with the T4 stage. 69% of the present study cases were alive at follow-up, which included the cases that did not undergo any form of treatment. The majority of patients presenting at the T4 stage were not surgically operated, explaining the high incidence of cases receiving no treatment. We identified that different studies described their results based on different classification systems, histopathology [15], nature of the tumor (benign or malignant) [14], site of the tumor [18], grading of differentiation [13] and involved region [5,12].

In the present 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 (NCCN). According to NCCN, the standard of care for early-stage resectable (T1/T2) OSCC is surgery and/or RT; the majority of surgeons give preference to primary resection with or without elective neck dissection [24]. For early-stage disease, equivalent loco-regional control rates can be obtained in comparison to surgery; however, RT requires

both external beam and brachytherapy to be used together [25]. There is no robust prospective study comparing the 2 modalities against one another, but a single case series demonstrated superior loco-regional control with definitive surgical resection compared to definitive RT for early-stage OC [26]. However, previous authors pointed out that these patients received less intense treatment protocols than those recommended today [27]. Huang et al. performed a retrospective study of 148 patients with T1/T2, N0 disease, and documented clear margins after definitive surgical resection with >90% loco-regional control [28].

The RT by itself may be offered to patients with unresectable disease, the recurrent disease not amenable to further resection, patients who refuse surgery or are deemed too medically unstable for surgery (ie, significant comorbidities, poor functional status), as well as patients in whom RT is determined to avoid significant functional/cosmetic disability [27,29]. The advantage of surgical resection over RT may be several-fold; RT has sequelae that can significantly impact the quality of life, including xerostomia, dysphagia, and osteoradionecrosis [29]. Moreover, the treatment course can be close to 2 months, whereas surgical treatment of early OSCC has a quicker recovery [29]. 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 future recommendation includes that emphasis should be made to follow guidelines designed to standardize the screening and reporting of any observational study to perform comparative studies in different populations. The importance of the development of a consensus of the ontology of oral cancers is also stressed upon. This would ease the process of systematic searching of the available literature with the elimination of potential bias. A countrywide screening of potential cancer risk in different public and private tertiary care centers will facilitate in establishing cancer control and will play a pivotal role in spreading awareness of this disease. This report will serve as a database of the OC burden in Northeastern Peninsular Malaysia.

Conclusion

Despite the presence of a high incidence of metastasis and a high proportion of cases who did not receive any form of treatment, around three-fourth of the total oral cancer patients were alive at the time of this study.

Authors' Contributions

PA	---	Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Project Administration and Funding Acquisition.
AIA	https://orcid.org/0000-0001-8318-5546	Formal Analysis, Investigation, Data Curation and Funding Acquisition.
MJ	---	Formal Analysis and Investigation.
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MKA	https://orcid.org/0000-0001-7131-1752	Conceptualization and Funding Acquisition.
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JAA	https://orcid.org/0000-0002-1785-6126	Conceptualization, Methodology, Writing - Original Draft and Writing - Review and Editing.
All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.		

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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