RISK FACTORS ASSOCIATED WITH LOCAL RECURRENCE IN ORAL SQUAMOUS CELL CARCINOMA (OSCC) PATIENTS

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KUALA LUMPUR

2024

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ORAL SCIENCE

FACULTY OF DENTISTRY
UNIVERSITI MALAYA
KUALA LUMPUR

2024

UNIVERSITY OF MALAYA

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) which is the most common histological subset of oral cancer remains a significant global health concern. The overall reported survival rate of OSCC is still poor and one of the main contributing factors for poor survival is local recurrence (LR) of the disease. Various clinicopathological factors are known to influence the LR of the OSCC. **Objective**: To identify the sociodemographic, clinicopathological characteristics and type of surgical interventions that influence the LR of OSCC. **Methods**: The socio-demographic, clinicopathological, and follow-up data of all the surgically treated OSCC cases from the year 2005 till September 2023 was obtained from the Diagnostic Oral Pathology Unit (DOPU) archive, which includes histopathological reports and H&E slides. **Results**: Out of 181 OSCC patients, 12 (6.6%) had LR. Of these, 8 were male and 4 females, with a mean age of 58. Malays had the highest LR percentage at 14.3%, followed by Chinese at 10% and Indians at 2.9%. Among 123 patients with risk habits, 9 (7.3%) had LR compared to 3 (5.2%) without habits. Primary tumours were mainly non-tongue regions, with 10 out of 12 LR cases present in the buccal mucosa, palate, and retromolar trigone. Among patients who underwent surgical resection only, 3 out of 40 (7.0%) developed LR. In contrast, among those who had both surgical resection and neck dissection, 9 out of 129 (6.5%) experienced LR. Bone invasion was present in 35 patients, with 6 (14.6%) experiencing LR. Multiple logistic regression identified race ($p=0.024$) and primary tumour site ($p=0.020$) as significant predictors of LR, with Malay and non-tongue tumours having a higher risk of developing LR. The model had an area under the ROC of 0.737, indicating moderate discrimination.

Conclusion: Race and primary tumour site emerged as significant independent risk factors for LR. These findings highlight the need for targeted monitoring and tailored interventions to improve OSCC outcomes.

Keywords: Oral cancer, Oral squamous cell carcinoma, Local recurrence, Clinicopathological factors

FAKTOR RISIKO YANG DIKAITKAN DENGAN PENGULANGAN TEMPATAN DALAM PESAKIT KARSINOMA SEL SKUAMOSA MULUT (OSCC)

ABSTRAK

Latar belakang: Karsinoma sel skuamosa mulut (OSCC) yang merupakan subset histologi yang paling biasa bagi kanser mulut kekal menjadi kebimbangan kesihatan global yang ketara. Kadar kelangsungan hidup keseluruhan OSCC yang dilaporkan masih lemah dan salah satu faktor penyumbang utama untuk kelangsungan hidup yang lemah ialah pengulangan tempatan (LR) penyakit itu. Pelbagai faktor klinikopatologi diketahui mempengaruhi LR OSCC. **Objektif**: Untuk mengenal pasti sosiodemografi, ciri klinikopatologi dan jenis campur tangan pembedahan yang mempengaruhi LR OSCC. Kaedah: Data sosio-demografi, klinikopatologi dan susulan semua kes OSCC yang dirawat melalui pembedahan dari tahun 2005 hingga September 2023 diperoleh daripada arkib Unit Patologi Mulut Diagnostik (DOPU), yang merangkumi laporan histopatologi dan slaid H&E. **Keputusan**: Daripada 181 pesakit OSCC, 12 (6.6%) mempunyai LR. Daripada jumlah ini, 8 adalah lelaki dan 4 perempuan, dengan purata umur 58. Orang Melayu mempunyai peratusan LR tertinggi pada 14.3%, diikuti oleh Cina pada 10% dan India pada 2.9%. Antara 123 pesakit dengan tabiat risiko, 9 (7.3%) mempunyai LR berbanding 3 (5.2%) tanpa tabiat. Tumor utama adalah terutamanya kawasan bukan lidah, dengan 10 daripada 12 kes LR hadir dalam mukosa bukal, lelangit, dan trigon retromolar. Antara pesakit yang menjalani pembedahan pembedahan sahaja, 3 daripada 40 (7.0%) mengalami LR. Sebaliknya, di kalangan mereka yang mempunyai kedua-dua pembedahan pembedahan dan pembedahan leher, 9 daripada 129 (6.5%) mengalami LR. Pencerobohan tulang hadir dalam 35 pesakit, dengan 6 (14.6%) mengalami LR. Regresi logistik berganda mengenal pasti kaum (p=0.024) dan tapak tumor primer (p=0.020) sebagai peramal penting LR, dengan kaum Melayu dan tumor bukan lidah lebih

berkemungkinan untuk berulang. Model ini mempunyai kawasan di bawah ROC 0.737, menunjukkan diskriminasi sederhana.. **Kesimpulan**: Bangsa dan tapak tumor primer muncul sebagai faktor risiko bebas yang signifikan untuk LR. Penemuan ini menyerlahkan keperluan untuk pemantauan yang disasarkan dan campur tangan yang disesuaikan untuk meningkatkan hasil OSCC.

Kata kunci: Kanser mulut, Karsinoma sel skuamosa mulut, Faktor klinikopatologi

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest gratitude to the Almighty. This journey has been challenging in so many ways, and I am profoundly thankful to God for giving me the strength to keep going and completing this research on time.

I would also like to express my gratitude to both of my supervisors, Associate Prof. Dr. Zuraiza Mohamad Zaini, and my co-supervisor, Dr. Nur Fauziani binti Zainul Abidin for their belief in me and guidance through every step of this journey. My knowledge on research has broadly expanded in many ways upon completing this research.

To my dear colleagues, Dr. Fatin, Dr. Vetha, Dr. Low, and Dr. Hazwani and my dearest best friend Nisha, thank you for being there. Your constant support and many moments of happiness in between have made tough times much more bearable.

Above all, my deepest appreciation goes to my beloved son, Niwan Yajwin. You have been my main source of strength, and my greatest form motivation. Every step of this journey has been for you, and your presence in my life gives me the courage to keep pushing forward especially during difficult times. Amma loves you very much.

Lastly, to my wonderful parents, Mr. Eirutharajan and Mrs. Jogeswary, thank you from the bottom of my heart. I am immensely grateful for all your sacrifices and unconditional love.

TABLE OF CONTENTS

Abstract iii

Abstrak v

Acknowledgements vii

Table of Contents viii

List of tables xi

List of abbreviations xii

CHAPTER 1: INTRODUCTION 1

1.1 Background 1

1.2 Research question 2

1.3 Null hypothesis 2

1.4 Aim 2

1.5 Objective 3

CHAPTER 2: LITERATURE REVIEW 4

2.1 Definition and Prevalence 4

2.1.1 Oral Cancer 4

2.1.2 Local Recurrence (LR) 4

2.2 Socio-demographic Factors Affecting LR of OSCC 7

2.2.1 Gender 7

2.2.2 Age 7

2.2.3 Race 7

2.2.4 Habits 8

2.3 Clinicopathological Factors Affecting LR of OSCC 9

2.3.1 Comorbidities 9

2.3.2 Tumour Site 9
2.3.3 Type of Surgical Intervention 10
2.4 Histopathological Factors Affecting LR of OSCC 10
2.4.1 TNM Staging 10
2.4.2 Depth of Invasion (DOI) 11
2.4.3 Extranodal Extension (ENE) 12
2.4.4 Tumour Grading 12
2.4.5 Perineural Invasion (PNI) & Lymphovascular Invasion (LVI) 13
2.4.6 Worst Pattern of Invasion (WPOI) 13
2.4.7 Lymphocytic Host Response (LHR) 13
2.4.8 Bone Invasion 14
2.4.9 Surgical Margins 15
2.4.10 Epithelial Dysplasia at Surgical Margins 15

CHAPTER 3: MATERIAL AND METHOD 17
3.1 Study Design 17
3.2 Sample Selection 17
3.3 Data Collection 18
3.3.1 Sociodemographic Characteristics 18
3.3.2 Clinical Characteristics 18
3.3.2.1 Local Recurrence (LR) 19
3.3.3 Histopathological Characteristics 19
3.4 Statistical Analysis 20

CHAPTER 4: RESULTS 22
4.1 Sociodemographic Characteristics of OSCC Patients with LR 22
4.2 Clinicopathologic Characteristics of Patients with LR 23

4.3 Types of Surgical Intervention Associated with LR in Patients with OSCC 26

4.4 Association of Socio-demographic, Clinical and Histopathological Characteristics with LR of OSCC. 28

4.5 Multivariate Logistic Analysis of Sociodemographic and Clinicopathological Factors Associated with LR 31

CHAPTER 5: DISCUSSION 32

5.1 The Prevalence of LR in OSCC Patients 32

5.2 Sociodemographic Characteristics and LR in OSCC 33

5.3 Clinicopathological Characteristics and LR in OSCC 34

5.4 Treatment interventions and LR in OSCC 35

5.5 Limitation 36

CHAPTER 6: CONCLUSION 37

References 38

LIST OF TABLES

Table 3.1 References and the Grouping for the Histopathological Characteristics of OSCC Patients 19

Table 3.2 Cut-off value for Age and Tumour Dimension..... 21

Table 4.1: Distribution of Sociodemographic Characteristics of OSCC Patients with LR ……22

Table 4.2: Distribution of Clinicopathological Characteristics of OSCC Patients with LR ….....24

Table 4.3: Types of Surgical Interventions Associated with LR in Patients with OSCC …….27

Table 4.4: Univariate Logistic Analysis of Sociodemographic and Clinicopathological Factors Associated with LR 28

Table 4.5: Independent Risk Factors for LR Using Multiple Logistic Regression Analysis….....31

LIST OF ABBREVIATIONS

AJCC	:	American Joint Committee on Cancer
CCI	:	Charlson Comorbidity Index
DOPU	:	Diagnostic Oral Pathology Unit
DOI	:	Depth of Invasion
DPRU	:	Dental Postgraduate Research Grant
ENE	:	Extranodal extension
GLOBOCAN	:	Global Cancer Observatory
H&E	:	Haematoxylin & eosin
HG	:	Hemiglossectomy
HNSCC	:	Head and neck squamous cell carcinoma
LHR	:	Lymphocytic Host Response
LVI	:	Lymphovascular invasion
LR	:	Local recurrence
LRR	:	Loco-regional recurrence
MOCTBS	:	Malaysian Oral Cancer Database and Tissue Bank System
OPMD	:	Oral potentially malignant disorder
OR	:	Odds ratio
OS	:	Overall survival
OSCC	:	Oral squamous cell carcinoma
OSF	:	Oral submucous fibrosis
pN	:	Pathological node
PNI	:	Perineural invasion
pT	:	Pathological tumour

RFS	:	Recurrence-free survival
RR	:	Regional recurrence
SFT	:	Second field tumour
SPSS	:	Statistical Package for the Social Sciences
SPT	:	Second primary tumour
TD	:	Tumour dimension
TNM	:	Tumour, Node, Metastasis (staging system)
ROC	:	Receiver Operating Characteristic
WE	:	Wide excision
WHO	:	World Health Organization
WPOI	:	Worst pattern of invasion
OED	:	Oral epithelial dysplasia

CHAPTER 1: INTRODUCTION

1.1 Background

Oral cancer remains a significant global health concern with approximately 370,000 reported new cases and nearly 170,000 deaths resulting from lip and oral cavity cancers worldwide in year of 2020 (Sung et al., 2021). In Malaysia, oral cancers rank as the 19th most frequently diagnosed cancers (Sung et al., 2021). It is vital to emphasize here that the term oral cavity and lip cancers are almost synonymous with oral squamous cell carcinoma (OSCC), with it being the most common histological subset of this disease and accounting for as high as 90% of its overall cases (Sung et al., 2021). Despite robust development in diagnostic tools and treatment modalities over the recent years, the overall 5-year survival rate of oral cavity cancers has only marginally improved over the past decade. From 1992 to 1996 the survival rate of oral cavity cancer was 51.1%, followed by an obvious increase to 62.9% in the years 2002 to 2006 with a significant rise of 11.8% (Pulte & Brenner, 2010). However, in the years 2012 to 2018, the survival rate has only improved by 5.1% with a rate of 68% (Oral Cancer 5-Year Survival Rates by Race, Gender, and Stage of Diagnosis, n.d.). Local control of the disease plays a significant role in the survival rate as failure to do so may result in local recurrence (LR) or locoregional recurrences (LRR) of OSCC. Camisasca et al. (2011) have reported a 5-year survival rate of 92% in OSCC patients without recurrence whereas only 30% in patients with recurrence ($P < 0.001$, log-rank test). Although surgical margins have long been thought to be a significant determinant in local control of the disease, some studies have demonstrated that recurrences can also result when surgical margins are negative (Sorroche et al., 2021). This indicates the presence of other factors, such as sociodemographic or clinicopathological characteristics of the patient and tumour respectively, influence the occurrence of recurrences in OSCC. Several studies conducted in different parts of the world over the last few decades have revealed a prevalence of LR

ranging from 7% to as high as 47.4% (Brands et al., 2019; Jones et al., 1992; Weckx et al., 2019; W. Wang et al., 2012). It is important to note that there has only been limited study on the prevalence of OSCC recurrence, especially LR, in Malaysia, and that the contributing factors have not been entirely explored. Uncovering the potential significant risk factors that might be used to identify patients who are at risk of developing LR is therefore crucial to improve the disease outcome and survival rate of patients with OSCC. As clinicians still heavily lean on the TNM staging, it is important to emphasize that a combination of the TNM staging and assessment of patients' sociodemographic profile and clinicopathological characteristics of the tumour can be used to identify patients who are at risk of developing LR. This in turn can help to build suitable individualized therapeutic strategies and assist in planning close-up surveillance among the identified high-risk group.

1.2 Research question

What are the sociodemographic and clinicopathological characteristics of patients with OSCC as well as the surgical interventions that are significantly associated with LR in OSCC?

1.3 Null hypothesis

H_o

There is no association between local recurrence and sociodemographic, clinicopathological characteristics, and type of surgical interventions in OSCC patients.

1.4 Aim

To identify the sociodemographic, clinicopathological characteristics and type of surgical interventions that influence the LR of OSCC.

1.5 Objective

i. To assess the sociodemographic characteristics of OSCC patients with LR.

ii. To identify the clinicopathological characteristics of OSCC patients with LR.

iii. To determine the type of surgical intervention associated with LR in patients with OSCC.

iv. To determine the association between LR and sociodemographic, clinicopathological, and type of surgical intervention.

CHAPTER 2: LITERATURE REVIEW

2.1 Definition and Prevalence

2.1.1 Oral Cancer

The term "oral cancer" includes all malignancies arising from the lips, oral cavity, oropharynx, nasopharynx, hypopharynx, and other ill-defined sites within the lip, oral cavity, and pharynx (World Health Organization., 2016). It is particularly important to emphasize here that the most prevalent subset of oral cancer is OSCC which arises from a dysplastic mucosal surface squamous epithelium (Sung et al., 2021). According to the Malaysian National Cancer Registry data, 864 cases of mouth cancer were documented between the years 2012 to 2016 (Azizah AM. & Nadia SMR., 2019). A concerning prediction is that between 2020 and 2040, there will be roughly twice as many new cases of oral cancer reported in Malaysia, from 742 in 2020 to 1410 in 2040. (Cancer Tomorrow, n.d.).

2.1.2 Local Recurrence (LR)

Given the prediction of the rising number of cases over the years, the prime focus of the clinician should be on the prevention of the disease occurrence itself or prevention of recurrences in established cases as it can significantly impact the overall survival (OS) of the patient. Recurrence simply refers to the return of the disease after undergoing a primary treatment with a curative intent. They are typically categorized into local recurrence (LR), locoregional recurrence (LRR) and regional recurrence (RR) depending on the site in which it is involved (Yanamoto et al., 2012). In short, LR refers to lesions arising at the same anatomical site as the primary tumour, LRR refers to tumours arising in both the primary site and the neck and RR refers to tumours solely arising from the neck (Yanamoto et al., 2012).

LR is particularly a subject of interest here as it highlights local control failure which is a critical determinant of survival especially in early-stage OSCC (Sinha et al., 2018). To date, there is no mutual consensus regarding a standard definition for LR (Rohde et al., 2020). This confusion has arisen given the incidence of second primary tumours (SPT) which is often found to be close to the primary lesions site similar to LR. This is when the concept of "field cancerization" was proposed by Slaughter et al. in 1953 to explain the emergence of several primary tumours and tumours recurring locally close to the site of the primary site tumour. Two theories have been proposed to explain this concept (Braakhuis et al., 2002). Theory one considers the development of malignant cells originates from a monoclonal population that spreads throughout the mucosa and eventually turns malignant. The second theory suggests that prolonged exposure to cancer-causing agents leads to the independent transformation of various epithelial cells to different degrees at different times which might result in the development of multiple tumours. Theory one explains the formation of malignant cells is LR tumours, and the second theory implies that multiple tumours formed are SPTs. Since then, to differentiate between these two entities, several studies have used Warren and Gates criteria from 1932 whereby SPTs were considered when; (1) each tumour is malignant, (2) each must be distinct, and (3) the probability of one being a metastasis of the other must be excluded (Warren, 1932). However, this criterion did not mention any specific distance to differentiate two distinct tumours which could potentially be a SPT or a LR. Therefore, other studies have attempted to include additional information such as a specific distance, an anatomical separation, or a temporal separation based on this criterion. Hong et al. (1990) and Jovanoic et al. (1944) both defined the distance of SPT to be more than 2cm from the primary tumour site, whereas Braakhius et al. (2002) determined SPT to be separated by anatomical site. A few studies have also included temporal separation within the range of 3 to 5 years. Hong et al. (1990) and Zukausite et al. (2018) both defined LR

tumours in their methodology as a new adjacent carcinoma arising within 3 years of treatment. SEER, which is a manual used for cancer staging, has defined LR as a tumour that occurs within 5 years post-treatment. However, to date, there has not been a clear justification for this temporal separation, and which one accurately describes the occurrence of LR. A systematic review by Rodhe et al. (2020) summarized a definition for LR of head and neck squamous cell carcinoma (HNSCC) tumours to be (1) the same anatomical subsite within 3 cm of the primary lesion, (2) time-interval no more than 3 years post-primary treatment and (3) same p16- status for oropharyngeal carcinoma. In addition to this, it is also particularly important to mention a study done by Braakhuis et al. (2002) which proposed a new classification for secondary tumours that develop after the primary ones based on its molecular profiling. In the study, LR is a secondary tumour that shares the same molecular profile as the primary while a secondary tumour having a molecular profile that is only partially similar to the primary tumour is called a second field tumour (SFT). On the other hand, a second primary tumour (SPT) is a second tumour that harbours a molecular profile that is different from its primary tumour. Therefore, it is impossible to differentiate between these three entities clinically unless molecular profiling is carried out.

It is important to distinguish between LRs and SPTs as they affect the treatment choice and the prognosis of the patients (Rohde et al., 2020). A more extensive treatment approach would be needed for LR tumours compared to SPT, as LRs are known to be more aggressive compared to SPTs (González-García et al., 2009; Rohde et al., 2019). Treatment for LR usually involves excision followed by radiotherapy, however, in SPTs, radical excision will usually suffice without any additional treatment later (Braakhuis et al., 2002). This can be further supported by the fact that the survival rate was markedly decreased in patients with an LR (28.6% and 24.5% at 3 and 5 years postoperatively,

respectively) compared with patients with SPTs (73.2% and 54.2% at 3 and 5 years postoperatively, respectively (González-García et al., 2009).

2.2 Socio-demographic Factors Affecting LR of OSCC

2.2.1 Gender

The incidence of OSCC recurrence was generally found to be more common among men than women (Blatt et al., 2022; Ghantous et al., 2018; Y. Wang et al., 2023). The fact that men have a higher incidence of recurrence could be attributed to their carcinogenic lifestyle factors which include smoking, alcohol intake, and betel nut chewing as they are more commonly seen among men than women (Lin et al., 2020). Despite noticeable differences between genders, Blatt et al. (2022) have found that gender did not influence the recurrence of OSCC.

2.2.2 Age

Besides gender, age is also known to play a role in the recurrence of OSCC. Y. Wang et al., (2023) recently published a study that found a significant correlation between the recurrence interval and age (P=0.045). The age group of recurrence reported in his study ranged from 34 to 82 years, with an average age of 44±7.23 years (Y. Wang et al., 2023). In another retrospective study, Chang et al. (2017) discovered that over 85% of the 4,839 patients with recurrent HNSCC were of working age, with the majority being under 65. This study particularly mentioned that the cancer burden in working-age patients is worrisome and has a profound effect on the families, carers, and the economy in numerous ways, hence, emphasizing the importance of recognizing high-risk groups and prevention of recurrence (Chang et al., 2017).

2.2.3 Race

Race is another sociodemographic component that can influence the recurrence of OSCC. Literature on different groups of ethnicities and their association with the

recurrence of OSCC has been scarce, but it is important to note that, in a multiracial country such as Malaysia, the incidence of oral cancer has been the highest among the Indian population, which accounts for almost half of the cases reported (Ghani et al., 2018). This finding was further supported by various other studies done in Malaysia (Azizah et al., 2016; Zain et al., 1997). This correlates well with the frequency of betel nut chewing, which is a proven risk factor for the recurrence of oral cancer, which was highest among this group of the population (Ghani et al., 2011).

2.2.4 Habits

Three main risk habits that are widely known to be associated with the recurrence of oral cancer are tobacco smoking, alcohol consumption and betel quid chewing. Day et al. (2014) demonstrated the impact of both the frequency and duration of smoking and alcohol intake on the recurrence of OSCC. They have found that the risk of developing a recurrence was increased substantially, particularly for those who smoked 40 or more cigarettes daily for more than 29 years. Similarly, individuals who consumed 15 or more alcoholic drinks per week faced a 3.5-fold increase in risk for recurrence compared to light drinkers who had just four drinks per week (Deleyiannis et al., 1996). Importantly, discontinuing the smoking habit has been significantly linked to improved survival outcomes and a lower incidence of recurrence. According to the statistics of GLOBOCAN 2020, Southeast Asia had the highest incidence of oral cancer, and it was primarily known to be associated with a high rate of betel quid chewing among this population. Betel quid chewing is one of the established risk factors of OSCC as it contains various carcinogens such as slaked lime and arecoline which in long-term usage can lead to a condition called Oral Submucosal Fibrosis (OSF) (Chuang et al., 2022). OSF is regarded as an oral potentially malignant disorder (OPMD) which can develop into malignancy (Chuang et al., 2022). A qualitative study conducted to assess the effect of betel quid cessation among oral cancer patients has noted that those who quit betel quid due to oral cancer usually

quit tobacco and alcohol as well and had a lesser chance of recurrence of OSCC (Lee et al., 2018). Y. Wang et al. (2023), found a significant correlation by Log-rank test between the recurrence interval and chewing betel nut (P=0.048). The study is to our best the first to show a significant association between the recurrence interval and betel nut chewing.

2.3 Clinicopathological Factors Affecting LR of OSCC

2.3.1 Comorbidities

Underlying comorbidities among patients who have been diagnosed with OSCC play a crucial role in the overall survival (OS) and recurrence-free interval (RFS) (Bøje et al., 2014). Patients with comorbidities were affected in terms of the suitability of the intervention and the recovery process (Ghanizada et al., 2020). Up to 20% of oral cancer patients receive suboptimal intervention due to their underlying medical condition (Ghanizada et al., 2020). The Charlson Comorbidity Index (CCI) is a widely accepted validated index to predict survival among cancer patients (Charlson et al., 2022). According to Chang et al. (2017), a CCI score > 6 was a significant independent prognostic risk factor for the overall survival of recurrent head and neck squamous cell carcinoma (HNSCC) patients. A retrospective study revealed that patients with a CCI score of zero had a 5-year overall survival rate of 60%. However, patients who had CCI scores of one, two, or three or higher exhibited a 5-year relapse-free survival (RFS) rate of 51%, 37%, 33%, and 36%, respectively (Bøje et al., 2014). This demonstrates an inverse relationship between the CCI score and the relapse-free survival rate of the patients, indicating that as the CCI score increases, the chances of recurrence of the HNSCC also increase.

2.3.2 Tumour Site

The main tumour site also plays a pivotal role in predicting both the OS and recurrence after surgery. This is contributed by the anatomical differences in terms of blood supply,

lymphatic supply as well as proximity to many vital structures in various parts of the oral cavity. In previous reports, tumours of the floor of the mouth and buccal mucosa had a worse local control compared to tumours from other sites of the oral cavity (Liao et al., 2006; Sessions et al., 2000;). Ghantous et al. (2018), noted that OSCC originating from the buccal mucosa is much more aggressive and more likely to result in recurrence even during the early stages of the disease. Camisasca et al. (2011) on the other hand, reported that tongue being the primary site has contributed to a higher incidence of LR.

2.3.3 Type of Surgical Intervention

Aside from the risk factors already discussed, LR is also shown to be associated with the type of surgical intervention. The common surgical treatment for OSCC of the tongue is a wide excision (WE) of the lesion or a hemiglossectomy (HG). Parikh et al. (1998) found that the LR was significantly higher in the WE group, 25% compared with 9% in the HG group. In another study on OSCC involving the mandible, the LRs were compared between patients who underwent marginal mandibulectomy and those who received segmental mandibulectomies, and the data showed that the former was not associated with a higher risk of OSCC recurrence (p=0.75) (Sproll et al., 2020).

2.4 Histopathological Factors Affecting LR of OSCC

2.4.1 TNM Staging

The TNM staging was first proposed by Pierre Denoix between the year of 1943 to 1952.TNM is a notation system that describes the stage of cancer using alphanumeric codes: T describes the size of the primary tumour, the involvement of adjacent structures and DOI; N describes nearby (regional) lymph nodes that are involved; M describes distant metastasis (Lydiatt et al., 2017). The T category includes T1, T2, T3, and T4 indicating tumour dimension (TD) in ascending order, increasing depth of invasion (DOI) and invasion into adjacent structures, N or node describes the absence or presence of

nodal metastases and the extent of regional lymph node metastasis which also included extranodal extension (ENE). The N category includes N0, N1, N2, and N3 which again indicates an increasing extent or volume of nodal disease. The M or metastasis category indicates the absence of distant metastasis (M0) or the presence of distant metastatic disease (M1). Based on the individual values of T, N and M scores, a stage grouping of I to IV will be done, with stage I being the most favorable and stage IV being the least favorable one. This staging has been further subtyped to clinical TNM (cTNM) and pathological TNM (pTNM). TNM is based on pretreatment information and helps to provide a guide on the use and selection of therapy required. pTNM on the other hand, serves as a guide post-surgery and helps clinicians to decide if any additional adjuvant surgeries are required for the patient. In terms of recurrence, Ebrahimi et al. (2011), reported that T stage and N stage were important factors affecting RR in OSCC. In another study, patients in stages III and IV showed a higher incidence of LR (Slieker et al., 2020). Ghantous et al. (2018), found that the pT stage was significantly associated with recurrence (P value=0.05), however, this similar study yielded contradictory results compared to others, whereby, the overall pathological staging was not correlated with recurrence (P value=0.70).

2.4.2 Depth of Invasion (DOI)

In the recent addition of the American Joint Committee of Cancer (AJCC 8th Edition) staging, Depth of Invasion (DOI) has been incorporated as a reliable prognosticator for OSCC (Almangush et al., 2015). DOI is measured by first finding the intact basement membrane of the neighboring squamous epithelium and a perpendicular line is established from the selected basement membrane to the deepest point of tumour invasion (Amin et al., 2017). The classification indicates 5 mm and 10 mm as the cut-off values for the staging of tumours whereby, the T1 tumour has a DOI less than 5 mm and the T3 tumour has a DOI greater than 10 mm (Amin et al., 2017). An increase in DOI, in a

clinically negative neck, was positively correlated with an increased risk of nodal metastasis and increased risk of LRR in OSCC (Shinn et al., 2018). In another study, DOI of more than 10 mm, was known to have three times fold risk of developing LR (Faisal et al., 2018) .

2.4.3 Extranodal Extension (ENE)

ENE is defined as the extension of a nodal metastasis through the lymph node capsule into adjacent tissue (Amin et al., 2017). The term ENE_{mi} is used when the ENE is measured microscopically less than 2 mm. Macroscopic ENE (ENE_{ma}) on the other hand is used when either the ENE is visible to the unaided eye during dissection or extension that extends microscopically beyond the lymph node capsule by more than 2 mm. To define pathological ENE (+) nodal status, only ENE_{ma} is used (Amin et al., 2017). ENE (+) is known to be a robust predictor of OS as well as loco-regional recurrence. Patients with macroscopic ENE were 1.5 times more likely to develop regional recurrence as compared with patients with microscopic ENE (Jadhav & Gupta., 2013). Safi et al. (2017) also found a significant correlation between locoregional recurrence and ENE ($p= 0.028$).

2.4.4 Tumour Grading

Additionally, tumour grading is also found to be associated with the recurrence of OSCC. WHO scoring system for tumour differentiation is divided into four grades: Grade I (well differentiated), Grade II (moderately differentiated), grade III (poorly differentiated) and Grade IV (undifferentiated). Overall, well-differentiated OSCCs are less aggressive than poorly differentiated or undifferentiated carcinomas ("Textbook of Oral Cancer," 2020). Poorly differentiated or high-grade, are more likely to recur, and are associated with a poor prognosis. In contrast, well-differentiated tumours often exhibit a more favorable prognosis and a lower recurrence rate (Fortin et al., 2001). According to

the study by Blatt et al. (2022), there was a strong association between advanced grading and recurrence of OSCC(p=0.01).

2.4.5 Perineural Invasion (PNI) & Lymphovascular Invasion (LVI)

PNI is another key histopathological recurrence. PNI denotes a tropism of tumour cells for nerve bundles (Majumdar et al., 2017). Various studies have found PNI to be an independent prognosticator of local recurrence (Liu et al., 2013; Slieker et al., 2018; T. Huang et al., 2010). LVI on the other hand is defined by the presence of tumour cells within the lumen or in the wall of lymphatics and blood vessels (Majumdar et al., 2017). In a study involving recurrent OSCC of the maxilla, vascular invasion was found to be the sole risk factor with a significant value of (p=0.03) (Slieker et al., 2020).

2.4.6 Worst Pattern of Invasion (WPOI)

POI is another histopathological factor found in several studies to be associated with OSCC recurrence. POI represents the pattern of the tumour infiltrating at its tumour/host interface. Originally there were four identified POI (type I to type IV), however, a fifth pattern was added by Brandwein-Gensler's Group for cases with tumour satellites that are 1 mm away from the tumour perimeter which is also designated as WPOI-5. WPOI-5 was a good predictor of locoregional recurrence in low-stage OSCC >4 mm DOI, with a high incidence of 42% (Y. Li et al., 2012).

2.4.7 Lymphocytic Host Response (LHR)

LHR was first incorporated in Brandwein-Gensler's histological risk model in 2005 as one of the histologic prognosticators of LR (Brandwein-Gensler et al., 2005). Maleki et al. (2011) later used this classification and categorized it as either strong, intermediate, or weak, based on the presence of lymphoid nodules. In the study, lymphoid nodules were defined as a dense collection of lymphocytes adjacent to the tumour host interface (Maleki et al., 2011). Tumours with strong LHR were defined as having at least one nodule at the

tumour interface per each low power 4x microscopic field. Tumours with lymphoid response below this threshold, but with one or more lymphoid nodules, were categorized as intermediate LHR. Weak LHR was assigned for when they lack any lymphoid nodules. The pattern of host inflammatory response was shown to influence the progression of the lesion. A study by Lundqvist et al. (2011) revealed no recurrences were noted in 63% of their patients with dense lymphoid infiltrate. Camisasca et al. (2011) discovered tumours with little or no lymphocytic infiltration were related to poor cancer-specific and overall survival (p=0.005). On the other hand, some authors have found an opposite effect whereby, the tumours with dense inflammatory cells contribute to the progression of OSCC by increasing the aggressiveness of the tumour cells leading to deeper invasion into the tissues (Dourado et al., 2017; Salo et al., 2014).

2.4.8 Bone Invasion

The presence of bone invasion in OSCC automatically categorizes the tumour to T4a by the 8th AJCC classification. Bone invasion is divided into two types based on their histological pattern which is erosive and infiltrative types. An erosive pattern is characterized by a tumour mass having a clear border between the resorbed bones. It is separated by a connective tissue layer, and there are no residual bone islands seen within the tumour. On the other hand, in infiltrative type, the connective tissue layer is breached, and the tumours islands can be seen invading into the bone. In this type, the presence of bone islands is seen within the tumors (Brown et al., 2002). It was shown that the probability of recurrence to occur is affected by type bone invasion, and the highest frequency was found among the infiltrative type (Pink et al., 2023). In one of the studies done by Fan et al. (2010), bone invasion was significantly associated with local-regional recurrence. It was said that the malignant cells spread through the inferior alveolar canal contributing to bone metastasis ("Textbook of Oral Cancer," 2020).

2.4.9 Surgical Margins

Aside from all these risk factors, surgical margins are an extremely important component in assessing the LR and success of the primary treatment. Though there is much debate on the categorization of surgical margin clearance, the widely accepted guideline is still by the UK College of Pathologists in 1998. In this guideline, the 'clear' margin is said to be more than >5mm, close is between 5mm to 1mm and involved is < 1mm. Yanamoto et al. (2012) reported that surgical margin status is an independent predictive factor for LR. Slieker et al. (2022) recently showed that a significant proportion of their patients with positive or close margins (36%), who had subsequently undergone post-radiotherapy was correlated with a higher risk of LR. In a recent study, every additional mm of tumour-free margin (with a maximum of 5.0 mm), was associated with reduced hazard for LRs to occur (Adriaansens et al., 2023).

2.4.10 Epithelial Dysplasia at Surgical Margins

Surgical excision of an OSCC is carried out with the intent of complete excision of the tumour with clear margins. The rationale for this is to ensure recurrence-free survival. During the excision of the OSCC tumour, there is a possibility of finding oral epithelial dysplasia (OED) at the mucosal margins which increases the likelihood of LR occurring (Jerjes et al., 2010). OED is defined as a spectrum of architectural and cytological epithelial changes resulting from an accumulation of genetic alterations, usually arising in a range of oral potentially malignant disorders (OPMDs), indicating a risk of malignant transformation to squamous cell carcinoma (*WHO Classification of Tumours Editorial Board. Head and neck tumours [Internet]*, 2023). The three-tier grading system by WHO is the gold standard for histological diagnosis of OED. OED is graded as mild, moderate, and severe based on whether the dysplastic features were restricted to the lower third, middle third, and upper third of the epithelium, respectively. According to Jerjes et al. (2012), dysplasia at the excision margin was significantly associated with local recurrence

($p<0.05$, Hazard ratio: 0.418). In another study, the relative risk of recurrence is five times higher for patients with dysplasia at the margins when compared to patients devoid of dysplasia (Kurita et al., 2010). However, in a more recent study, histopathological examination of surgical margins showing dysplasia may not reliably predict patient outcomes, highlighting the need for molecular analysis to assess the risk accurately (Pei et al., 2022).

CHAPTER 3: MATERIAL AND METHOD

3.1 Study Design

This is a retrospective study that investigates the factor(s) that are associated with local recurrence in OSCC. This study was approved by the Medical Ethics Committee, Faculty of Dentistry, University of Malaya [DF OS2318/0091 (L)]. This research is financed by a Dental postgraduate research grant (DPRU), Faculty of Dentistry, University of Malaya.

3.2 Sample Selection

This study includes surgically treated OSCC cases retrieved from the archive of the Diagnostic Oral Pathology Unit (DOPU) and Malaysian Oral Cancer Database and Tissue Bank System (MOCDTBS), Faculty of Dentistry, University Malaya from the year 2005 until September 2023. A convenience sampling method was used, whereby patients were selected according to predefined inclusion and exclusion criteria as below:

The inclusion criteria were:

i. Cases with a first primary tumour located in the oral cavity and confirmed histopathologically.
ii. Cases that underwent primary surgery with curative intent.
iii. Cases in which local recurrence develops at the same anatomical subsite within 3 cm from the primary lesion.
iv. Cases where recurrence occurred after 6 months and during the 3-year follow-up period.

The exclusion criteria were:

i. Oral malignancies other than OSCC.
ii. Cases where patients received pre-operative chemotherapy or radiotherapy.

iii. Cases in which recurrence occurs more than 3 cm from the primary lesion.

iv. Cases where recurrence occurred within 6 months and more than 3 years from the follow-up period.

3.3 Data Collection

From the DOPU archive, 408 cases of OSCC that underwent primary curative-intended surgery between the years 2005 and September 2023 were retrieved. Out of these, 15 cases had a history of malignancies other than OSCC, and 8 cases underwent prior neoadjuvant therapy and were subsequently removed, leaving 385 cases for screening. The sociodemographic, clinical, and histopathological data of interest were extracted and recorded from the diagnostic report. When needed, hematoxylin and eosin-stained (H&E) slides were reviewed to update any incomplete histopathological information. Of the 385 cases, only 181 had complete data hence it was included in the final study cohort.

3.3.1 Sociodemographic Characteristics

Sociodemographic data of interest that was collected for this study includes age, gender, risk habits and race. The racial groups were categorized as Malay, Chinese, Indian and others. Data for risk habits that were gathered in this study include alcohol intake, smoking and betel nut chewing. For statistical purposes, the habits were grouped as with or without habit.

3.3.2 Clinical Characteristics

The site of the primary tumour, the patient's underlying medical illness and the type of surgical intervention were the clinical data recorded for this study. To achieve stability in statistical analysis the variables were grouped as tongue and non-tongue, present or absent of comorbidities and surgical resection alone or surgical resection with neck dissection respectively.

3.3.2.1 Local Recurrence (LR)

LR for this study was defined as relapse of OSCC within 3cm of the first primary and within 3 years after completion of curative intended surgery (Rohde et al., 2020). The relapse that occurred within six months post-surgery was excluded in this study as it was considered a residual tumour.

3.3.3 Histopathological Characteristics

They were classified according to the literature and some modifications to the groupings were made to fit the statistical analysis as seen in **(Table 3.1)**. The histopathological features that were included in this study were OSCC variant, tumour differentiation, DOI, TD, p(T), p(N), pTNM staging, WPOI, LHR, surgical margin status and presence of dysplasia at the margin.

Table 3.1 References and the Grouping for the Histopathological Characteristics of OSCC Patients

Histopathological Characteristics (Reference)	Grouping of Histopathological Variables for Analysis
OSCC Variants (World Health Organization (WHO) classification)	1. Conventional
	2. Non-conventional: Papillary Adenosquamous Basaloid Acantholytic Spindle cell
Tumour differentiation (World Health Organization (WHO) classification)	1. Well-differentiated
	2. Moderate and poorly differentiated

'Table 3.1 continued'

Histopathological Characteristics (Reference)	Grouping of Histopathological Variables for Analysis
Depth of invasion (DOI) (AJCC 8th Edition)	1. ≤10mm
	2. >10mm
Tumour size (pT) (AJCC 8th Edition)	1. pT1 and pT2
	2. pT3 3. pT4
pTNM (AJCC 8th Edition)	1. Stage I and II
	2. Stage III
	3. Stage IV
Worst Pattern of Invasion (WPOI) (Brandwein-Gensler histological risk model (2005))	1.Type I and II
	2. Type III, IV and V
Lymphocytic Host Response (LHR) (Maleki et al. (2011))	1. Strong
	2. Intermediate and weak
Surgical margins (UK Royal College of Pathologists in 1998)	1. Clear: > 5mm from the tumour
	2. Not clear: Close (tumour is ≤ 5mm and ≤ 1mm from margin) and Involved (< 1mm from margin)
Dysplasia at the margin (World Health Organization (WHO) criteria for OED (2017))	1.Absent
	2.Present
Bone invasion (International Collaboration on Cancer Reporting (ICCR))	1. Absent
	2.Present: include both infiltrative and erosive type of invasion

3.4 Statistical Analysis

Statistical analysis was performed using SPSS software (version 29, IBM). For descriptive statistics, frequency and percentage were used for categorical data. The cutoff point for the continuous variables of age and TD were determined using the Receiver Operating Characteristic (ROC) curve. Each sample's age and TD value were plotted to generate the ROC curve, and the closest score to the point with maximum sensitivity and

specificity was selected as the cut-off value. The age and TD were dichotomised based on the acquired cut-off value.

Table 3.2 Cut-off value for Age and Tumour Dimension

Characteristics	The area under the curve	Cut-off value
Age	0.458	64.5
Tumour dimension (TD)	0.581	30.5

Univariate logistic regressions were performed for each sociodemographic and clinicopathological factor as well as surgical interventions to assess their association with LR, and variables with a p-value less than 0.25 were selected for the next step (Bursac et al., 2008). The high p-value in the first step was selected ensure potentially important variables were not prematurely excluded. Subsequently, a backward stepwise regression method was employed to systematically eliminate the variables with p-value, $p>0.05$ to identify the model that best explains the relationship (Bursac et al., 2008). A multiple logistic regression was then performed to identify the independent risk factors associated with LR to get the final model. Findings were presented as a crude and adjusted odds ratio with a 95% confidence interval. A p-value of less than 0.05 was considered statistically significant for all analyses.

CHAPTER 4: RESULTS

4.1 Sociodemographic Characteristics of OSCC Patients with LR

A total of 181 OSCC cases met the inclusion criteria and were included in this study. Out of 181 patients, 12 (6.6%) had LR and 2 (1.1%) had LRR. The sociodemographic characteristics of patients with LR were listed in **(Table 4.1)**. There were 4 female and 8 male patients who had recurrence with a mean age of 58±11.314, ranging from 37 and 71. The age in each group was stratified based on a cut-off value of 64.5 using ROC curve analysis. For race, 3 out of 21 (14.3%) Malay OSCC patients had LR, and for Indian patients, while being the largest group of this study cohort (n=102), only 3 developed LR (2.9%). Regarding risk habits, a total of 123 patients with habits that included smoking, alcohol consumption, betel quid chewing, or combinations had OSCC, and out of that 9 had LR with a percentage of 7.3%.

Table 4.1: Distribution of Sociodemographic Characteristics of OSCC Patients with LR

Characteristics		**Local Recurrence**	
		No n (%)	**Yes, n (%)**
No. of cases Total, n=181		169 (93.4)	12(6.6)
Age			
Mean ± standard deviation, range:		**60.12±12.850,23-94**	**58±11.314, 37-71**
	≤64.5	105 (94.6)	6 (5.4)
	>64.5	64(91.4)	6 (8.6)
Gender			
	Male	69 (89.6)	8 (10.4)
	Female	100 (96.2)	4 (3.8)
Race			
	Malay	18 (85.7)	3 (14.3)

'Table 4.1 continued'

Characteristics		Local Recurrence	
		No n (%)	Yes, n (%)
No. of cases Total, n=181		169 (93.4)	12(6.6)
Race			
	Chinese	43 (89.6)	5 (10.4)
	Indian	99 (97.1)	3 (2.9)
	Others	9 (90.0)	1 (10.0)
Risk habit			
	No habit	55 (94.8)	3 (5.2)
	With habit[δ]	114 (92.7)	9 (7.3)

[δ]Smoking, alcohol consumption, betel quid chewing, or a combination of more than one habit.

4.2 Clinicopathologic Characteristics of Patients with LR

Primary tumours that developed on sites other than tongue were the most prevalent in this study (n=103, 56.9%). 10 out of 12 patients with LR had primary tumours at these sites as the following: buccal mucosa (n=4,3.9 %), palate (n=1,1.0%), floor of the mouth (n=1,1.0%), retromolar trigone (n=1,1.0%), maxilla (n=1,1.0%), and mandible (n=2,1.9%). In terms of pTNM staging, 70 (38.7%) patients were diagnosed with stage IV OSCC out of which 6 of them developed LR showing the highest percentage of 8.6%, followed by 2 out of 25 for stage III at 8%, and 4 out of 86 for stages I and II at 4.7%. A similar pattern was observed in the pT grouping, with a higher LR percentage seen in later stages. Out of 35 patients with pT3, 3 had LR at 8.6% and out of 39 patients with pT4, 3 had LR at a percentage of 7.7%. Among the patients analyzed for LR in different pN categories, the highest percentage was in the N1 category, with 13.3% of patients, or 2 out of 14, experiencing LR. Neck dissection was not done in 43 out of 181 patients and of that, 3 (7%) had LR. Nodal involvement was observed in 5 out of 12 patients with LR and among them, 3 (7.9%) had ENE.

In this study, 115 (63.5%) OSCC patients had tumours with a DOI of less than 10mm, of which 8 (6.9%) experienced LR. The remaining 4(6.6%) with LR had a DOI greater than 10mm. Bone invasion was present in 35 patients (85.4%) with 6 (14.6%) of them developing LR. All 6 LR cases had the infiltrative type of bone invasion. Surgical margins were involved in 115 patients (63.5%), and 6 (5.2%) out of those had LR. OED was present in the surgical margins of 62 patients and 5 (8.1%) had LR. In the LR group, the most frequent OED grading was severe and moderate, each at 3.2% (n=2), followed by mild at 1.6% (n=1).9 out of 12 patients with LR had moderately differentiated tumours at 6.6%. LVI was absent in 10 out of 12 patients with LR. PNI was present in 55 patients, with 3 (5.5%) of them subsequently developing LR. The TD in both groups was stratified based on the cut-off value of 30.5mm following ROC curve analysis. The clinicopathological characteristics of patients with LR are summarised in **(Table 4.2)**.

Table 4.2: Distribution of Clinicopathological Characteristics of OSCC Patients with LR

Characteristics	**Local Recurrence (LR)**	
	No n (%)	**Yes, n (%)**
No. of cases Total, n=181	169 (93.4)	12(6.6)
Comorbidity		
Absent	77 (96.3)	3 (3.8)
Present	66 (97.1)	2 (2.9)
ϕUnknown	26 (78.8)	7 (21.2)
Primary tumour site		
♂Non-tongue	93 (90.3)	10 (9.7)
Tongue	76 (97.4)	2 (2.6)
OSCC variant		
•Non-Conventional	12 (100)	0 (0)
Conventional	157 (92.9)	12 (7.1)
pTNM staging¶		
Stage I +II	82 (95.3)	4 (4.7)
Stage III	23 (92.0)	2 (8.0)

'Table 4.2 continued'

Characteristics	Local Recurrence (LR)	
	No n (%)	Yes, n (%)
No. of cases **Total, n=181**	169 (93.4)	12(6.6)
pTNM staging[ŋ]		
Stage IV	64 (91.4)	6 (8.6)
p(T)[ŋ]		
pT1 + pT2	101 (94.4)	6 (5.6)
pT3	32 (91.4)	3 (8.6)
pT4	36 (92.3)	3 (7.7)
p(N)[ŋ]		
Not performed	40 (93.0)	3 (7.0)
N0	72 (94.8)	4 (5.2)
N1	12 (86.7)	2 (13.3)
N2	14 (93.3)	1 (6.7)
N3	31 (93.9)	2 (6.1)
Nodal involvement		
Not Done	40 (93.0)	3 (7.0)
Absent	72 (94.8)	4 (5.2)
Present	57 (92.1)	5 (7.9)
ENE		
Not done	40 (93.0)	3 (7.0)
Absent	94 (94.0)	6 (6.0)
Present	35 (92.1)	3 (7.9)
Depth of invasion		
≤10 mm	107 (93.1)	8 (6.9)
> 10mm	62 (94)	4 (6.0)
Worst pattern of invasion[φ]		
Type I +II	16 (88.9)	2 (11.1)
Type III + IV+ V	153 (93.9)	10 (6.1)
Lymphocytic host response		
Strong	100 (91.7)	9 (8.3)
Weak + Intermediate	69 (95.8)	3 (4.2)
Bone invasion		
Absent	134 (95.7)	6 (4.3)
Present	35 (85.4)	6 (14.6)

'Table 4.2 continued'

Characteristics	Local Recurrence	
	No n (%)	Yes, n (%)
No. of cases Total, n=181	169 (93.4)	12(6.6)
Surgical margin		
Not-clear	109 (94.8)	6 (5.2)
Clear	60 (90.9)	6 (9.1)
Dysplasia at the surgical margin		
Absent	112 (94.2)	7 (5.8)
Present	57 (91.9)	5 (8.1)
Tumour grading		
Well	42 (93.3)	3 (6.7)
Moderate + Poor	127 (93.4)	9 (6.6)
Perineural invasion		
Absent	117 (92.9)	9 (7.1)
Present	52 (94.5)	3 (5.5)
Lymphovascular invasion		
Absent	146 (93.7)	10 (6.3)
Present	23 (92.0)	2 (8.0)
Tumour dimension		
≤30.5mm	103 (95.4)	5 (4.6)
>30.5mm	66 (90.4)	7 (9.6)

p(T), pathological tumour stage; *p(N)*, pathological lymph node stage; *OSCC*, oral squamous cell carcinoma; *ENE*, extra nodal extension.
ϕ Information could not be retrieved.
δ Lip, buccal mucosa, alveolar mucosa, retromolar, palate, floor of the mouth, maxilla & mandible.
• Basaloid, adenosquamous, spindle cell, papillary, acantholytic types.
ŋ According to the 8th edition of AJCC.
φ According to the Brandwein-Gensler histological risk model (2005)

4.3 Types of Surgical Intervention Associated with LR in Patients with OSCC

There were eleven types of surgical interventions performed on patients with OSCC in this study based on the site of the primary tumour. Of 181 patients, 43 (23.8%) had surgical resection alone and 138 (76.2%) had both tumour resection and neck dissection done. The majority (9 out of 12) of patients who developed LR in this study were from the latter group. The types of surgical interventions and their association with LR are

summarized in **(Table 4.3)**. Subsequently, univariate analysis was done for the type of surgical treatment.

Table 4.3: Types of Surgical Interventions Associated with LR in Patients with OSCC

Characteristics	Local Recurrence	
	No n (%)	Yes, n (%)
No. of cases Total, n=181	169 (93.4)	12(6.6)
Primary surgical intervention		
Wide local excision	78 (94.0)	5 (6.0)
Hemiglossectomy	33 (100.0)	0 (0.0)
Subtotal glossectomy	1 (100.0)	0 (0.0)
Hemimandibulectomy	9 (81.8)	2 (18.2)
Segmental mandibulectomy	18 (90.0)	2 (10.0)
Marginal mandibulectomy	5 (100.0)	0 (0.0)
Partial mandibulectomy	9 (81.8)	2 (18.2)
Subtotal maxillectomy	6 (85.7)	1 (14.3)
Segmental mandibulectomy and partial maxillectomy	7 (100.0)	0 (0.0)
Hemimandibulectomy and hemiglossectomy	2 (100.0)	0 (0.0)
Subtotal glossectomy and hemimandibulectomy	1 (100.0)	0 (0.0)
Type of neck dissection		
Not performed	40 (93.0)	3 (7.0)
Unilateral selective neck dissection	44 (97.8)	1 (2.2)
Bilateral selective neck dissection	20 (87.0)	3 (13.0)
Unilateral radical neck dissection	6 (85.7)	1 (14.3)
Unilateral modified neck dissection	35 (92.1)	3 (7.9)
Bilateral modified neck dissection	4 (100.0)	0 (0.0)
Selective and radical neck dissection	2 (100.0)	0 (0.0)
Modified and selective neck dissection	18 (94.7)	1 (5.3)
Type of surgical treatment		
Surgical resection only	40 (93.0)	3 (7.0)
Surgical resection with neck dissection	129 (93.5)	9 (6.5)

4.4 Association of Socio-demographic, Clinical and Histopathological Characteristics with LR of OSCC.

The univariate logistics analysis of this study has revealed six variables, p< 0.25 which is gender (p =0.092), Indian race (p=0.046), presence of risk habits (p=0.059), primary tumour site other than a tongue (p=0.075), bone invasion (p= 0.027) and TD (p=0.197). Apart from that, there were no other sociodemographic and clinicopathological features that were significantly associated with LR. These are shown in (**Table 4.4**). A backward stepwise regression method was then performed on these six variables. Variables with p-values p>0.05 were sequentially removed one at a time, starting with the highest p-value, and the model was re-fit each step. The elimination process was stopped when all remaining variables had p-values, p < 0.05).

Table 4.4: Univariate Logistic Analysis of Sociodemographic and Clinicopathological Factors Associated with LR

Characteristics	**Local Recurrence**		**Odds ratio (95% CI)**	**P value**
No. of cases Total, n=181	**No n (%)**	**Yes, n (%)**		
	169 (93.4)	12(6.6)		
Age				
≤64.5*	105 (94.6)	6 (5.4)		
>64.5	64 (91.4)	6 (8.6)	1.64 (0.51, 5.31)	0.408
Gender				
Male*	69 (89.6)	8 (10.4)		
Female	100 (96.2)	4 (3.8)	0.35 (0.10, 1.19)	**0.092**
Race				
Malay*	18 (85.7)	3 (14.3)		
Chinese	43 (89.6)	5 (10.4)	0.70 (0.15, 3.23)	0.645
Indian	99 (97.1)	3 (2.9)	0.18 (0.03, 0.97)	**0.046**
Others	9 (90)	1 (10)	0.67 (0.06, 7.35)	0.741
Risk habits				
No Habits*	55 (94.8)	3 (5.2)		
With Habits	114 (92.7)	9 (7.3)	1.45 (0.38, 5.56)	**0.059**
Comorbidity				
Absent*	77 (96.3)	3 (3.8)		
Present	66 (97.1)	2 (2.9)	0.78 (0.13, 4.80)	0.787

'Table 4.4 continued'

Characteristics No. of cases Total, n=181	Local Recurrence No n (%)	 Yes, n (%)	Odds ratio (95% CI)	P value
	169 (93.4)	12(6.6)		
Primary tumour site				
Non-tongue*	93 (90.3)	10 (9.7)		
Tongue	76 (97.4)	2 (2.6)	0.25 (0.05, 1.15)	**0.075**
Type of surgical treatment				
Surgical Resection Only*	40 (93.0)	3 (7.0)		
Surgical Resection with Neck Dissection	129 (93.5)	9 (6.5)	0.93 (0.24, 3.60)	0.917
pTNM staging				
Stage I +II*	82 (95.3)	4 (4.7)		
Stage III	23 (92.0)	2 (8)	1.78 (0.30, 10.35)	0.520
Stage IV	64 (91.4)	6 (8.6)	1.92 (0.52, 7.10)	0.327
p(T)				
pT1 + pT2*	101 (94.4)	6 (5.5)		
pT3	32 (91.4)	3 (8.6)	1.58 (0.37, 6.67)	0.535
pT4	36 (92.3)	3 (7.7)	1.40 (0.33, 5.90)	0.644
OSCC variant**				
Non-Conventional	12 (100)	0 (0)	-	
Conventional	157 (92.9)	12 (7.1)	-	1.000
p(N)				
Not performed*	40 (93.0)	3 (7.0)		
N0	72 (94.8)	4 (5.2)	0.741(0.16, 3.48)	0.704
N1	12 (86.7)	2 (13.3)	2.222(0.33,14.87)	0.411
N2	14 (93.3)	1 (6.7)	0.952(0.09,9.92)	0.967
N3	31 (93.9)	2 (6.1)	0.860(0.14,5.47)	0.873
Nodal involvement				
Not Done*	40 (93.0)	3 (7.0)		
Absent	72 (94.8)	4 (5.2)	0.741(0.16, 3.48)	0.704
Present	57 (92.1)	5 (7.9)	1.170 (0.26,5.18)	0.836
Depth of invasion				
≤10 mm*	107 (93.1)	8 (6.9)		
> 10 mm	62 (94.0)	4 (6.0)	0.863(0.25, 2.98)	0.816

'Table 4.4 continued'

Characteristics	Local Recurrence		Odds ratio (95% CI)	P value
	No n (%)	Yes, n (%)		
	169 (93.4)	12(6.6)		
Worst pattern of invasion				
Type I +II*	16 (88.9)	2 (11.1)		
Type III + IV+ V	153 (93.9)	10 (6.1)	0.523(0.11, 2.60)	0.428
Lymphocytic host response				
Strong*	100 (91.7)	9 (8.3)		
Weak + Intermediate	69 (95.8)	3 (4.2)	0.483(0.13, 1.85)	0.288
Bone invasion				
Absent*	134 (95.7)	6 (4.3)		
Present	35 (85.4)	6 (14.6)	3.83(1.16,12.6)	**0.027**
Surgical margin				
Involved*	109 (94.8)	6 (5.2)		
Not involved	60 (90.9)	6 (9.1)	1.817(0.56,5.88)	0.319
ENE				
Not done*	40 (93.0)	3 (7.0)		
Absent	94 (94.0)	6 (6.0)	0.851(0.20,3.57)	0.826
Present	35 (92.1)	3 (7.9)	1.143(0.22,6.03)	0.875
Tumour grading				
Well*	42 (93.3)	3 (6.7)		
Moderate + Poor	127 (93.4)	9 (6.6)	0.992(0.26,3.83)	0.991
Perineural invasion				
Absent*	117 (92.9)	9 (7.1)		
Present	52 (94.5)	3 (5.5)	0.750(0.20,2.88)	0.675
Lymphovascular Invasion				
Absent*	146 (93.7)	10 (6.3)		
Present	23 (92)	2 (8.0)	1.270(0.26,6.17)	0.767
Dysplasia at the surgical margin				
Absent*	112 (94.2)	7 (5.8)		
Present	57 (91.9)	5 (8.1)	1.40 (0.43, 4.62)	0.577
Tumour dimension				
≤30.5 mm*	103 (95.4)	5 (4.6)		
>30.5 mm	66 (90.4)	7 (9.6)	2.18 (0.67, 7.17)	**0.197**

p(T), pathological tumour stage; *p(N)*, pathological lymph node stage; *CI*, confidence interval; *OSCC*, oral squamous cell carcinoma; *ENE, extranodal extension.*
Significant level: p=0.05
*Reference group

**Fisher exact test. Due to the presence of a subgroup with zero, an odd ratio was not obtained.
Values set in bold are variables with p < 0.25

4.5 Multivariate Logistic Analysis of Sociodemographic and Clinicopathological Factors Associated with LR

The multiple logistic regression analysis resulted in a model in which race and primary tumour site were identified as independent risk factors for predicting LR, with p-values of 0.024 and 0.020 respectively **(Table 4.5)**. Indians were less likely to develop LR compared to Malay patients with an OR=0.137. Patients with primary tumours located on the tongue are also less likely to develop LR compared to the non-tongue subgroup with an OR=0.148. In conclusion, Malay patients and those with primary tumors located at non-tongue sites were identified as having the highest risk of developing LR. The area under the ROC is 0.737 with a non-significant Hosmer Lameshow test indicating that the logistic regression model moderately discriminates the outcome, and it is fit.

Table 4.5: Independent Risk Factors for LR Using Multiple Logistic Regression Analysis

Characteristics	Adjusted odds ratio	95% CI	Wald statistic	P value
Race				
Malay	-	-	7.241	0.065
Chinese	0.887	0.179, 4.418	0.020	0.887
Indian	0.137	0.024, 0.768	5.107	**0.024**
Others	0.866	0.067, 9.762	0.028	0.866
Primary tumour site				
Non-tongue[δ]	-	-	-	-
Tongue	0.148	0.030, 0.738	5.436	**0.020**

Significant level: *p*=0.05
Values set in bold were statistically significant.
[δ] Lip, buccal mucosa, alveolar mucosa, retromolar, palate, floor of the mouth, maxilla & mandible.

CHAPTER 5: DISCUSSION

OSCC is a multifactorial disease whereby various sociodemographic and clinicopathological factors as well as the type of treatment received by the patients come into play in determining the outcome of this disease. LR is one of the disease outcomes with a significant impact on the overall prognosis. This retrospective study investigated the association between various sociodemographic, clinical and histopathological characteristics as well as treatment strategies with LR in OSCC patients.

5.1 The Prevalence of LR in OSCC Patients

Over the decade, the global prevalence of LR varied from 6.8% to 46.7% (Govindaraj et al., 2021; Safi et al., 2017; Slieker et al., 2022; Wang et al., 2023; Zittel et al., 2022). Although low, the prevalence of LR among OSCC patients in this study is 6.6% which is consistent with the global prevalence. The wide range in reported prevalence is due to several factors, the first being the lack of a standardized definition for LR. Studies with a temporal separation of 5 years, such as those by Govindaraj et al. (2021) and Yanamoto et al. (2012), showed a higher prevalence of LR, with values of 46.7% and 16%, respectively. In contrast, this study used a temporal separation of only 3 years, with any recurrence beyond this period being considered a SPT. In addition, a systematic review by Rohde et al. (2020) analyzing the definition of LR across different studies showed that there were variations in their spatial definitions as well, while some studies did not specify any at all, making inter-study comparisons challenging. Secondly, the inclusion criteria of each study also varied; for example, Yanamoto et al. (2012), considered recurrence from the primary site as well as the neck as LR, whereas other studies including ours, regarded cervical involvement as RR or LRR. The true prevalence of LR can only be estimated accurately when a standardized definition of LR is used across studies. Thirdly,

as mentioned by Wang et al. (2023), the global imbalance of medical care and the continuous advancement in OSCC diagnostic tools and treatment may have contributed to this as well.

5.2 Sociodemographic Characteristics and LR in OSCC

The sociodemographic of our study population with LR aligns with the typical profile of oral squamous cell carcinoma (OSCC) patients. Although the difference was not statistically significant, LR was more frequently observed in male patients, consistent with findings from other studies (Blatt et al., 2022; Ghantous et al., 2018; Y. Wang et al., 2023). Tobacco smoking, alcohol consumption and betel quid chewing were not only well-established risk factors of OSCC but also strongly linked to the occurrence of LR. In this study, 9 out of 12 patients with LR had risk habits, in concordance with various other studies which showed risk habits as one of the risk factors for LR (de Aguiar et al., 2007; Haque et al., 2022; Sood et al., 2022; Wang et al., 2023). Malaysia is renowned for its ethnic diversity, with a majority of its citizens being Malay, Indian, or Chinese. A significant proportion of OSCC cases in Malaysia have been diagnosed among the Indian population, accounting for 44.4% of cases, primarily due to the strong association with betel nut chewing habits (Ghani et al., 2019). This is consistent with our findings, where 56.4% of our study cohort comprised of patients of Indian race accounting for the majority. Despite this, our study revealed that the Indian population was significantly less likely to develop LR compared to other races, with an odds ratio of 0.18, indicating an 86% reduction in the likelihood of recurrence. Till date, studies examining the association between different racial groups and LR are limited. However, Ding et al. (2019) found that non-white patients with OSCC had a 2.47 times higher risk of locoregional failures compared to other racial groups in their study. More in-depth research is needed to explore potential genetic factors contributing to these differences.

5.3 Clinicopathological Characteristics and LR in OSCC

According to the 8th edition of AJCC staging, the presence of bone invasion increased the staging of the tumour and directly led to a poorer overall prognosis. Bone invasion was found to be statistically significant with a p-value of 0.027 (a p-value of 0.05 was considered significant in univariate analysis though $p<0.25$ was used as selection criteria for the statistical model) in this study but not in the multivariate analysis. In a similar manner, Fan et al. (2010), also showed bone invasion as being statically significant in their univariate analysis, but not in their multivariate with a p-value of 0.03. They have also demonstrated that patients with bone invasion have a 63% 3-year recurrence-free survival rate compared to 74% for those without bone invasion. Additionally, 6 out of 12 patients with LR who had bone invasion in this study exhibited infiltrative type of bone invasion. In a study done by Pink et al. (2023), bone invasion, specifically the infiltrative type, showed a higher frequency of locoregional recurrences with a poorer prognosis. Although not significant, their study showed the highest locoregional recurrence ought to occur in 77% of infiltrative type. Therefore, early detection of bone invasion by careful imaging and appropriate surgical interventions, such as radical resections with clear margins, are crucial to minimize LRs and improve patient overall survival. Regular clinical follow-up along with imaging is also essential to monitor for LR in a patient with a history of bone invasion in their primary tumour especially with the ones that exhibited infiltrative patterns.

The tumour site in OSCC significantly influences the likelihood of LR due to its proximity to various anatomical structures such as nerves, blood vessels, and bones making it more challenging for the clinician to achieve clear margins during surgery. Tumours that arise in other anatomical sites in the mouth other than the tongue were known to be the most common location of LR among our study cohort. The majority of the patients with LR in this study had primary tumours arising from the buccal mucosa.

This finding was consistent with Reichal et al. (2024) in which buccal mucosa was the most affected site in both primary and recurrent OSCC cases with a p-value of 0.001. In another study, SCC originating from the buccal mucosa was proven to have a high risk of recurrence, with a relapse rate of 13% and a statistically significant risk of recurrence p-value of 0.003 (Ghantous et al., 2018). This emphasizes the importance of site-specific considerations in the management of OSCC patients to reduce the likelihood of developing LR in future.

Nevertheless, factors including age, gender, comorbidities, type of surgical interventions, p(T), p(N), p(TNM), PNI, LVI, TD, surgical margin, dysplasia in the margin, DOI, tumour differentiation and ENE did not contribute to the development of LR in this study. Some of these variables were strong prognosticators in other studies, for example, ENE and DOI have been included in the recent 8th edition of AJCC classification and are an independent risk factor LR in studies by (Faisal et al., 2018; Jerjes et al., 2010). Initially, our dataset comprised of 385 cases, however, due to incomplete data, a substantial number of cases were excluded, leading to a final sample size of 181. It is possible that with a larger sample size, some of the listed established risk factors might have shown a significant association with LR.

5.4 Treatment interventions and LR in OSCC

Surgical resection remains the mainstay of treatment for OSCC cases. In this study, the types of surgical interventions were found to be not significant in their association with LR. Among the patients who underwent surgical resection alone, 3 out of 43 (7.0%) experienced LR. In contrast, among those who had surgical resection with neck dissection, 9 out of 138 (6.5%) experienced LR. This indicates that combination surgery might provide a marginally better outcome in terms of reducing the risk of LR. This is in line with a study done by D'Cruz et al. (2015), whereby results of their trial suggested

that elective neck dissection at the time of resection of the primary tumour resulted in a lower incidence of LR and improved the overall survival benefit in patients within an early stage who are clinically node-negative.

In terms of the type of neck dissection done, LR was most prevalent in patients who underwent unilateral radical neck dissection whereby out of the 7 patients, 1 had LR accounting for a percentage of 14.3%, However, this finding was not statistically significant. It is worth noting that, bilateral neck dissection should be offered for patients with a tumour of the oral tongue and/or floor of the mouth that is T3 or T4 or approaches midline because of the complex lymphatic drainage system that can facilitate further cancer spread and recurrence in this area (Koyfman et al., 2019).

5.5 Limitation

Our study had several limitations. The dataset used in this study was retrospective and a single center study and may not be truly representative of a broader population. Since the main source of patients' data was from the HPE report, we had no access to information related to patients' lifestyles, comorbidities, socioeconomic status, or details on the adjuvant therapies that were received by patients. These factors could have influenced the development of LR in the study population. Moreover, we were not able to cross-check with the actual case notes to validate the data retrieved. Despite these limitations, our study includes a large cohort of 181 patients and examines a wide range of variables to investigate its association with LR.

CHAPTER 6: CONCLUSION

This study highlights race and tumour sites to be independent factors associated with the emergence of LR in OSCC patients. Specifically, this study has found that Malays have the highest risk of developing LR compared to other races, as well as tumors located in areas other than the tongue were identified as an independent risk factor for LR. The findings of this study have contributed to our knowledge of the socio-demographic profile and clinicopathological factors associated with LR in OSCC within the Malaysian population. Recognizing these factors can be useful for clinicians to identify patients at risk of developing LR, and assist in providing individualized treatment plans, hence improving the disease outcomes. However, developing a dependable risk stratification model would require further research within this field. More longitudinal, prospective, and multicentric studies are necessary to validate these prognosticators and to establish their reliability in clinical practice.

Furthermore, the current literature lacks a clear definition of field cancerization, which may lead to SPTs being mistakenly reported as LR or vice versa. This lack of clarity can result in both underreporting and overreporting of LR cases. Therefore, more in-depth investigations on the molecular differences between these two entities should be explored to understand the disease better.

Overall, this study provides valuable insight into LR risk factors in OSCC, but it also reveals the need for further research in this area to validate these findings and to better understand concepts like field cancerization.

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