SURVIVAL RATE & MORTALITY RATE OF ORAL CANCER PATIENTS IN ORAL & MAXILLOFACIAL CLINICAL SCIENCES DEPARTMENT, FACULTY OF DENTISTRY, UNIVERSITY OF MALAYA: A RETROSPECTIVE STUDY

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FACULTY OF DENTISTRY
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RESEARCH REPORT SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER IN CLINICAL DENTISTRY (ORAL AND MAXILLOFACIAL SURGERY)

DEPARTMENT OF ORAL AND MAXILLOFACIAL CLINICAL SCIENCES, FACULTY OF DENTISTRY
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ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: Ahmad Fadhli Bin Ahmad Badruddin

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Field of Study: Oral and Maxillofacial Surgery

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ABSTRACT

Introduction: There have been great strides in the advancement of surgery and oncology however there have not been much improvement in survival rates of oral cancer patients. Limited studies have been performed in identifying significant predictors of survival rate for oral cancer in Malaysia. **Objectives:** The aim of this study was to investigate and analyze the survival rate and mortality rate of oral cancer patients presented at Oral & Maxillofacial Clinical Sciences Department, University of Malaya (OMCS, UM). **Methods:** This is a retrospective study involving 166 oral cancer patients seen in OMCS, UM from 1st March 1994 until 28th April 2019. Data collected include socio-demographic and clinic-pathologic factors. Survival analysis was done using SPSS version 23.0. Univariate and multivariate analysis were performed using the Kaplan-Meier method and Cox proportional hazards regression modal respectively. **Results:** The overall 5-year survival rate of oral cancer patients was 36.1% with a mean survival time of 159 months. Significant factors that influenced survival of oral cancer patients in this study were anatomic site, stage, histologic type, receiving treatment and surgery. Stage, receiving treatment and surgery were independent prognostic factors of survival rate. **Conclusion:** The 5-year survival rate of oral cancer patients in OMCS, UM were comparable to the survival rate reported for developing countries. Advanced stage of oral cancer and not receiving any treatment particularly surgery contributed to poor survival of oral cancer patients.

KEYWORDS: Oral cancer, survival rate, Malaysia

ABSTRAK

Pengenalan: Terdapat perkembangan yang pesat dalam bidang pembedahan dan onkologi namun tiada peningkatan dalam kadar kelangsungan hidup pesakit kanser mulut. Kajian terhad telah dilakukan dalam mengenal pasti peramal penting kadar kelangsungan hidup untuk kanser mulut di Malaysia. **Objektif:** Tujuan kajian ini adalah untuk menyiasat dan menganalisis kadar kelangsungan hidup dan mortaliti pesakit kanser mulut yang hadir di Jabatan Oral & Maxillofasial Klinikal Sains, Fakulti Pergigian, Universiti Malaya. **Kaedah:** Ini adalah kajian retrospektif yang melibatkan 166 pesakit kanser mulut yang dilihat di OMCS, UM dari 1 Mac 1994 hingga 28 April 2019. Data yang dikumpul termasuk faktor sosio-demografi dan klinikal-patologi. Analisis kelangsungan hidup dilakukan menggunakan SPSS versi 23.0. Analisis univariat dan multivariate dilakukan menggunakan kaedah Kaplan-Meier dan modal regresi hazard berkadaran Cox. **Keputusan:** Kadar kelangsungan hidup keseluruhan 5 tahun pesakit kanser mulut adalah 36.1% dengan masa hidup purata 159 bulan. Faktor penting yang mempengaruhi kelangsungan hidup pesakit kanser mulut dalam kajian ini adalah tapak anatomi, peringkat, jenis histologi dan pembezaan, dan rawatan yang diterima. Peringkat, menerima rawatan dan pembedahan adalah faktor prognostik bebas daripada kadar kelangsungan hidup. **Kesimpulan:** Kadar kelangsungan hidup 5 tahun pesakit kanser mulut di OMCS, UM adalah setanding dengan kadar kelangsungan yang dilaporkan untuk negara-negara membangun. Tahap lanjut dan tidak menerima apa-apa rawatan terutama pembedahan yang menyumbang kepada kelangsungan hidup pesakit kanser mulut.

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LIST OF SYMBOLS AND ABBREVIATIONS

AJCC	:	American Joint Committee of Cancer
DNA	:	Deoxyribonucleic acid
FOM	:	Floor of mouth
ICD	:	International Classification of Disease
NCCN	:	National Comprehensive Cancer Network
OMCS	:	Oral & Maxillofacial Clinical Sciences
OS	:	Overall survival
OSCC	:	Oral squamous cell carcinoma
SCC	:	Squamous cell carcinoma
UM	:	University of Malaya
WHO	:	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Background

Cancer carries a global burden to the world population. In 2018, 18.1 million new cancer cases and 9.6 million cancer deaths were reported. (GLOBOCAN 2018). Oral cancer ranks as the 6th most common cancer worldwide. More than 300,000 new cases of oral cancer were reported worldwide, with two-thirds diagnosed in developing countries (Bray et al., 2018). The highest incidence of these cancers is mainly reported in South and Southeast Asia and some countries in southern Europe. Oral squamous cell carcinoma (OSCC) constitutes 90% of oral malignancies making it as the most common oral cancer. In Malaysia, the prevalence of oral cancer was reported as 0.04% (R. B. Zain et al., 1997).

According to National Comprehensive Cancer Network (NCCN), the main treatment modalities for oral cancer are surgery, chemotherapy, radiotherapy or a combination. However, despite advances in management of patients, the survival rate of oral cancer remains low. Various studies have quoted that the 5-year survival rate of oral cancer is from 30-80%. This large range is due to a multitude of demographics and clinico-pathologic factors. Currently, there are not many studies conducted on oral cancer in Malaysia even though oral cancer is one of the top 10 cancers in the Indian ethnic group (Malaysian National Cancer Registry Report 2007-2011). According to World Health Organization (WHO), oral cancer deaths in Malaysia is as high as 1587 deaths in 2011. This highlights the importance of looking into prognostic factors that affect survival rates of oral cancer patients in Malaysia to assist in overall treatment planning that may improve patient outcome.

Research questions:

1. What are the survival and mortality rates of oral cancer patients?
2. Are there any socio-demographic or clinico-pathologic factors that influence the survival of oral cancer patients?

Aim:

To determine survival among oral cancer patients in OMCS, UM

Objectives:

1. To establish the survival and mortality rates of oral cancer patients
2. To identify any socio-demographic factors that influence the survival of oral cancer patients
3. To identify any clinico-pathologic factors that influence the survival of oral cancer patients

Null hypothesis:

Socio-demographic and clinico-pathological factors do not influence the survival of oral cancer patients

Clinical relevance of study:

Although there has been a huge amount of research and advances in the fields of oncology and surgery, the mortality rate of cancer remains largely unchanged. This shows the need for further research looking into factors associated with survival rates in oral cancer in order to provide better management and outcomes to individual patients.

CHAPTER 2: LITERATURE REVIEW

2.1 Definition of oral cancer

Oral cancer include cancers of the mucosal lip, tongue, gum, floor of the mouth, palate, and mouth. The World Health Organization (WHO) has developed the International Classification of Diseases (ICD), which is often used in defining oral cancer. The ICD allows specific anatomical sites in the mouth to be defined with specific codes. However it is impossible to fully define which sites of the mouth is considered oral cancer due to the complexity of the mouth (Moore et al., 2000). Therefore many studies have used a combination of selected ICD sites to allow proper representation of oral cancer such as the shown below.

Table 2.1: Classification of Anatomic Site of Oral Cancer According to ICD-10

ICD-10 Codes	Subsites
C00	Malignant neoplasm of lip
C00.0	External upper lip
C00.1	External lower lip
C00.2	External lip, unspecified
C00.3	Upper lip, inner aspect
C00.4	Lower lip, inner aspect
C00.5	Lip, unspecified, inner aspect
C00.6	Commissure of lip, unspecified
C00.8	Overlapping sites of lip
C00.9	Lip, unspecified
C01	Malignant neoplasm of base of tongue Applicable To • Malignant neoplasm of dorsal surface of base of tongue • Malignant neoplasm of fixed part of tongue NOS • Malignant neoplasm of posterior third of tongue
C02	Malignant neoplasm of other and unspecified parts of tongue
C02.0	Dorsal surface of tongue
C02.1	Border of tongue
C02.2	Ventral surface of tongue
C02.3	Anterior two-thirds of tongue, part unspecified
C02.4	Lingual tonsil
C02.8	Overlapping sites of tongue
C02.9	Tongue, unspecified

Table 2.2: Classification of Anatomic Site of Oral Cancer According to ICD-10, continued

C03	Malignant neoplasm of gum
C03.0	Upper gum
C03.1	Lower gum
C03.9	Gum, unspecified
	Includes • malignant neoplasm of alveolar (ridge) mucosa • malignant neoplasm of gingiva
C04	Malignant neoplasm of floor of mouth
C04.0	Anterior floor of mouth
C04.1	Lateral floor of mouth
C04.8	Overlapping sites of floor of mouth
C04.9	Floor of mouth, unspecified
C05	Malignant neoplasm of palate
C05.0	Hard palate
C05.1	Soft palate
C05.2	Uvula
C05.8	Overlapping sites of palate
C05.9	Palate, unspecified
C06	Malignant neoplasm of other and unspecified parts of mouth
C06.0	Cheek mucosa
C06.1	Vestibule of mouth
C06.2	Retromolar area
C06.8	Overlapping sites of other and unspecified parts of mouth
C06.80	Overlapping sites of unspecified parts of mouth
C06.89	Overlapping sites of other parts of mouth
C06.9	Mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08	Malignant neoplasm of other and unspecified major salivary glands
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified

2.2 Epidemiology of oral cancer

OSCC accounts for more than 90% of oral malignancy. According to Warnakulasuriya (2009), there is a wide geographical variation in the incidence of oral cancer. High incidence rates of oral cancer are found in the South and Southeast Asia, pats of Western and Eastern Europe, parts of Latin America and Caribbean and in the Pacific regions.

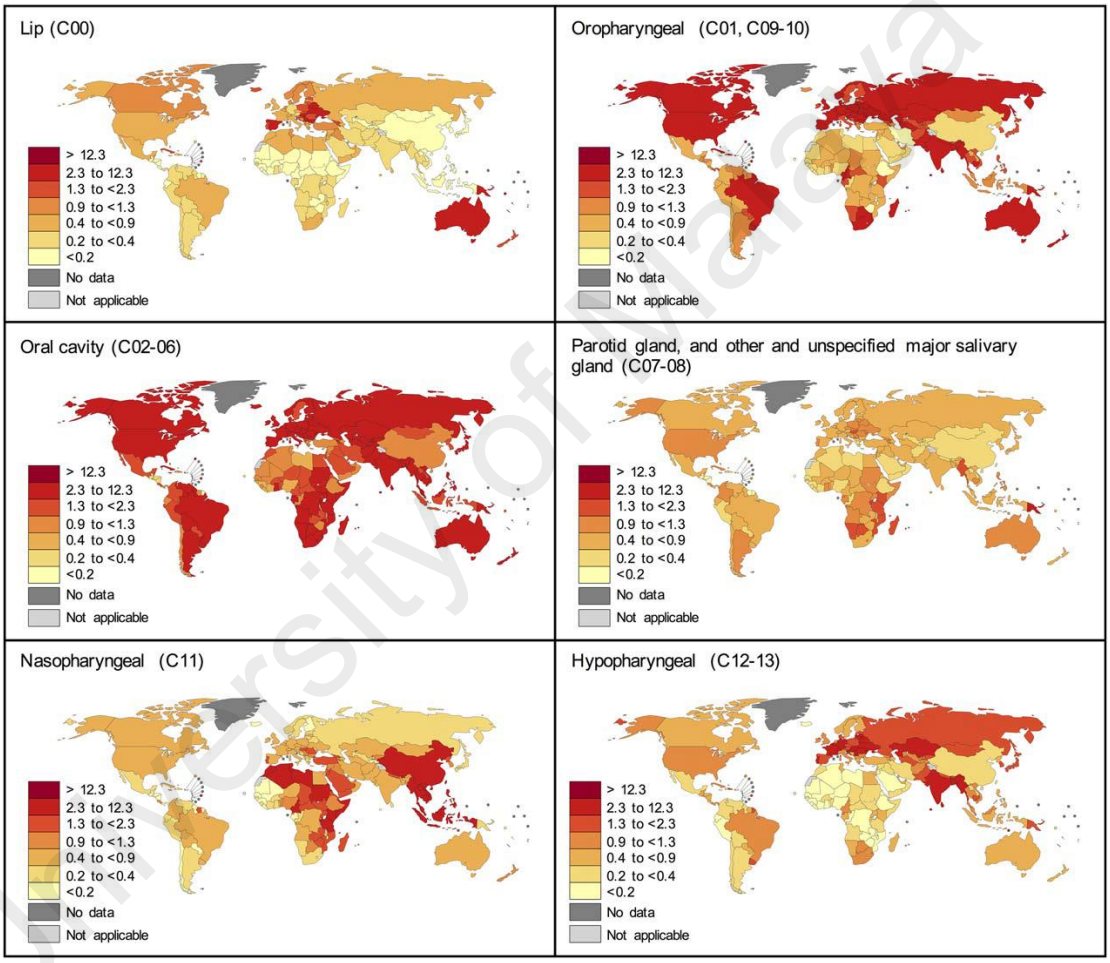

Figure 2.1: World Map of Age-Standardized Incidence Rates (per 100,000) of Lip, Oral Cavity, and Pharyngeal Cancers by Subsite in 2012 among Men.

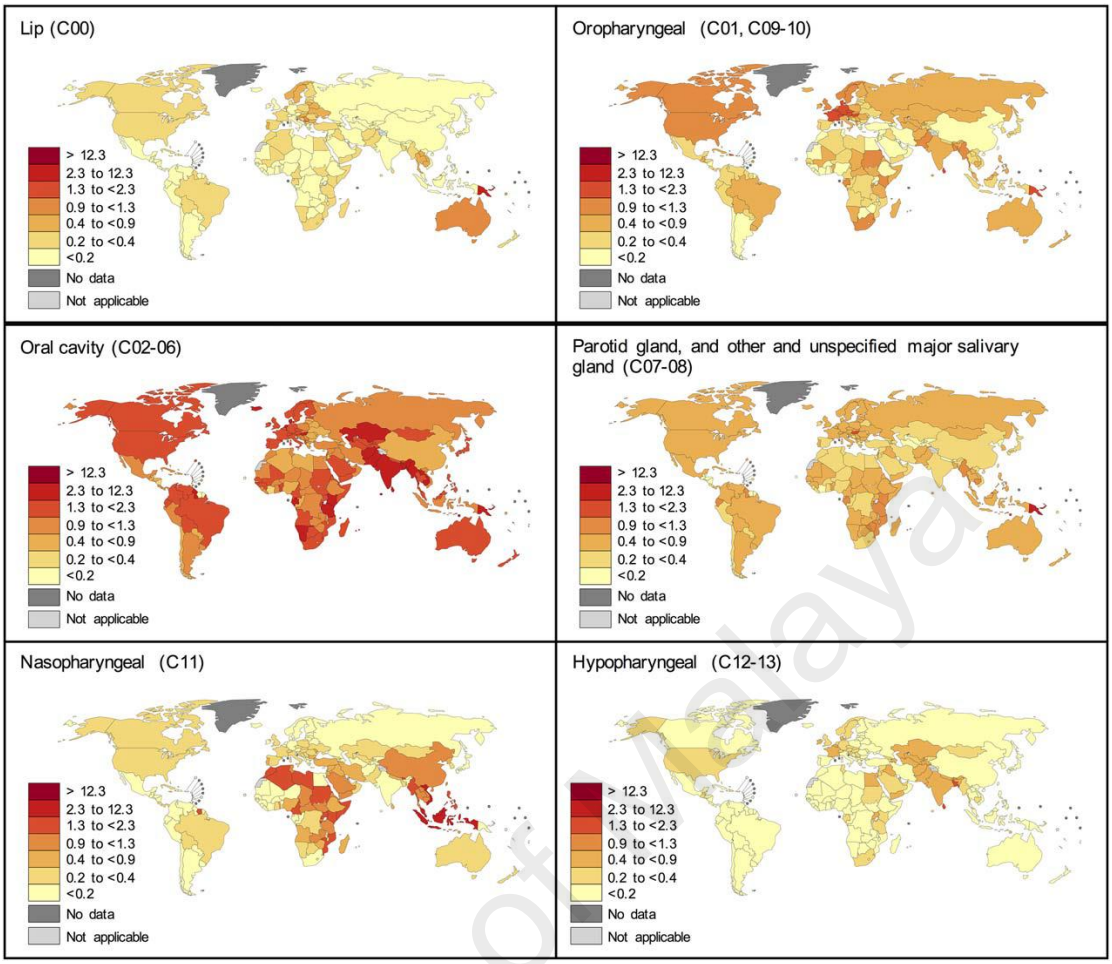

Figure 2.2: World Map of Age-Standardized Incidence Rates (per 100,000) of Lip, Oral Cavity, and Pharyngeal Cancers by Subsite in 2012 among Women.

As shown in Figure 2.1 and 2.2, oral cancer is more commonly found in men compared to in women in most countries. This could be due to heavier indulgence of risk habits. However there is a rising trend for incidence in females. It is also more commonly seen in people aged above 50 years old however in high-incidence countries, many cases are also reported in those below 45 years old with an increase in trend due to the combination of HPV infection and cigarette smoking (M Schwartz et al., 1998). In terms of anatomic sites, tongue has been reported as the most common site among European and US population however in Asian population, buccal and gingiva cancers are more common due to betel quid chewing habits.

In Malaysia, Hirayama (1966) observed that the incidence of oral cancer varied according to states, where the highest rate was seen in Selangor. Hirayama attributed this to a higher proportion of the Indian ethnic group residing in Selangor compared to other states. Other studies done in Malaysia also showed that oral cancer were higher in the Indian ethnic group compared to other ethnic groups (H Ng et al., 1986).

2.3 Risk factors

There have been a number of studies looking into the etiology of oral cancer and it is considered to be multifactorial. According to available evidences, the risk factors of oral cancer could be grouped as established, strongly suggestive, possible and speculative factors as the table shown below.

Table 2.3: Risk factors for Oral Cancers and Precancers by Warnakulasuriya (2009)

Established	Strongly suggestive	Possible	Speculative
Smoking	Sunlight (Lip)	Viruses	Mouthwash
Chewing tobacco	Radiation	Immune deficiency	Mate drinking
Snuff dipping		Dentition?	Periodontal disease
Alcohol misuse		Ethnicity?	Familial
Betel quid			
Syphilis			

Oral cancer is considered a preventable disease, as the major risk factors are habits such as smoking, alcohol consumption and betel quid chewing. Smokers are three times more likely to develop oral cancer compared to nonsmokers (Gandini et al., 2008). The cigarette smoke contains several elements that promotes gingivitis, periodontitis and oral cancer by weakening the oral immunity. These elements such as nitrosamines, benzopyrenes and aromatic amines are precarcinogens (Rivera, 2015b).

Alcohol (ethanol) is one of the risk factor that can act both systematically and locally. It increases the permeability of oral mucosa towards carcinogens and interferes in DNA synthesis and repair resulting in a higher susceptibility to infections and neoplasms (Reidy et al., 2011). Smoking and alcohol consumption have a synergic effect where heavy smokers and drinkers have an increased risk of 38 times of oral cancer.

Betel quid chewing is another established risk factor for oral cancer that is associated with lifestyle habit especially in the South and Southeast Asia and Pacific Islands. It was demonstrated by a few studies that betel quid chewing without tobacco elevates the risk of multiple oral precancerous lesions (Jacob et al., 2004). Guha et al. (2014) demonstrated that risk of oral cancer is increased with increasing duration and frequency of betel quid chewing. In Malaysia, betel quid chewing is practiced by the Indians, the elderly Malays and the indigenous people of Sabah and Sarawak (R. Zain & Ghazali, 2001).

It is interesting to note that for oral cancer in young people (under the age of 45 years old), about 25% of these group had little, if any, exposure to the major risk factors of oral cancer (Llewellyn et al., 2004).

2.4 Staging of oral cancer

Oral cancer is often diagnosed in advanced stages and according to a study done by Markopoulos (2012) this is due to patient ignorance or initial misdiagnosis by the treating professional. As in most other cancers, the prognosis of oral cancer is largely dependent on several factors such as continuation of high-risk lifestyle habits, medical comorbidity and the stage of the cancer.

The TNM staging system is a classification system maintained by the American Joint Committee of Cancer (AJCC). It classifies the stages of cancer according to the

primary tumor (T), regional lymph nodes (N) and distant metastasis (M) as outlines in the table below.

Table 2.4: The 8th edition of TNM staging system by AJCC

Definition of Primary Tumor (T)	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤ 2cm with depth of invasion (DOI) ≤ 5mm
T2	Tumor ≤ 2cm with DOI* > 5mm Or Tumor > 2cm and ≤ 4cm with DOI* ≤ 10mm
T3	Tumor > 2cm and ≤ 4cm with DOI* > 10mm Or Tumor > 4cm with DOI* ≤ 10mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor > 4cm with DOI* > 10mm Or tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face) Note : Superficial erosion of bone/tooth socket by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery
*DOI is depth of invasion and not tumor thickness	
Definition of Regional Lymph Node (N) Clinical N (cN)	
N Category	**cN Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in single ipsilateral node, 3cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in single ipsilateral node, larger than 3cm but not larger than 6cm in greatest dimension, and ENE(-); Or metastasis in multiple ipsilateral lymph nodes, none larger than 6cm in greatest dimension, and ENE(-); Or in bilateral or contralateral lymph nodes, none larger than 6cm in greatest dimension, and ENE(-)
N2a	Metastasis in single ipsilateral node, larger than 3cm but not larger than 6cm in greatest dimension, and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6cm in greatest dimension, and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6cm in greatest dimension, and ENE(-)

Table 2.5: The 8th edition of TNM staging system by AJCC, continued

N3	Metastasis in a lymph node larger than 6cm in greatest dimension and ENE(-); Or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6cm in greatest dimension and ENE(-)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).

Definition of Distant Metastasis (M)

The terms pM0 and Mx are NOT valid categories in the TNM system. Assignment of the M category for clinical and pathological classification maybe cM0, cM1, or pM1.

M Category	**M Criteria**
cM0	Regional lymph nodes cannot be assessed
cM1	No regional lymph nodes metastasis
pM1	Distant metastasis

AJCC Prognostic Stage Groups

When the T is…	When the N is…	When the M is…	And the stage group is…
Tis	N0	M0	0
T0	N0	M0	I
T1	N0	M0	II
T2	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Clinical examination and imaging are used to obtain a clinical stage (cTNM), which allows treatment planning for the patient. A pathologic stage (pTNM) is derived from resected tumour and regional lymph nodes, which is useful in deciding postoperative adjuvant therapy. Both clinical and pathologic stage can be used to stratify patients into early stage (Stage I and II) and advanced stage (Stage III and IV).

2.5 Treatment of oral cancer

To improve the survival of oral cancer patients, early diagnosis and treatment is essential (Mehrotra & Gupta, 2011). Treatment approaches to oral cancer include surgery, radiation and chemotherapy or a combination of these approaches. In addition to the gold standard treatment modalities available, the new emerging role of immunotherapy in head and neck cancer shows the promising role of the immune system in oncogenesis and tumor evolution (Economopoulou et al., 2016). The decision for which treatment modality is best for individual patient is dependent of a variety of factors including the stage, the medical comorbidities and patient's choice. According to Rivera (2015a) surgery is still considered superior to all alternative therapies in resectable oral cancer.

Due to oral cancers being in a highly visualized area, patients have to cope with devastating consequences after treatment affecting their quality of life. Apart from that, there is a higher risk of multiple primary cancer in younger patients, those who continue to smoke and consume alcohol after therapy and those treated with radiotherapy alone (Warnakulasuriya, 2009).

2.6 Survival rate of oral cancer

Generally, the prognosis of oral cancer decreases with advanced disease. For patients diagnosed in Stage I and II of oral cancer, the cure rates are quite high at 80% for Stage I and 65% for Stage II. However, as most oral cancer cases are diagnosed in advanced stages (Stage III and IV), the 5 years survival rate is less than 50% (Viet & Schmidt, 2012). Untreated patients or those with distant metastasis show about 4 months of survival (Kowalski et al., 2000).

2.7 Factors affecting survival rate of oral cancer

Various amount of studies have looked into factors affecting or associated with survival rates of oral cancer. These factors are divided into socio-demographic factors and clinico-pathologic factors. Socio-demographic factors look into the combination of social and demographic information of the patient while clinico-pathologic factors are factors involving clinical and pathological findings of the cancer.

2.7.1 Socio-demographic factors

Massano et al. (2006) reviewed articles that looked into factors that influence prognosis of oral cancer patients. In terms of gender, Massano et al. (2006) reported no prognostic differences between genders however Leite and Koifman (1998) reported lower survival rates in females due to lower acceptance of treatment. Johnson (2001) conversely, reported lower rates in males due to increased exposure to carcinogenic factors such as tobacco and alcohol.

In terms of age, the correlation with prognosis is controversial. Many studies reported no relationship (Chandu et al., 2005; El-Husseiny et al., 2000; Lo et al., 2003; Sargeran et al., 2008). However Leite and Koifman (1998) and Ribeiro et al. (2003) showed worse prognosis in older patients. Ribeiro theorised older patients have more medical comorbidity thus worsening the outcome. A study done by Balasundram et al. (2012) in Malaysia showed significant difference of overall survival between the Malay and Chinese race groups and attributed this to earlier presentation of Chinese patients as a contributing factor for better survival rates.

As tobacco, alcohol and betel quid chewing are major risk factors for oral cancer, it can be speculated that these factors are associated with poorer survival rates however various studies have found no associated between survival and tobacco or alcohol consumption (Y. K. Chen et al., 1999; Lo et al., 2003; Vallecillo Capilla et al., 2008).

However, Leite and Koifman (1998) found higher mortality rates in smokers and alcohol drinkers as they are at higher risk of developing second primary cancers thus giver poorer outcome. Apart from that, Lo et al. (2003) found that betel quid whether consumed alone or in combination with smoking and/or alcohol increased the likelihood of death thus affecting survival.

2.7.2 Clinico-pathologic factors

Different anatomic sites of the lip and oral cavity have various vascular and lymphatic networks therefore site of cancer would be an important influence of prognosis as it influences the ease of early diagnosis and surgical accessibility in getting sufficient margins. Leite and Koifman (1998)showed higher mortality rates in patients with tongue cancer than those with lip cancer.

Warnakulasuriya (2009) found that the TNM stage at presentation significantly affects the 5-year survival. It was reported that the 5-year survival for stage I disease is 80% whereas for stage IV, the survival drops to 15%. This is further supported by other studies that reported advance stages of oral cancer at time of diagnosis is associated with shorter survival (Sargeran et al., 2008; Vallecillo Capilla et al., 2008; Yeole et al., 2003).

Histological examination of tumour classifies cancer cell differentiation into well, moderate and poorly differentiated carcinomas. According to Fortin et al. (2001), well-differentiated OSCC usually invades connective tissues, muscle or bone before metastasizing to regional lymph nodes whereas poorly-differentiated OSCC is more aggressive and tends to metastasize early in the course of the disease. Apart from that, Robert et al. (2018) reported that there was a clear overexpression of resistance genes in cancer cells compared to the normal cells to chemotherapeutic drugs and observed that well-differentiated tumour which mostly resembles normal cells have better prognosis compared to poorly differentiated tumours. However other studies found no association

between different histologic types and prognosis (El-Husseiny et al., 2000; Leite & Koifman, 1998).

Regarding treatment modalities, the overall survival rate of surgical treatment and surgical treatment accompanied by postoperative radiotherapy was reported by Brown et al. (2012) as 71% and 54% respectively. Zheng et al. (2008) hypothesized this is because only patients with early stage cancer would be recommended for surgery alone. A study conducted by Abdul Razak et al. (2010) reported all untreated patient died and none that was treated with radiotherapy or chemotherapy alone survived for 5 years. Similar outcomes were also reported by P. H. Chen et al. (2004); Leite and Koifman (1998) and Sargeran et al. (2008).

CHAPTER 3: METHODOLOGY

3.1 Materials

The records of 221 patients with oral cancer from 1st March 1994 to 28th April 2019 in OMCS, UM were reviewed. 55 patients were excluded due to incomplete records. A total of 166 patients were included for data analysis.

3.2 Methods

Ethical approval was obtained from The Medical Ethics Committee, Faculty of Dentistry, UM. The medical files of the 166 patients were analyzed and reviewed. Upon confirmation of oral cancer according to the primary histopathological report from biopsy, the details of patients were obtained. The collected data included demographic data such as age, gender, race, high-risk habits (smoking, alcohol, betel quid) and clinico-pathologic data such as primary anatomic tumour site, TNM stage, date of diagnosis, histologic type and differentiation, treatment received, presence of recurrence and current status (alive or deceased). Validation of survival status was done until 30th April 2019 either by checking last review input on the year of 2018 and 2019 or by calling via telephone to determine duration and survival status of patients.

Collected data was then input in Microsoft Excel (version 2013) and analyses of these results were done using the SPSS for Windows (version 23.0). Descriptive statistics were used to summarize the study data. The Overall Survival (OS) was defined as the interval between the date of diagnosis and the date of death or last follow up. OS was determined by survival analysis life tables. Univariate analysis of the variables was performed using the Kaplan-Meier method and log rank test. Multivariate analysis was done using the Cox Proportional Hazards Regression Model to analyze independent prognostic properties. Statistical significance was defined as a 2-tailed *p*-value of < 0.05.

Data on 4 demographic (age, gender, race and risk habits) and 5 clinico-pathologic (anatomic site, stage, histologic type and differentiation, treatment modalities) factors on each patients were compiled as covariates for analysis.

CHAPTER 4: RESULTS

4.1 Characteristics of patients

Out of 166 patients diagnosed with oral cancer that was included in this study, a total of 61 patients have deceased giving a mortality rate of 36.7%. The mean survival time is 129.9 months. 80.1% of patients survived at least 1 year after diagnosis and 55.4% survived for the first 3 years. A total of 60 patients survived after 5 years of diagnosis giving an overall 5-year survival rate of 36.1%. The survival probability curve is presented in Figure 4.1. The survival curves shows that there is a steady decline within the first 80 months and then it gradually stabilizes.

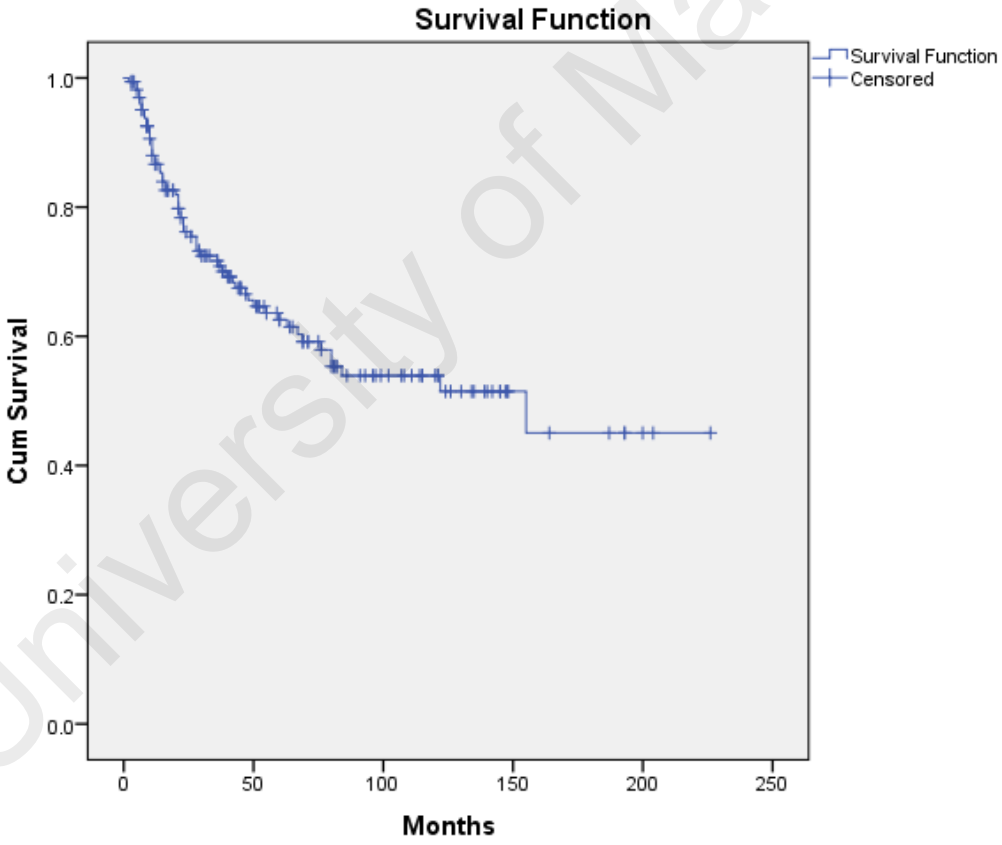

Figure 4.1: Kaplan-Meier Curve for Oral Cancer Survival among Oral Cancer Patients in OMCS, UM.

4.2 Socio-demographic factors

There is a wide age range for 166 patients in this study between the ages of 18 to 92 years old. The mean age was 59.6 ± 13.7 years old. Most patients were above 60 years old (n=87). In terms of gender, the male-to-female ratio was 1:1.4 (67 males, 99 females). The mean survival time for female was 135.6 ±12.1 months and 105.9 ±12.7 months for male. For race, the majority for this study were Chinese (45.8%) followed by Indian (37.3%), Malay (13.9%) and other ethnic groups (3%).

Data on risk factors of oral cancer such as smoking, alcohol consumption and betel quid chewing were obtained. More than 30 patients had two or more risk factors. At the time of diagnosis, 24.1% of patients were smoking, 18.1% were consuming alcohol and 21.2% were chewing betel quid. There were no significant statistical correlation between survival rate and age, gender, race or risk factors (smoking, alcohol or betel quid) as shown in Table 4.1.

Table 4.1: *p*-values of Socio-demographic variables on Kaplan-Meier survival analysis

Variables	N	Survival	95% CI	χ 2 (d.f.)	*p*-value
Age (years)					
< 60	79	148.6	124.9, 172.2	3.588 (1)	0.058
≥ 60	87	96.1	74.3, 118.0		
Gender					
Male	67	105.9	81.0, 130.8	0.828 (1)	0.363
Female	99	135.6	111.8, 159.3		
Race					
Malay	23	92.5	65.6, 119.4	3.738 (3)	0.291
Chinese	76	127.8	104.7, 150.9		
Indian	62	124.3	97.4, 151.3		
Others	5	40.8	8.7, 72.7		
Risk Factor					
Yes	83	106.8	85.4, 128.2	3.956 (1)	0.047
No	81	144.7	115.7, 173.8		
Smoking					
Ever	41	99.0	70.0, 127.9	1.600 (1)	0.206
Never	125	135.7	113.7, 157.8		
Alcohol					
Ever	30	109.1	74.8, 143.4	0.379 (1)	0.538
Never	136	131.6	110.9, 152.3		
Betel quid					
Ever	36	103.0	72.8, 133.2	2.592 (1)	0.107
Never	130	135.9	113.5, 158.4		

p – value < 0.005

4.3 Clinico-pathologic factors

Some of the clinico-pathologic factors that was studied included anatomic site, TNM stage, histologic differentiation and treatment received as shown in Table 4.2. There was a significant statistical correlation between anatomic site, stage, treatment and survival.

Table 4.2: *p*-values of Clinico-pathologic Variables on Kaplan-Meier Survival Analysis

Variables	N	Survival	95% CI	χ 2 (d.f.)	*p*-value
Anatomic site					
Lip	4	99.7	75.1, 124.2	26.4 (9)	0.002
Base of tongue	0	0	0, 0		
Other parts of tongue	65	151.0	121.4, 180.5		
Gingiva	25	88.5	81.6, 115.5		
FOM	3	57.3	37.4, 77.3		
Palate	4	32.0	13.6, 50.4		
Buccal mucosa	42	119.9	90.6, 149.2		
Retromolar	4	30.3	10.0, 50.5		
Salivary glands	10	94.0	59.0, 129.0		
Mandible	4	16.0	10.3, 21.7		
Maxilla	5	83.0	42.3, 123.7		
TNM Stage					
Stage I	37	174.8	155.1, 194.4	21.4 (3)	< 0.001
Stage II	32	151.2	115.0, 187.4		
Stage III	24	94.2	64.8, 123.6		
Stage IV	73	91.7	69.3, 114.1		
Histologic differentiation					
Well differentiated	61	106.9	82.7, 131.0	2.772 (2)	0.250
Moderately differentiated	68	133.0	109.3, 156.7		
Poorly differentiated	5	58.2	13.3, 103.1		
Treatment					
None	7	8.714	7.4, 10.0	80.2 (1)	< 0.001
Yes	159	135.6	116.3, 154.8		
Surgery	131	152.4	131.6, 173.1	51.3 (1)	< 0.001
Radiotherapy	87	102.7	80.3, 125.0	3.048 (1)	0.081
Chemotherapy	38	66.2	47.7, 84.8	7.473 (1)	0.006

p – value < 0.005; SCC, squamous cell carcinoma

Of the sites of oral cancer, the tongue (n=65) and the buccal mucosa (n=42) accounted for more than half of the cases (64.5%). Less frequent sites include lip (2.4%),

floor of the mouth (1.8%), palate (2.4%), retromolar (2.4%), mandible (2.4%) and maxilla (3%). Salivary glands accounted for 6% of the patients whereas 15.1% were at the gingiva.

Three (1.8%) were found to have distant metastasis on the first visit which received focal radiation with chemotherapy for tumour control. Most of the patients presented at an advanced stage (Stage III and Stage IV). 44% of patients were Stage 4 whereas only 22.3% and 19.3% were of Stage I and Stage II respectively. The 5-year survival rates were 23.3% for Stage I, 35% for Stage II, 21.7% for Stage III, and 20% for Stage IV patients which showed lower rates for advance stage compared to early stage of oral cancer. 147 out of 166 patients (88.6%) were diagnosed with oral squamous cell carcinoma (OSCC) in which the majority of tumors showed a moderately differentiated pattern, (68 out of 134; 50.7%).

Only 7 patients did not have any treatment done and none survived more than 1 year after diagnosis. 78.9% of patients had surgery done within a month of diagnosis. About half of the patients (n=87) were given radiotherapy and a quarter (n=38) received chemotherapy.

Multivariate analysis using Cox proportional hazard regression modal identified 3 significant prognostic factors of oral cancer among patients in OMCS, UM. The significant independent variables were stage of cancer, treatment and surgery as shown in Table 4.3.

Table 4.3: Significant Prognostic Factors for Oral Cancer Patients using the Cox Proportional Hazards Regression Model

Variable	b Coefficient	Adjusted HR	95% CI	*p*-value
Stage	0.448	1.566	1.139, 2.151	0.006
Surgery	-1.430	0.239	0.122, 0.468	<0.001
Treatment	-1.733	0.177	0.059, 0.534	0.002

p – value < 0.005

CHAPTER 5: DISCUSSION

This study retrospectively analyzed the records of 166 cases of oral cancer mainly oral squamous cell carcinoma (SCC) collected from 1st March 1994 to 28th February 2019 in OMCS, UM to determine the survival and mortality rates and also to identify the socio-demographics and clinico-pathological characteristics of oral cancer patients that are associated with survival. Results obtained from this study showed a mortality rate of 36.7% due to oral cancer. The five-year survival rate is 36.1%, which is higher than a study conducted by Abdul Razak et al. (2010) in Hospital Universiti Sains Malaysia, Kelantan, however similar to that reported from other developing countries (Sargeran et al., 2008).

In terms of demographic factors, this study looked into age, gender, race and risk factors of oral cancer patients. The results showed that all the demographic factors were not associated with the overall survival of oral cancer patients. Oral cancer has been seen as a disease of the older age group where the risk developing oral cancer increases with age (Warnakulasuriya, 2009). Although there have been studies reporting age association with survival rates, our findings did not find the correlation.

In terms of gender, there seems to be no clear association between gender and oral cancer survival rates. Traditionally, oral cancer has been reported as a disease in males however there is an increasing incidence in females being reported. Some studies have shown that males had poorer survival rate however other studies reported no difference

in survival between male and female patients. This study showed no correlation between gender and survival rates of oral cancer patients.

The Malaysian population is multi-ethnic with the largest ethnic group of Malays (50.8%). Other ethnic groups are Chinese (26.3%), Indians (7.5%) and others (3.5%). According to a survey conducted by the Division of Stomatology at the Malaysian Institute of Medical Research, oral cancers occurred more commonly amongst the Indian ethnic group (59.3%). The result of this study showed that race is not significantly associated with survival rates of oral cancer.

Warnakulasuriya (2009) established that tobacco and alcohol consumption are risk factors for oral cancer which may act synergistically or separately. Previous researches have shown that the combined use of cigarette smoking and alcohol consumption is associated with poorer prognosis (Gervásio et al., 2001). However it is unclear whether these risk factors act independently on survival rates. The results for this study showed cigarette smoking and alcohol were not associated with the survival of oral cancer patients.

In Malaysia, areca nut exposure via betel quid chewing is also an established risk factor for oral cancer where it is the most common single habit among the population (Ghazali et al., 2006). Although Y. K. Chen et al. (1999) and Lo et al. (2003) demonstrated that betel quid chewing in Taiwan increased the likelihood of death due to oral cancer, this was not seen in this study.

In terms of clinic-pathological factors, this study looked into anatomic site, TNM staging, histopathological examination and treatment modalities. Vallecillo Capilla et al. (2008) emphasized the importance of the primary tumour site on prognosis where the study showed oral cancer occurrence at gingiva and retromolar trigone area caries a

greater risk of mortality compared to palate, tongue, floor of the mouth and other sites in the oral cavity. This result of this study showed that most patients developed oral cancer at tongue. According to ICD-10 (CD02) this covers all areas of the tongue except for base of the tongue. The results of this study showed that anatomic site is significantly associated with survival rate. Although Leite and Koifman (1998) showed a higher mortality rate in tongue cancers compared to lip, this study reported otherwise. This could be because most of the tongue cancer cases (53.8%) in this study presented at early stage (Stage I and Stage II). Retromolar region had one of the worst survival rate in this study likely because it is an area of limited surgical accessibility therefore difficult to achieve safe oncological margins.

One of the most important prognostic factor for oral cancer is clinical stage presentation. TNM staging is often used for staging cancers especially head and neck cancers. The latest edition of TNM staging by AJCC looks into the size and depth of invasion (T), spread of cancer into regional lymph nodes (N) and metastasis of cancer to other parts of the body (M). 58.5% of the patients in this study presented to our centre at Stage III and IV where the survival rate is significantly lower as compared to Stage I and Stage II. One of the reasons why most of the patients in this particular study presented at a late stage is due to our centre being a tertiary centre at a teaching hospital. Patients that are being referred are usually challenging cases where other hospitals are unable or not fully equipped to handle such cases. Apart from that, according to a study conducted by Ghani et al. (2013), only a minority of Malaysian are able to recognize early signs of cancer leading to patients presenting at a much later stage. Many studies such as Yeole et al. (2003) and Sargeran et al. (2008) have showed that advanced stages of oral cancer at the time of diagnosis are associated with shorted survival. This is shown in this study as well.

Most of oral cancer comprises of oral squamous cell carcinoma (OSCC) where it is often graded into types of differentiation in histopathological aspect such as well-differentiated, moderately differentiated and poorly differentiated. Types of differentiation has no association with survival rate in this study. This could be due to misrepresentation of differentiation based on biopsy results instead of surgical histopathological grading.

Furthermore, this study showed that undergoing treatment is one of the independent significant predictor of survival for oral cancer. Patients who did not undergo treatment died in less than a year. Surgery is significantly associated with higher survival rates compared to radiotherapy and chemotherapy. Surgery is still deemed as the best treatment modality when treating oral cancer (Shah & Gil, 2009) and it is often the choice of treatment for those diagnosed in early stage. Other authors such as Brown et al., (2012) have showed that surgery is associated with better survival rates. In addition to surgery, this study also showed that chemotherapy is significantly associated with better survival rates although radiotherapy showed no association. This could be because chemotherapy is often given as an adjuvant to surgery however radiotherapy could be offered as a primary treatment modality for oral cancer.

CHAPTER 6: CONCLUSSION

In conclusion, cancer remains one of the most common causes of morbidity and mortality today. The global incidence of oral cancer is on the rise with the highest incidence rates reported in the Asian region. In Malaysia, oral cancer is the 19th most common cancer where it predominantly occurs in the Indian ethnic group. However, despite effective treatment efforts and advancement in the field of oncology, the 5-year survival rate for head and neck cancer is less than 50%.

This study showed that the 5-year survival rate for oral cancer patients presented in OMCS, UM was 36.1% and the mortality rate was 36.7%. This figure is comparable to other studies that have been reporting a wide range of survival rate between 30%-80%. Apart from that, this study also showed several clinico-pathologic factors that correlated with survival rates. The stage of oral cancer upon diagnosis, receiving treatment and having surgery were shown to be independent prognostic factors of survival rate. An advanced stage (Stage III and Stage IV), not receiving any treatment and not having surgery reduces patient survival.

There are several limitations to this study. Although this study looked into oral cancer patients during a long period of time, many patients had to be excluded from the study due to incomplete or missing data. This highlights the importance of meticulous note-keeping and continuous follow-up. Apart from that, this study only looked into oral cancer patients presented at OMCS department rather than all the departments in UM that manages oral cancer patients as well. Therefore, the figures given in this study may represent only a small population of oral cancer patients.

Further studies are needed to produce a complete survival analysis on oral cancer patients that would greatly accommodate clinicians in giving high standards of care and

management to patients. A prospective study controlling various socio-demographic and clinico-pathologic factors in determining independent prognostic factors on survival rate might yield a more accurate result.

REFERENCES

Abdul Razak, A., Saddki, N., Naing, N. N., & Abdullah, N. (2010). *Oral Cancer Survival among Malay Patients in Hospital Universiti Sains Malaysia, Kelantan* (Vol. 11).

Balasundram, S., Mustafa, W. M. W., Ip, J., Adnan, T. H., & Supramaniam, P. (2012). Conservative neck dissection in oral cancer patients: a 5 year retrospective study in Malaysia. *Asian Pacific Journal of Cancer Prevention, 13*(8), 4045-4050.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin, 68*(6), 394-424. doi:10.3322/caac.21492

Brown, J. S., Shaw, R. J., Bekiroglu, F., & Rogers, S. N. (2012). Systematic review of the current evidence in the use of postoperative radiotherapy for oral squamous cell carcinoma. *Br J Oral Maxillofac Surg, 50*(6), 481-489. doi:10.1016/j.bjoms.2011.08.014

Chandu, A., Adams, G., & Smith, A. C. H. (2005). Factors affecting survival in patients with oral cancer: an Australian perspective. *International Journal of Oral and Maxillofacial Surgery, 34*(5), 514-520. doi:https://doi.org/10.1016/j.ijom.2004.10.006

Chen, P. H., Ko, Y. C., Yang, Y. H., Lin, Y. C., Shieh, T. Y., Chen, C. H., & Tsai, C. C. (2004). Important prognostic factors of long-term oropharyngeal carcinoma survivors in Taiwan. *Oral Oncol, 40*(8), 847-855. doi:10.1016/j.oraloncology.2004.03.006

Chen, Y. K., Huang, H. C., Lin, L. M., & Lin, C. C. (1999). Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan. *Oral Oncol, 35*(2), 173-179.

Economopoulou, P., Perisanidis, C., Giotakis, E. I., & Psyrri, A. (2016). The emerging role of immunotherapy in head and neck squamous cell carcinoma (HNSCC): anti-tumor immunity and clinical applications. *Ann Transl Med, 4*(9), 173. doi:10.21037/atm.2016.03.34

El-Husseiny, G., Kandil, A., Jamshed, A., Khafaga, Y., Saleem, M., Allam, A., . . . Flores, A. D. (2000). Squamous cell carcinoma of the oral tongue: an analysis of prognostic factors. *British Journal of Oral and Maxillofacial Surgery, 38*(3), 193-199. doi:https://doi.org/10.1054/bjom.1999.0235

Fortin, A., Couture, C., Doucet, R., Albert, M., Allard, J., & Tetu, B. (2001). Does histologic grade have a role in the management of head and neck cancers? *J Clin Oncol, 19*(21), 4107-4116. doi:10.1200/jco.2001.19.21.4107

Gandini, S., Botteri, E., Iodice, S., Boniol, M., Lowenfels, A. B., Maisonneuve, P., & Boyle, P. (2008). Tobacco smoking and cancer: A meta-analysis. *International journal of cancer, 122*(1), 155-164.

Gervásio, O., Dutra, R. A., Tartaglia, S., Vasconcellos, W. A., Barbosa, A. A., & Aguiar, M. (2001). Oral squamous cell carcinoma: a retrospective study of 740 cases in a Brazilian population. *Braz Dent J, 12*(1), 57-61.

Ghani, W. M., Doss, J. G., Jamaluddin, M., Kamaruzaman, D., & Zain, R. B. (2013). Oral Cancer Awareness and its Determinants among a SelectedMalaysian Population. *Asian Pacific Journal of Cancer Prevention, 14*(3), 1957-1963.

Ghazali, N., Zain, R. B., Samsudin, A. R., & Raman, R. A. (2006). The Incidence of Mouth, Tongue and Lip Cancers in Kelantan, Malaysia. *Malaysian Dental Journal, 27*(2), 82-89.

Guha, N., Warnakulasuriya, S., Vlaanderen, J., & Straif, K. (2014). Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. *Int J Cancer, 135*(6), 1433-1443. doi:10.1002/ijc.28643

H Ng, K., H Siar, C., Ramanathan, K., Murugasu, P., & I Chelvanayagam, P. (1986). *Squamous cell carcinoma of the oral mucosa in Malaysia. Any change?* (Vol. 16).

Hirayama, T. (1966). An epidemiological study of oral and pharyngeal cancer in Central and South-East Asia. *Bull World Health Organ, 34*(1), 41-69.

Jacob, B. J., Straif, K., Thomas, G., Ramadas, K., Mathew, B., Zhang, Z. F., . . . Hashibe, M. (2004). Betel quid without tobacco as a risk factor for oral precancers. *Oral Oncol, 40*(7), 697-704. doi:10.1016/j.oraloncology.2004.01.005

Johnson, N. (2001). Tobacco use and oral cancer: a global perspective. *J Dent Educ, 65*(4), 328-339.

Kowalski, L. P., Bagietto, R., Lara, J. R. L., Santos, R. L., Silva Jr, J. F., & Magrin, J. (2000). Prognostic significance of the distribution of neck node metastasis from oral carcinoma. *Head & Neck, 22*(3), 207-214. doi:10.1002/(SICI)1097-0347(200005)22:3<207::AID-HED1>3.0.CO;2-9

Leite, I. C. G., & Koifman, S. (1998). *Survival analysis in a sample of oral cancer patients at a reference hospital in Rio de Janeiro, Brazil* (Vol. 34).

Llewellyn, C. D., Linklater, K., Bell, J., Johnson, N. W., & Warnakulasuriya, S. (2004). An analysis of risk factors for oral cancer in young people: a case-control study. *Oral Oncol, 40*(3), 304-313.

Lo, W. L., Kao, S. Y., Chi, L. Y., Wong, Y. K., & Chang, R. C. (2003). Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. *J Oral Maxillofac Surg, 61*(7), 751-758.

M Schwartz, S., R Daling, J., R Doody, D., Wipf, G., Carter, J., Madeleine, M., . . . Galloway, D. A. (1998). *Oral Cancer Risk in Relation to Sexual History and Evidence of Human Papillomavirus Infection* (Vol. 90).

Markopoulos, A. K. (2012). Current aspects on oral squamous cell carcinoma. *Open Dent J, 6*, 126-130. doi:10.2174/1874210601206010126

Massano, J., Regateiro, F. S., Januário, G., & Ferreira, A. (2006). Oral squamous cell carcinoma: review of prognostic and predictive factors. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontology, 102*(1), 67-76.

Mehrotra, R., & Gupta, D. K. (2011). Exciting new advances in oral cancer diagnosis: avenues to early detection. *Head & Neck Oncology, 3*(1), 33. doi:10.1186/1758-3284-3-33

Moore, S. R., Pierce, A. M., & Wilson, D. F. (2000). 'Oral cancer'--the terminology dilemma. *Oral Dis, 6*(3), 191-193.

Reidy, J., McHugh, E., & Stassen, L. F. A. (2011). A review of the relationship between alcohol and oral cancer. *The Surgeon, 9*(5), 278-283. doi:https://doi.org/10.1016/j.surge.2011.01.010

Ribeiro, K. D. B., Kowalski, L. P., & Latorre, M. D. D. D. (2003). Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. *Archives of Otolaryngology-Head & Neck Surgery, 129*(2), 219-228. doi:DOI 10.1001/archotol.129.2.219

Rivera, C. (2015a). The challenge of the state of susceptibility to oral cancer. *Journal of Oral Research, 4*(1), 8-9.

Rivera, C. (2015b). Essentials of oral cancer. *International journal of clinical and experimental pathology, 8*(9), 11884-11894.

Robert, B. M., Dakshinamoorthy, M., Ganapathyagraharam Ramamoorthy, B., Dhandapani, M., Thangaiyan, R., Muthusamy, G., . . . Prasad, N. R. (2018). Predicting Tumor Sensitivity to Chemotherapeutic Drugs in Oral Squamous Cell Carcinoma Patients. *Scientific Reports, 8*(1), 15545. doi:10.1038/s41598-018-33998-4

Sargeran, K., Murtomaa, H., Safavi, S. M. R., Vehkalahti, M. M., & Teronen, O. (2008). Survival after diagnosis of cancer of the oral cavity. *Br J Oral Maxillofac Surg, 46*(3), 187-191. doi:10.1016/j.bjoms.2007.11.004

Shah, J. P., & Gil, Z. (2009). Current concepts in management of oral cancer--surgery. *Oral Oncology, 45*(4-5), 394-401. doi:10.1016/j.oraloncology.2008.05.017

Vallecillo Capilla, M., Nuria Romero Olid, M., Victoria Olmedo Gaya, M., Reyes Botella, C., & Bustos Ruiz, V. (2008). *Factors related to survival from oral cancer in an Andalusian population sample (Spain)* (Vol. 12).

Viet, C. T., & Schmidt, B. L. (2012). Biologic mechanisms of oral cancer pain and implications for clinical therapy. *Journal of dental research, 91*(5), 447-453. doi:10.1177/0022034511424156

Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol, 45*(4-5), 309-316. doi:10.1016/j.oraloncology.2008.06.002

Yeole, B. B., Ramanakumar, A. V., & Sankaranarayanan, R. (2003). Survival from oral cancer in Mumbai (Bombay), India. *Cancer Causes Control, 14*(10), 945-952.

Zain, R., & Ghazali, N. (2001). *A Review Of Epidemiological Studies Of Oral Cancer And Precancer In Malaysia* (Vol. 8).

Zain, R. B., Ikeda, N., Razak, I. A., Axell, T., Majid, Z. A., Gupta, P. C., & Yaacob, M. (1997). A national epidemiological survey of oral mucosal lesions in Malaysia. *Community Dent Oral Epidemiol, 25*(5), 377-383.

Zheng, J.-w., Qiu, W.-l., & Zhang, Z.-y. (2008). Combined and sequential treatment of oral and maxillofacial malignancies: an evolving concept and clinical protocol. *Chinese medical journal, 121*(19), 1945-1952.