EVALUATION OF SUBMANDIBULAR GLAND INVOLVEMENT IN ORAL SQUAMOUS CELL CARCINOMA PATIENTS

PREVEENA BALAKRISHNAN

FACULTY OF DENTISTRY
UNIVERSITI MALAYA KUALA LUMPUR

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

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EVALUATION OF SUBMANDIBULAR GLAND INVOLVEMENT IN ORAL SQUAMOUS CELL CARCINOMA PATIENTS

ABSTRACT

Background: The oncological necessity for the excision of the submandibular gland (SMG) in neck dissection of oral squamous cell carcinoma (OSCC) management remains a debate. Although it is routinely excised in neck dissection, literature on the actual indication for removal is limited. **Aim**: This study aims to analyse the frequency of SMG involvement in OSCC patients and the impact of its removal on the survival status of these patients. **Objectives:** To investigate the prevalence of SMG in OSCC patients and to analyse the association between the involvement of SMG and the status of Ib lymph node involvement. Next was to analyse the association between the overall survival (OS) and disease-free survival (DFS) of patients with OSCC and the involvement of SMG. **Methods:** Retrospective data of patients diagnosed with OSCC between 2000 to 2020 and who underwent neck dissection were included and analysed. Descriptive studies were used to analyse the prevalence. Pearson Chi-Square test was done to analyse the association between SMG and level Ib lymph node. Kaplan-Meir and the log-rank test were used for the survival analysis. **Results:** A total of 142 patients were included in this study. The prevalence of SMG involvement was 3.52% (95% CI). There was no statistically significant association between the SMG and level Ib lymph node status. The 5-year OS status in patients with SMG-positive and negative was 60% and 88.8% respectively (p-value = 0.013). The 5-year DFS status for SMG-positive and negative was 80% and 95.8% (p-value < 0.001). The SMG status has a significant influence on the OS and the DFS of patients with SMG involvement. **Conclusions:** The involvement of SMG in OSCC cases is rare. The status of the level Ib lymph node does not significantly

influence the SMG status. The status of SMG involvement in OSCC cases has significant impact on the OS and DSF and is reason enough to explore the option of preserving the SMG in selected cases. To learn more about the oncological safety and actual impact of SMG preservation on quality of life, prospective research in the future is warranted.

Keywords: neck dissection; oral squamous cell carcinoma; submandibular gland; submandibular gland involvement; survival status.

PENILAIAN PENGLIBATAN KELENJAR SUBMANDIBULAR DALAM PESAKIT-PESAKIT KARSINOMA SEL SKUAMOSA MULUT (OSCC)

ABSTRAK

Latar belakang: Keperluan onkologi untuk pengasingan kelenjar submandibular (SMG) dalam pengurusan pembedahan leher bagi karsinoma sel skuamosa mulut masih menjadi perdebatan. Walaupun SMG memainkan peranan yang penting dalam penghasilan air liur, ia secara rutin dibuang semasa pembedahan leher. Berdasarkan kajian yang lepas, kedudukan SMG yang berdekatan dengan tumor utama merupakan sebab utama kelenjar ini dikeluarkan secara rutin semasa pembedahan leher. Persoalan tentang penglibatan sebenar SMG dalam kes karsinoma sel skuamosa mulut masih dipertikaikan dalam penyelidikan perubatan. **Matlamat**: Kajian ini adalah untuk menentukan kelaziman SMG dalam pesakit-pesakit karsinoma sel skuamosa mulut (OSCC) dan kesan penyingkirannya terhadap status kelangsungan hidup pesakit-pesakit ini. **Objektif:** Untuk menyiasat kekerapan SMG dalam pesakit OSCC. Untuk menganalisa perkaitan antara penglibatan SMG dan status Ib nodus limfa penglibatan. Untuk menganalisa hubungan antara kelangsungan hidup keseluruhan (OS) pesakit dengan OSCC dan status SMG. Untuk menganalisa persatuan kelangsungan hidup tanpa penyakit (DFS) pesakit dengan OSCC dan penglibatan SMG. **Kaedah:** Data retrospektif pesakit yang didiagnosa dengan OSCC antara 2000 hingga 2020 dan yang menjalani pembedahan leher dimasukkan dan dianalisis. Kajian deskriptif digunakan untuk menganalisis kekerapan penglibatan SMG dalam OSCC. Ujian Pearson Chi-Square telah dilakukan untuk menganalisis perkaitan antara SMG dan nodus limfa tahap Ib. Analisa Kaplan-Meir digunakan untuk analisa kelangsungan hidup. **Keputusan:** Seramai 142 pesakit telah dimasukkan dalam kajian ini. Kelaziman penglibatan SMG ialah 3.52% (95% CI).

Terdapat perkaitan yang tidak ketara antara status nodus limfa tahap Ib dan SMG .Status kelangsungan keseluruhan (OS) pesakit dengan SMG-positif dan negatif masing-masing ialah 60% dan 88.8% (nilai p = 0.013). Status DFS 5 tahun untuk SMG-positif dan negatif ialah 80% dan 95.8% (p-value < 0.001). Status SMG mempunyai pengaruh yang ketara terhadap OS dan DFS pesakit dengan penglibatan SMG. **Kesimpulan:** Penglibatan SMG dalam karsinoma sel skuamosa mulut (OSCC) adalah jarang. Status nodus limfa tahap Ib tidak mempengaruhi status SMG dengan ketara. Kesan yang ketara dilaporkan terhadap kelangsungan hidup OS dan DFS pesakit-pesakit karsinoma sel skuamosa mulut (OSCC). Keadaan ini cukup untuk menerokai pilihan memelihara kelenjar dalam kes-kes terpilih. Bagi mempelajari lebih lanjut tentang keselamatan onkologi dan dampak pemeliharaan SMG terhadap kualiti hidup, penelitian prospektif di masa hadapan diperlukan.

Kata kunci: pembedahan leher, sel skuamosa mulut, kelenjar submandibular, penglibatan kelenjar submandibular, status kelangsungan hidup.

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LIST OF SYMBOLS AND ABBREVIATIONS

OSCC	:	Oral Squamous cell carcinoma
SMG	:	Submandibular gland
DOI	:	Depth of invasion
US	:	Ultrasound
CT	:	Computed Tomography
MRI	:	Magnetic Resonance Imaging
GAG	:	Glycosaminoglycans
TIL	:	Tumor infiltrative lymphocyte
TSR	:	Tumor Stroma Ratio
LRC	:	Locoregional Control
END	:	Elective Neck Dissection
DFS	:	Disease-Free Survival
OS	:	Overall Survival
SCM	:	Sternocleidomastoid
IJV	:	Internal Jugular Vein
DSS	:	Disease Specific Survival
RT	:	Radiotherapy
CCRT	:	Concurrent Chemotherapy and Radiotherapy
AJCC	:	American Joint Committee on Cancer
NCCN	:	National Comprehensive Cancer Network
ECS	:	Extracapsular spread
H&E	:	Hematoxylin and Eosin

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CHAPTER 1: INTRODUCTION

Annually, there is an estimation of 657,000 cases of cancer of the oral cavity and pharynx, and more than 330,000 deaths worldwide (World Health Organization, 2021). Almost 90% of oral cancer cases are Squamous Cell Carcinoma (SCC) (Bugshan & Farooq, 2020; Pires et al., 2013; Sangeet Kumar Agarwal, 2016). These lesions are prevalent in South Asian developing nations and are frequently linked to alcohol, betel nut, and tobacco usage. These lesions frequently affect the floor of the mouth, the tongue, and the buccal mucosa.

The cervical lymph node status is the most significant prognostic factor for patients with oral squamous cell carcinoma (OSCC). Approximately 50% of the survival diminishes with the involvement of even a single lymph node (S. K. Agarwal et al., 2016; Ferlito et al., 2002; Shah, 1990). Thus, lymph node clearance is crucial in the treatment of these patients. Neck dissection has been deemed the standard treatment in the management of oral cancer patients. Even in oral cancer patients without evidence of neck node involvement, neck dissection has been proven to be of oncological benefit (Kramer et al., 2001; S. Yang, 2019). Radical neck dissection was initially advocated by Crile, who emphasized en-bloc clearance of cellular tissues of the neck, along with the spinal accessory nerve, the digastric, stylohyoid, and sternocleidomastoid (SCM) muscles, and internal jugular vein and the submandibular gland (SMG). A more conservative approach to neck dissection was advocated by Bocca in 1967, to reduce the complications caused by the radical approach (Bocca & Pignataro, 1967; Yang et al., 2019). Over time, with the improvement in scientific knowledge, several modifications have been done to the neck dissection approach.

Though a more selective and functional approach is preferred, the SMG is sacrificed invariably regardless of the type of neck dissection (Feller &
Lemmer, 2012). Studies have shown that the direct involvement of SMG in early oral cancer cases is rare (Akshat Malik, 2016; Cakir Cetin et al., 2018; Malik et al., 2016). The SMG's location at level Ib is frequently used as justification for excision. Although level Ib nodal metastasis in OSCC was shown to be statistically more common in clinically and pathologically node-positive necks. The authors of a study noted that there was no statistically significant correlation between SMG involvement in the same instances (Cakir Cetin et al., 2018). The SMG contributes to 60-70% of unstimulated saliva. The SMG is both an exocrine and endocrine gland. Saliva plays an important role in oral health, hence, even the removal of a unilateral gland can cause a decrease in the salivary flow rate and subject the patient to xerostomia, thus affecting the quality of life of the patient.

Based on the presumption that it is not possible to get complete clearance of the level Ib lymph nodes during neck dissection, then SMG is routinely removed. The SMG is also believed to be at risk of metastasis (Dhiwakar et al., 2011; Pires et al., 2013). Although OSCC commonly metastasizes to the level Ib lymph nodes, studies have shown the rate of OSCC metastases to the SMG is low (Jalisi, 2005; Razfar et al., 2009). Submandibular gland invasion by OSCC caused by peri glandular nodal metastasis is seen in 0.3%-1.7% of all the cases (Yang et al., 2019)

Despite the routine removal of the SMG in both therapeutic and elective neck dissection, the adverse effect of the removal cannot be overlooked. Hence, the safety of preserving the SMG in the management of the neck for OSCC remains a controversy (Dundar et al., 2019). Therefore, this study aims to focus on SMG

involvement in OSCC cases and how its involvement may impact the overall and disease-free survival of the patients.

1.1 Aim

The study aims to determine the frequency of submandibular gland (SMG) involvement and the impact of SMG involvement on the survival of oral squamous cell carcinoma (OSCC) patients.

1.2 Objectives

1. To investigate the prevalence of SMG involvement in OSCC patients.
2. To analyze the association between the involvement of the SMG and the status of the level Ib lymph nodes.
3. To analyze the association between the overall survival (OS) of patients diagnosed with OSCC and the involvement of the SMG.
4. To analyze the association between disease-free survival (DFS) of patients diagnosed with OSCC and the involvement of the SMG.

CHAPTER 2: LITERATURE REVIEW

2.1 Oral Squamous Cell Carcinoma (OSCC)

Annually, there is an estimation of 657,000 cases of cancer of the oral cavity and pharynx, and more than 330,000 deaths worldwide (World Health Organization, 2021). Nearly 90% of cases of oral cancer are Squamous Cell Carcinoma (Bagan et al., 2010; Bugshan & Farooq, 2020; Pires et al., 2013). South Asian emerging nations have been reported to have a high prevalence of these lesions. There are many causes

of oral squamous cell carcinoma (OSCC). The two main risk factors for OSCC reported in the literature, are frequent alcohol intake and usage of tobacco or betel quid chewing (Feller & Lemmer, 2012). Similar risk factors have also accounted for the prevalence of OSCC amongst the Indian population (Attar et al., 2010). Another study also added a deficiency of dietary micronutrients to the list of risk factors for OSCC (Petti, 2009). Other possible risk factors that have been suggested, include genetic predisposition, high-risk type of HPV (HPV type 16, especially), and candida infections (Pires et al., 2013). Increased risk of developing OSCC is also associated with medical conditions such as Fanconi anaemia, immunosuppression post organ transplantation secondary to chemotherapy and autoimmune disorders. (Scully & Bagan, 2009).

However, studies have also found that not everyone who engages in high-risk behaviours will develop OSCC. Other factors, such as an individual's genetic makeup and environmental factors, may either provide protection from OSCC or may predispose a person to it (Feller & Lemmer, 2012).

2.2 Demographic Characteristics of Oral Squamous Cell Carcinoma

According to the literature, men are frequently more affected by OSCC than women (Warnakulasuriya, 2009). However, recent studies have reported an increase in the proportion of affected women, with a mean male: female ratio of under 2:1. This is most likely due to changes in social and everyday activities relating to the social profile and way of life of contemporary women, which are attributed to exposure to causative agents such both biologic agents such as high-risk HPV subtypes and

carcinogenic agents like tobacco and alcohol (Andisheh-Tadbir et al., 2008; Effiom et al., 2008; Kruse et al., 2011). With increased age and age-related mutagenesis and epigenetic alterations, the likelihood of developing OSCC increases along with exposure to risk factors. The median age of OSCC diagnosis in the USA is 62 years old. However, the prevalence of OSCC in people under 45 is rising (Warnakulasuriya, 2009).

In Malaysia, regardless of gender, the incidence of OSCC mostly affects the elder age group. The average age at diagnosis of Malaysian men is 59 years old and women are 53 years old respectively. The probability of developing OSCC, with exposure to known risk factors, is said to be increased with age and age-related mutagenesis and epigenetic changes (Warnakulasuriya, 2009).

2.3 Clinical Characteristics of Oral Squamous Cell Carcinoma

All sites in the oral cavity are susceptible to OSCC. The lesions also have the possibility of invading adjacent structures. In America and Europe, the lateral border of the tongue has been identified as the most prevalent site for OSCC. However, studies have also found that the floor of the mouth, alveolar mucosa, ventral surface of the tongue and gingiva are also commonly affected by OSCC (Larsen et al., 2009). In other parts of the globe, different sites have been found to be prevalent. In South Asia, the buccal mucosa has been found to be a common site of OSCC. This is associated with the common local habits of tobacco and areca nut chewing (Johnson et al., 2011). Studies have also discovered gender-based differences in the most common OSCC sites. Oral sites such as the gingiva, floor of the mouth and lateral border of the tongue are mostly seen in males, while the buccal mucosa is mostly

affected in females (Pires et al., 2013). In another study, authors reported that 50% of the OSCC cases in their study had gingiva and alveolar ridge involvement. This could be associated with the range of causative factors of OSCC amongst the Thai population (Jainkittivong et al., 2009). According to a study on Nigerians, patients with OSCC more frequently affected the upper gingiva affected (Effiom et al., 2008).

2.4 Clinical Presentation of Oral Squamous Cell Carcinoma

Oral SCC can manifest with several clinical presentations. Clinically, OSCC can present with a delusive benign appearance (Janotha & Tamari, 2017). Typical OSCC clinical features include leukoplakia (white patches), erythroplakia (red patches) and erythroleukoplakia (red and white) lesions (Farah et al., 2014). These oral potentially malignant disorders may turn into ulcerations with indurated, raised, irregular borders that appear necrotic or exophytic masses with a broad base and a smooth, verrucous, or pebbled surface (Feller & Lemmer, 2012). Homogenous leukoplakia is at a lower risk of malignant transformation when compared with non-homogenous leukoplakia (Farah et
al., 2014).

The authors of a study stated that until proven otherwise, white, or red lesions or oral ulcers and oral lumps that are non-healing for over 3 weeks should be suspicious of cancer (Scully & Bagan, 2009).

Similarly, non-healing intraoral red and white patches and sores that do not heal over 14 days are considered early signs of cancer. Intraoral bleeding, palpable neck mass

and difficulty swallowing are also signs that may be an indication of cancer (Sharma et al., 2018).

According to Bagan, these malignant lesions usually present as erytholeukoplastic lesions at their early stage (Bagan et al., 2010). This consists of well-bounded mixed red and white lesions. The soft tissue undergoes changes in its elasticity making it harder in texture. At this stage, it may cause discomfort but infrequently causes pain. Classical features described in the advanced stages of OSCC include ulceration, nodularity as well as fixation to underlying tissues. Elevated ulcerations with irregular margins and floors that are hard on palpation are the common forms of OSCC. Exophytic tumours with poorly defined boundaries and irregular surfaces that are hard on palpation, may also be seen (Mallet et al., 2009; Ribeiro et al., 2009; Scully & Bagan, 2009).

The lack of symptoms is reported as the reason most early carcinomas go undetected (Bagan et al., 2010). Clinical manifestations of OSCC may also include dysphagia, unexplained weight loss, or numbness under the chin. Less frequently, these manifestations may also include poor healing at the site of tooth extraction (Scully & Bagan, 2009). When a lymph node exhibits hardness or fixation, neck metastases are often linked to advanced OSCC patients. On rare occasions, even in the absence of a primary tumour, growth of the cervical lymph node may be seen (Scully & Bagan, 2009). Pain is a common symptom of OSCC. However, it usually arises once the lesion is of significant size, and only then does the patient seek medical attention (Cuffari et al., 2006). OSCC is often painless unless it is secondarily infected. Larger OSCC lesions are often followed by difficulties chewing, swallowing, or speaking normally (Feller &

Lemmer, 2012).

Advanced OSCC usually has recognizable cancer signs. However, in the early stages, a misdiagnosis could occur (Bagan et al., 2010; Sankaranarayanan et al., 2002). Therefore, a clinical diagnosis alone is insufficient, and a biopsy and histological analysis are necessary to make the proper diagnosis (Rapidis et al., 2009). The 5-year survival rate of OSCC patients drops by 3% to 38% when metastasis is found (Janotha & Tamari, 2017). Therefore, the overall survival (OS) and prognosis of the patient are greatly influenced by the early discovery of the cancer.

2.5 Clinical TNM staging.

In the management of OSCC, the initial assessment of the patient is crucial in determining the prognosis as well as deciding on the suitable treatment for the patient. The American Joint Committee of Cancer (AJCC) introduced a cancer staging system, TNM staging. This staging system represents the body's tumour burden based on the tumour size (T), locoregional lymph node involvement (N) and distant metastases (M). These clinical details are obtained prior to the administration of any treatment, including surgery and adjuvant therapy (Almangush et al., 2020). For data to be considered clinical data, it must be collected between 4 months of the diagnosis or before the definitive treatment. If it is decided for the patient not to have any therapy and instead to be on active surveillance, the window period for gathering clinical data ends then (AJCC, 2010). Biopsy and imaging in addition to the physical examination should be done to obtain diagnostic information.

Clinical tumour size (cT) is a measure of the tumor's size and dimensions. The T scales from T0 to T4 depend on size, and each higher number denotes a larger or

more advanced tumour. There are two subcategories of T4: T4a, which refers to moderately advanced local disease, and T4b, which refers to severely advanced local disease.

The ulcerated surface and the tumour's exophytic or endophytic nature are characteristics that are specified in the clinical stage. Clinical examinations can also determine the physical deep muscle involvement and fixation to bone. Imaging techniques have been shown to be helpful in determining the amount of cancer at the clinical stage. To assess the extent of the tumour, imaging modalities like CT, MRI, and ultrasound are frequently used. The easiest way to determine mucosal level involvement is by a physical exam, however, various radiological modalities are better at determining the size and extent of the tumour. A biopsy is required to confirm the histology of all clinical tumours. (AJCC, 2010).

Table 2.1: Tumour Size (cT & pT).

Primary Tumor (T)	Description
Tis	Carcinoma in situ.
T1	Tumor 2cm or less in greatest dimension.
T2	Tumor more than 2cm but not more than 4cm in greatest dimension.
T3	Tumor more than 4cm in greatest dimension.
T4a	Moderately advanced local disease: (Lip) Tumor invades through cortical bone, the inferior alveolar nerve, the floor of the mouth, or the skin of the face, that is chin/nose. (Oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone) [mandible or maxilla] into the deep [extrinsic] muscle of the tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, the skin of the face).
T4b	Very advanced local diseases: Tumor invades masticator space, pterygoid plates, or skull base and /or encases internal carotid artery.

It is not uncommon for oral cancers to spread to the regional lymph nodes. Drainage from the primary tumour site to the cervical lymph nodes can be predicted based on the anatomical sites of the tumour. The depth of tumour invasion has been found to have an influence on the possibility of nodal involvement.

Based on anatomical landmarks, the neck can be divided into several levels to evaluate the regional lymph node involvement. The neck nodes are traditionally categorized into levels Ia, Ib, IIa, IIb, III, IV, and V based on anatomical landmarks (Robbins et al., 2008).

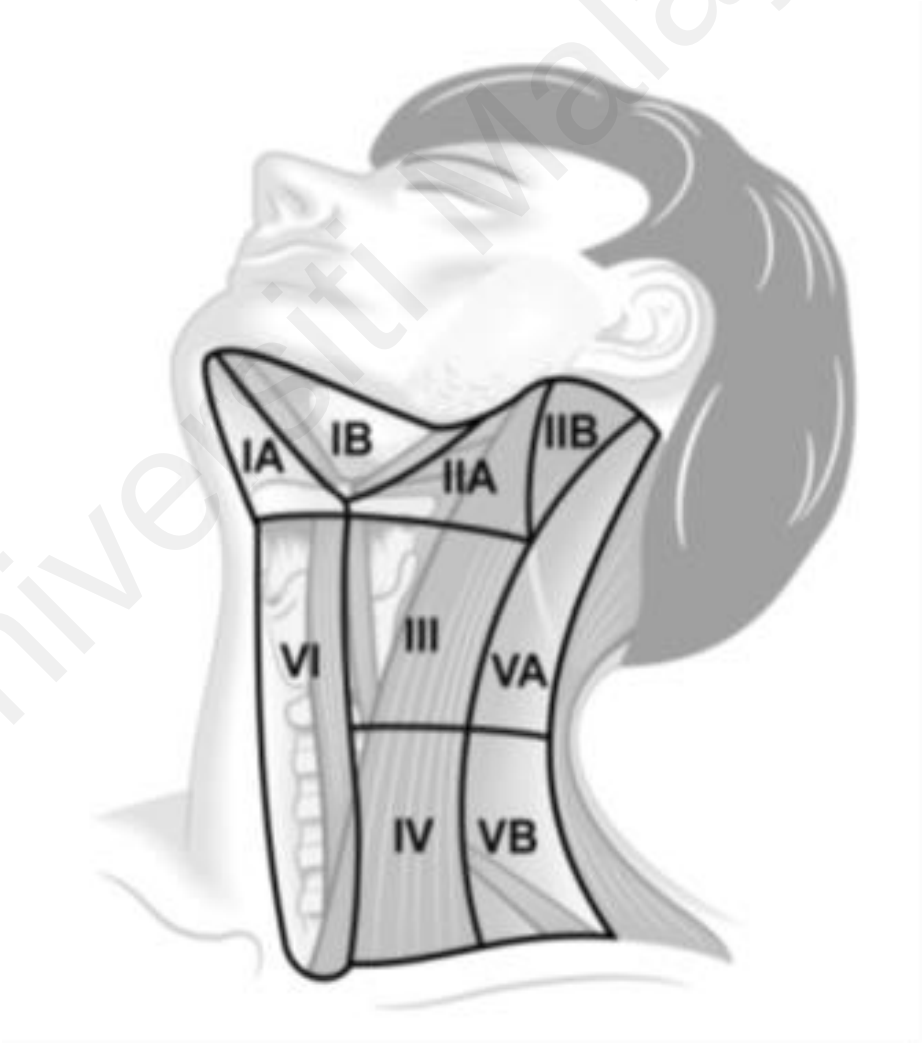

Figure 2.1: Anatomic diagram of the neck depicting the boundaries of the six neck levels and three neck sub-levels. (Figure Adapted from Robbins et al. 2008)

Table 2.2: Describes the boundaries of the neck levels (Robbins et al 2008).

Level	Lymph node group	Boundaries of the neck levels
IA	Submental	Between the anterior bellies of the digastric muscle
IB	Submandibular	Between the boundaries of the anterior belly of the digastric muscle, the stylohyoid muscle, and the mandible
II	Upper Jugular	Includes nodes located around the upper third of the internal jugular vein and spinal accessory nerve. This extends from the skull base above to the inferior border of the hyoid bone below. The anterior boundary is the stylohyoid muscle, and the posterior boundary is the posterior border of the sternomastoid muscle.
IIA		Anterior to the vertical plane defined by the spinal accessory nerve
IIB		Posterior to the vertical plane defined by the spinal accessory nerve
III	Middle jugular	Includes nodes located around the middle third of the internal jugular vein extending from the inferior border of the hyoid bone above to the inferior border of the cricoid cartilage below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is he posterior border of sternocleidomastoid muscle.
IV	Lower jugular	Includes nodes located around the lower third of internal jugular vein extending from the inferior border of the cricoid cartilage above to the clavicle below.
V	Posterior triangle	Includes nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in the posterior triangle group. The superior boundary of this level is the apex formed by convergence of sternomastoid and trapezius muscle.
VA		Above a horizontal plane marking the inferior border of the anterior cricoid
VB		Below a horizontal plane marking the inferior border of the anterior cricoid.
VI	Anterior compartment	Includes pre and paratracheal nodes, precricoid (Delphian node), and the perithyroid nodes including the nodes along the recurrent laryngeal nerves. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch. The lateral boundaries are the common carotid arteries.

The stylohyoid muscle, which is defined as the border separating levels Ib and IIa, cannot be recognised clinically or radiographically, therefore the author proposed

the posterior edge of the SMG as a substitute border between levels Ib and IIa. The postglandular nodes may occasionally be identified using this approach in level IIa rather than level Ib. However, this situation is not very common. The anterior central compartment of the neck should be defined using level VI, based to the American Head and Neck Society Neck Dissection Committee (Dundar et al., 2019).

The neck node involvement level, N, has prognostic significance. The prognosis is negatively correlated with the extent of neck involvement. The prognosis of the tumour is influenced by extracapsular spread (ECS), in addition to the nodal level. Clinically, palpation can be used to identify extracapsular nodes by the presence of matted nodes attached to the overlying skin. The involvement of the cranial nerves may potentially be a sign of ECS. Although imaging can detect clinical ECS, histology is currently the most accurate way to do so.

In addition to histology results, radiographic results are important in the recognition of lymph node involvement. Numerous radiological techniques exist, each with a different level of sensitivity and specificity. The sensitivity range for computed tomography (CT) is 40–68%, and the specificity range is 75–82%. The sensitivity and specificity of Positron Emission Tomography (PET)-CT are 57%-79% and 82%-96%, respectively, compared to the ranges of 55%-80% and 82%-92% offered by Magnetic Resonance Imaging (MRI). Considering these, it was determined that the use of a single modality may not be sufficient to demonstrate cervical lymph node metastases (Sharma et al., 2018; Yuen et al., 2009).

Ultrasonography is a non-ionizing imaging method. An efficient and trustworthy preoperative tool for assessing the neck is ultrasound. Lymph node metastases can be identified by ultrasound with a fair amount of sensitivity and

specificity (Dayanand et al., 2010). Loree et al, concluded in their study that sentinel biopsy is a safe and effective method which is minimally invasive in staging cN0 neck metastases cases (Loree et al., 2019). However, the debate on preferring neck dissection or direct radiotherapy in the cN0 neck is still ongoing.

Table 2.3: Nodal status (cN & pN).

Regional lymph node (N)	Description
Nx	Regional lymph node cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension.
N2	Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension.
N2a	Metastasis is single ipsilateral lymph node more than 3cm but not more than 6cm in greatest dimension.
N2b	Metastasis in single ipsilateral lymph nodes, none more than 6cm in greatest dimension.
N2c	Metastasis in bilateral contralateral lymph nodes, none more than 6cm in greatest dimension.
N3	Metastasis in a lymph node more than 6cm in greatest dimension.

Distant metastases of oral cancer can potentially spread to the lungs or the bones. Clinical history along with imaging is used to identify metastases of the cancer.

Table 2.4: Distant metastases (cM & pM).

Distant Metastasis (M)	Description
M0	No distant metastasis
M1	Distant metastasis

The nomenclature used for clinical staging is cT, cN and cM. These staging are then categorized into clinical stage groups which are anatomic/prognostic groups (AJCC, 2010). The prognostic staging is classified according to the severity of the

condition. Roman numerals of I to IV are used. Tumours which are small and less invasive with no nodal involvement are termed Stage I, whereas Stage II and III represent growing tumours or nodal extent. Stage IV includes cases that have distant metastases at the time of diagnosis.

Table 2.5: Anatomic/prognostic staging.

Stage	Tumour Size (cT/pT)	Nodal Status (cN/pN)	Distant Metastasis (cM/pM)
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3 Any	M0
	T4b	N	M0
Stage IVC	Any T	Any N	M1

2.6 Histopathology

A series of genetic alterations and epigenetic anomalies in the signalling pathway facilitates the formation of phenotypes that then lead to the development of OSCC (Hanahan & Weinberg, 2000). According to a study, the disruptions in the circuits that regulate the homeostasis and proliferation of normal cells, or cell injury led to the formation of cancer cells (Massano et al., 2006). In histological views,

following several preneoplastic damages, the cell then forms a malignant neoplasm (Fuentes et al., 2012).

Histopathologic evidence of the presence of oral epithelial dysplasia is the current gold standard in predicting malignant changes in oral potentially malignant diseases. Oral epithelial dysplasia is graded into 3 categories, which are mild, moderate, and severe dysplasia. The changes that are considered in grading epithelial dysplasia include both cytologic and architectural alterations. Loss of polarity in the basal cells, presence of rete ridges in drop-shape and keratin pearls, rise in cell division, abnormal mitosis in the surface, separation of the epithelial layers and irregular epithelial stratification are architectural changes seen in the dysplastic epithelium. Cellular changes seen are, anisonucleosis, nuclear pleomorphism, cellular pleomorphism, anisocytosis, abnormal mitotic cells, and prominent nucleoli with an increase in size and number (Ranganathan & Kavitha, 2019).

Oral SCC is a cancerous lesion that emerges from the squamous epithelium of the oral mucosa (Fuentes et al., 2012). After epithelial dysplasia, the dysplastic squamous cells proliferate differently on the epithelial layer's surface, and this causes the subepithelial basement membrane to break down, resulting in OSCC. The basement membrane deterioration leads to local destruction and distant invasion via metastasis. Local invasion is formed by epithelial cells extending into the underlying tissue as islets and cords (Fuentes et al., 2012).

2.7 Lymph node involvement in Oral Squamous Cell Carcinoma

An important prognostic factor in OSCC is the lymph node metastasis (Shingaki et al., 2003; Spoerl et al., 2021). The 5-year disease-free survival (DFS) rate varies drastically between 82% in the early stages and 49% in the advanced stages

(Massano et al., 2006). According to Sharma et al, a greater risk of cervical lymph node metastases is linked to OSCC, even in cases with small tumour size (T1 and T2) (Sharma et al., 2018).

Cervical node metastasis can be divided into clinical nodes and occult nodes. Occult nodes can be identified by hematoxylin and eosin staining or immunohistochemical or molecular analysis of the dissected lymph nodes (Massano et al., 2006). Distant metastasis and local and regional recurrence are associated with extracapsular spread (Scully & Bagan, 2009). Some authors have reported the extracapsular spread can be described as macroscopic, which can be seen with the naked eye clinically and microscopic, which is only demonstrated during histologic analysis (Massano et al., 2006).

2.8 Pathologic Staging of Oral Squamous Cell Carcinoma (pTNM)

Pathologic staging is obtained from the pathologic assessment of tissue resected during surgery, and before any supplemental treatment is given (AJCC, 2010). Table 2.1, Table 2.2, and Table 2.3 are used in pTNM as well. Unlike in the clinical assessment, the pT value can be obtained from direct measurement of the primary specimen from the surgery. Addition to the current T assessment includes the depth of invasion. This is measurement is taken from the adjacent normal mucosa to the basement membrane (Ota et al., 2021). Hence it can be assessed only in the pathological stage. Pathologic nodal status, pN is a more accurate assessment of nodal status. Metastatic nodes can be assessed for ECS. Gross ECS, is tumour that is visible beyond the nodal capsule and microscopic ECS is the presence of a metastatic tumour beyond the capsule of the lymph node. This can be confirmed with histologic

assessment Distant Metastases status follows clinical signs and symptoms supported by radiologic investigations and histopathological confirmed.

2.9 Grading of OSCC

In 1920, Broders first introduced the histopathological grading for lip cancer and later, more elaborate grading systems were introduced by Jakobsson et al and Anneroth et al and was later modified by Bryne et al (Anneroth & Hansen, 1984; Broders, 1920; Bryne et al., 1992). The systems consider features of the tumour such as differentiation, tumour invasion patterns, and inflammatory responses. However, the World Health Organisation endorses a straightforward grading system that recognises well-, moderately-, and poorly differentiated forms of the OSCC because grading alone does not correspond well with the prognosis (El-Naggar et al., 2017).

2.10 Treatment of OSCC

Oral SCC can be treated using surgery, chemotherapy, and radiation therapy, with surgery the treatment of choice for resectable lesions (Chinn & Myers, 2015). The survival rate is reduced by 50% with metastasis at regional lymph nodes. The absence of anatomic barriers, the extensive lymphatic drainage and the possibility of contralateral spread make achieving locoregional control (LRC) a challenge. Locoregional control is a critical matter and affects the overall 5-year survival rate of about 60%. Hence, effective neck management is crucial (L. G. Locatello, 2018; Locatello & Gallo, 2018).

The decision about the choice of the OSCC treatment strategy, particularly in cN0 patients, is an area of OSCC management that is the subject of the most debate

(Ren et al., 2015). Treatment for OSCC frequently involves neck dissection. At the very least, an ipsilateral modified radical neck dissection would be the preferred course of treatment in a condition that was clinically node positive. Recent studies indicate that elective neck dissection (END), as opposed to the wait-and-see approach, predicts higher diseasespecific survival and overall survival in a clinically node-negative neck (Locatello & Gallo, 2018; Wierzbicka & Napierała, 2017). The authors also added that the high diagnostic accuracy in the sentinel node biopsy has made it a more popular option amongst surgeons compared to END in the management of early-stage and cN0 OSCC (Locatello & Gallo, 2018). Excision of the main tumour in its entirety as well as neck dissection are all components of curative surgery. Even in cN0 necks, the T3/T4 OSCC warrants this. An ongoing debate exists, nonetheless, about early-stage cN0 treatment. (NCCN, 2019).

According to Ren et al (2015), over the last 5 decades, the treatment of early-stage OSCC remains controversial. However, surgery is still the go-to choice of treatment for cN0 OSCC. To address the neck involvement, there are two main strategies applied: (i) a more conservative approach which includes monitoring with a therapeutic neck dissection should nodal relapse be encountered and (ii) when the original tumour is removed, an elective neck dissection is performed.

A group of authors in favour of END, have cited that the END does offer a decrease in relapse rate as well as better disease-free survival (DFS) and overall survival rate (OS) (Capote et al., 2007; Huang et al., 2015; Keski-Santti et al., 2006). However, from the results of several randomized control trials and retrospective studies found no change that is statistically significant in the DFS and OS between therapeutic or elective neck dissections. When compared to the wait-and-watch

method, the END technique may increase the DFS and/or OS, preventing the need for a second surgical surgery in over 70% of patients. Studies have proven that END at the time of the primary tumour resection has the potential to reduce the loco-regional spread by almost 93.8% as opposed to the wait-and-watch strategy (Sharma et al., 2018). However, neck dissection does increase the cost of treatment and not to mention the risk of complications (Zhen-Hu Ren a, 2015).

A study reported that when the probability of occult metastases is more than 1520%, END should be performed to avoid the spread (Ibrahim et al., 2020). It is found that OSCC arising from the floor of mouth and tongue have a higher incidence of early metastases to cervical nodes, particularly levels I-III, as compared to OSCC from the hard palate and lip (Peng et al., 2014). Metastases from the floor of the mouth and tongue to the contralateral sides through their midline communications should also be taken into consideration. In view of that fact, those patients are best advised to END.

There is a lack of evidence in the prospective studies demonstrating the benefits of END and wait-and-watch strategy with therapeutic neck dissection (Sharma et al., 2018). Hence the debate still goes on as both wait and watch, and elective neck dissection has its proponents.

Jawdynski reported a systemic method for the en-bloc excision of cervical lymph nodes in the neck dissection in 1888, which was later popularised and illustrated by Crile in the early 20th century (Ferlito et al., 2006). The affected lymph nodes between the superficial and deep cervical fascia, as well as the neck structures close to the skull base and to the level of the clavicle, were totally resected during the en-bloc dissection. The spinal accessory nerve may be preserved if there is no gross

tumour near it. However, it was found that this approach caused long-term morbidity and deformities secondary to the sacrifice of the accessory nerve, sternocleidomastoid muscle (SCM), internal jugular vein (IJV), and the large incisions, skin flaps as well as the extent of the resection. Chronic neck and shoulder discomfort, shoulder dysfunction, and paresthesia are reported as the side effects of radical neck dissection (Fives et al., 2016).

Modification of the radical neck dissection, a technique that enabled the complete elimination of the lymph node tissue together with the primary tumour, whilst saving structures such as the SCM, omohyoid muscle, the SMG, the IJV and sometimes the spinal accessory (SA) nerve. This surgical procedure was eventually made popular by Bocca and Gavilan because it was less aggressive and equally effective for treating cancer that was in an advanced stage.

Since then, other modifications to the radical neck dissection technique have been used. The common element in these modified techniques is the removal of lymph nodes from levels I through V while preserving at least one non-lymphatic component that is sacrificed during radical neck dissection (Ferlito et al., 2006).

2.11 Submandibular Gland and its Relevance in Oral Squamous Cell Carcinoma

The SMG is a paired gland which is in the submandibular triangle. This corresponds to the level Ib neck nodes. The SMG consists of 2 lobes, a deep and a superficial lobe separated by the mylohyoid muscle. Its excretory duct is the Wharton duct which opens into the floor of the mouth at the sublingual caruncle (Bialek et al., 2006).

The SMG contributes about 70%-90% of the unstimulated salivary volume (Chen et al., 2009). Saliva is important for the lubrication of the oral cavity but is also necessary for the preparation of food for swallowing, remineralization of teeth, immunity maintenance of the oral mucosa, and antibacterial activity in the mouth (Byeon et al., 2009).

According to another researcher, the submandibular glands release roughly 70%– 75% of resting saliva when unstimulated. Even after the unilateral removal of one SMG, 21% of patients experience xerostomia. The prolonged feeling of dry mouth is strongly linked to speech and swallowing issues, impaired taste perception and an increased risk of dental caries, and oral candidiasis (Panda et al., 2015). Since salivary amylase is the enzyme that initiates the initial stage of carbohydrate digestion, decreased saliva volume may potentially have an impact on digestion. Decreased saliva may lead to gingivitis, periodontitis, and osteoradionecrosis of the mandible as a result of plaque build-up (Jaguar et al., 2010). The excision of the SMG would speed up these processes.

The dysfunction or the removal of the SMG is highly associated with xerostomia. Xerostomia is clinically associated with the alteration in taste sensation, mastication, and deglutition, which causes loss of appetite and hence weight loss. These debilitating conditions severely affect the quality of the patient's life (Okoturo et al., 2012b). The SMG, in contrast to other organs, has a poorly developed lymphatic and vascular system. (Byeon et al., 2009). In the year 1938, Rouviere and Tobies were the first to describe the perifacial lymph nodes surrounding the SMG, which were divided into the pre-glandular, pre-vascular, retro-vascular, retro-glandular, and intraglandular/intracapsular groups (S. K. Agarwal et al., 2016). Di Nardo in 1998,

added the deep submandibular nodes as a sixth group (Gu et al., 2020). In anatomical research, Di Nardo introduced the deep submandibular nodes, which may be found anyplace behind the hyoglossus muscle but underneath the SMG. The nodes were discovered to be few and irregularly distributed (DiNardo, 1998). Despite the fact that the authors of the numerous studies said there were no deep submandibular lymph nodes, some still hypothesized that if any did exist, they would be extremely rare (Dhiwakar et al., 2011; Gu et al., 2020; Yang et al., 2019). With a 0.7% incidence, the intracapsular/intraglandular lymph node presence is quite rare and is caused by advanced-stage illnesses (Chen et al., 2009).

It is extremely rare for SMG to be involved in oral cancer, especially in the early stages. (Chen et al., 2009). The rate of SMG involvement in OSCC according to the literature is around 0.096% which is around 2/2074 cases. Hence it is found to be an extremely rare occurrence (Panda et al., 2015).

It has been proposed that the SMG in OSCC cases may be involved via 3 routes. The first one is via direct extension from the primary tumour, where the cancer cells extend from the primary site and infiltrate the SMG. The second way is via extranodal extension from positive level Ib nodes, cancer cells from surrounding the nodes infiltrate the SMG. Thirdly, metastases to lymph nodes within the gland (Panda et al., 2015) In another study a fourth route was proposed, the spread of cancer via the duct of the SMG, Wharton duct (Yang et al., 2020).

Du et al. cited the most frequent model of SMG involvement is via direct invasion by tumour. This might account for 66%-100% of the cases. The floor of the mouth has the highest probability of a direct extension of the tumour to the SMG. Submandibular gland involvement through positive lymph nodes accounted as the

second model of involvement. The prevalence for this model was as low as 1.8%. The third model of involvement was metastasis via intraglandular lymph nodes. However, the authors acknowledged that there was no evidence of intraglandular nodes in their study, like previous studies in the literature (Du et al., 2020).

2.12 Preservation of Submandibular Gland in Oral Squamous Cell Carcinoma

The excision of the primary tumour and selective neck dissection of levels I to III or IV constitute the mainstay of treatment for the majority of OSCC patients. For the following reasons, the SMG has traditionally been removed during the procedure: (i) to resect level Ib lymph nodes, (ii) to shorten the time for level Ib resection, (iii) to check for potential SMG invasion, and (iv) to get a better clearance of level Ib (Dundar et al.,
2019).

The evidence of SMG invasion in OSCC cases remains a debate as recent studies show. Studies report that SMG preservation is oncologically safe in view of the low chances of SMG metastasis in oral cancer (Yang et al., 2019; Zeng et al., 2019). Byeon et al. conducted a pathologic analysis involving 201 SMG and concluded no SMG showed pathologic evidence of local extension of metastatic lymph nodes or isolated metastasis. Only two SMG presented with malignant involvement, in which cases the patients had a direct extension of the primary lesions at the retromolar trigone and floor of the mouth respectively (Byeon et al., 2009). Similarly, researchers discovered in another study that the involvement of the gland appears to be caused by the SMG's proximity to the main tumour. The authors claimed that SMG is involved directly, rather than indirectly, through lymphatics, via the

spread of metastatic lymph nodes with extra-nodal extension. In their investigation, no micrometastatic foci were seen near the glands that were affected (Yang et al., 2019). Studies indicate that the fibrous capsule of the SMG serves as a good barrier to the spread of SCC even when the gland is compressed by bulky metastatic disease (Woolgar & Triantafyllou, 2009).

The SMG can be preserved unless there is a direct extension of cancer to the SMG or nearby metastatic lymph nodes, according to research. Metastasis to the SMG itself is quite uncommon, and if the removal of the lymph nodes at level Ib is necessary, it is possible to do so. Pre-vascular and retro-vascular nodes, which are the main afferent draining nodes from the mouth cavity, are the most significant of the nodes around the

SMG (Takes et al., 2011). Dhiwakar et al. stated the lymphatic compartment of the level Ib, between the superficial and deep layers of the cervical fascia can be easily separated from the parenchyma of the SMG once the submandibular fascia is incised (Dhiwakar et al., 2011). Although the surgeons will need to take a longer time to clear out the nodes, this will enable the preservation of the SMG during neck dissection which is a feasible and safe option (Yang et al., 2020).

The strongest support for SMG preservation comes from survival analyses (Gu et al., 2020). The authors of a study indicated that among patients with buccal SCC, the 5year disease-free survival rates were 75% and 69%, respectively, and that the variations between these numbers were not statistically significant($p=0.83$) (Chen et al., 2009). The locoregional control (LCR) and disease-specific survival (DSS) of patients with SMG preservation were compared to those without SMG preservation in a study. The findings of the study indicated both LCR and DSS were insignificantly

affected by the SMG preservation (Du et al., 2020). For the greatest functional and oncologically safe outcomes, according to Lanzer et al., studies advise the preservation of the SMG in tumours that are node-negative and do not require radiotherapy (Lanzer et al., 2014).

The SMG, according to Zeng et al., has a high blood supply and is favourable in the correction of surgical defects postoperatively (Zeng et al., 2019). The SMG has a significant twist angle, making it suitable for the reconstructing of the tongue's ventral portion and the floor of the mouth. On the other hand, some surgeons believe that maintaining the SMG may result in a persistent palpable mass at the location of the patient's previous lymphadenectomy. Additionally, these glands frequently produce scars that the patient and the head and neck surgeon treating the patient may find concerning (Malgonde & Kumar, 2015). Hence, the preservation of SMG in OSCC cases remains a controversy.

CHAPTER 3: METHODOLOGY

3.1 Research Ethics

This study was approved by the Medical Ethics Committee, Faculty of Dentistry, Universiti Malaya (UM) [Reference number: DF OS2104/0012 (P)] and the Malaysian Research and Ethics Committee (MREC) under National Malaysian Research Register (NMRR) [Reference number: NMRR ID-21-00214-81g (IIR)].

3.2 Study Method and Population

This was a cross-sectional study utilizing retrospective data collected from the Department of Oral and Maxillofacial Clinical Sciences, Faculty of Dentistry, (UM) and Department of Oral and Maxillofacial Surgery, Tengku Ampuan Rahimah Hospital (HTAR), Klang. The study population included all cases diagnosed with oral squamous cell carcinoma (OSCC) from January 2000 to December 2020.

Inclusion criteria:

i. All cases which were diagnosed by histopathological examination (HPE) as squamous cell carcinoma (SCC).
ii. All cases are diagnosed with SCC with the primary site within the oral cavity.
iii. All cases have undergone neck dissection as part of the treatment modality for SCC.
iv. All cases of OSCC which have been followed up by a minimum of 1-year postoperatively.

Exclusion criteria:

i. Any OSCC cases that have received preoperative radiotherapy or chemotherapy.

ii. Any OSCC cases that have not been treated surgically.

iii. Any cases diagnosed with oral cancer other than SCC.

A case proforma was designed and used to record the details from the medical records of the selected cases. Details recorded include:

i. Demographic data such as age, gender, and ethnicity.

ii. Clinical parameters such as site, clinical tumour size (cT) (Table 3.1), clinical nodal status (cN) (Table 3.2), clinical distant metastasis (cM) (Table 3.3) and clinical TNM (cTNM) staging (Table 3.4) based on the 7th edition American Joint Committee on Cancer (AJCC).

iii. Histopathological parameters such as pathological tumour size (pT) (Table 3.1), pathological nodal status (pN) (Table 3.2), pathological distant metastasis (pM) (Table 3.7) and pathological TNM (pTNM) (Table 3.3) staging based on the 7th edition AJCC, submandibular gland status, and level 1b lymph node status. iv. Treatment data such as date of surgery, type of surgery and adjuvant therapies.

v. Recurrence data such as status (positive tumour finding at the same site/adjacent structures postoperatively) and date of recurrence.

vi. Survival status such as date of diagnosis, date of last visit and date of death. Overall survival (OS) status was calculated from the time of diagnosis till the date of death or the censor date, 31st of December 2021. Disease-free survival

was calculated from the date of treatment completion to the date of tumour recurrence or till the date of death or the censor date, 31st of December 2021.

Table 3.1: Clinical tumour size (cT) and pathological tumour size (pT) based on the 7th edition American Joint Committee on Cancer (AJCC).

Primary Tumor (T)	Criteria
Tis	Carcinoma in situ.
T1	Tumor 2cm or less in greatest dimension.
T2	Tumor more than 2cm but not more than 4cm in greatest dimension.
T3	Tumor more than 4cm in greatest dimension.
T4a	Moderately advanced local disease: (Lip) Tumor invades through cortical bone, the inferior alveolar nerve, the floor of the mouth, or the skin of the face, that is chin/nose. (Oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone) [mandible or maxilla] into the deep [extrinsic] muscle of the tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, the skin of the face).
T4b	Very advanced local diseases: Tumor invades masticator space, pterygoid plates, or skull base and /or encases internal carotid artery.

Table 3.2: Clinical lymph node status (cN) and pathological tumour status (pN) based on 7th edition American Joint Committee on Cancer (AJCC).

Regional lymph node (N)	Criteria
Nx	Regional lymph node cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension.
N2	Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension.
N2a	Metastasis is single ipsilateral lymph node more than 3cm but not more than 6cm in greatest dimension.
N2b	Metastasis in single ipsilateral lymph nodes, none more than 6cm in greatest dimension.
N2c	Metastasis in bilateral contralateral lymph nodes, none more than 6cm in greatest dimension.
N3	Metastasis in a lymph node more than 6cm in greatest dimension.

Table 3.3: Clinical distant metastasis (cM) and pathological distant metastasis (pM) based on 7th edition American Joint Committee on Cancer (AJCC).

Distant Metastasis (M)	Criteria
M0	No distant metastasis
M1	Distant metastasis

Table 3.4: Anatomic staging / prognostic groups.

Stage	Tumour Size	Nodal Status	Distant Metastasis
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M9
	T4a	N2	M0
Stage IVB	Any T T4b	N3 Any	M0
		N	M0
Stage IVC	Any T	Any N	M1

All clinical staging and pathological staging were recorded as per the 7th edition AJCC manual. The study included patients diagnosed with OSCC from the year 2000 to 2020. As the latest 8th edition AJCC manual was only issued in 2016. Therefore, for the purpose of standardization, 7th edition AJCC was used for reference.

The status of the submandibular gland (SMG) and lymph node of level 1b were recorded based on record on the histopathologic examination reporting as positive with tumour involvement or negative, free of tumour involvement. The type of neck management was recorded in terms of the patient's surgical procedure.

Postoperatively, the status of the patient having adjuvant radiotherapy, chemotherapy or both was also documented. Overall survival (OS) was recorded from the time of diagnosis till the last visit or date of the deceased or censor date 31st December 2021. Disease-free survival (DFS) is recorded from the time of treatment completion till the date of recurrence, the date of death or the date of the censor date,31st December 2021.

3.3 Study Algorithm

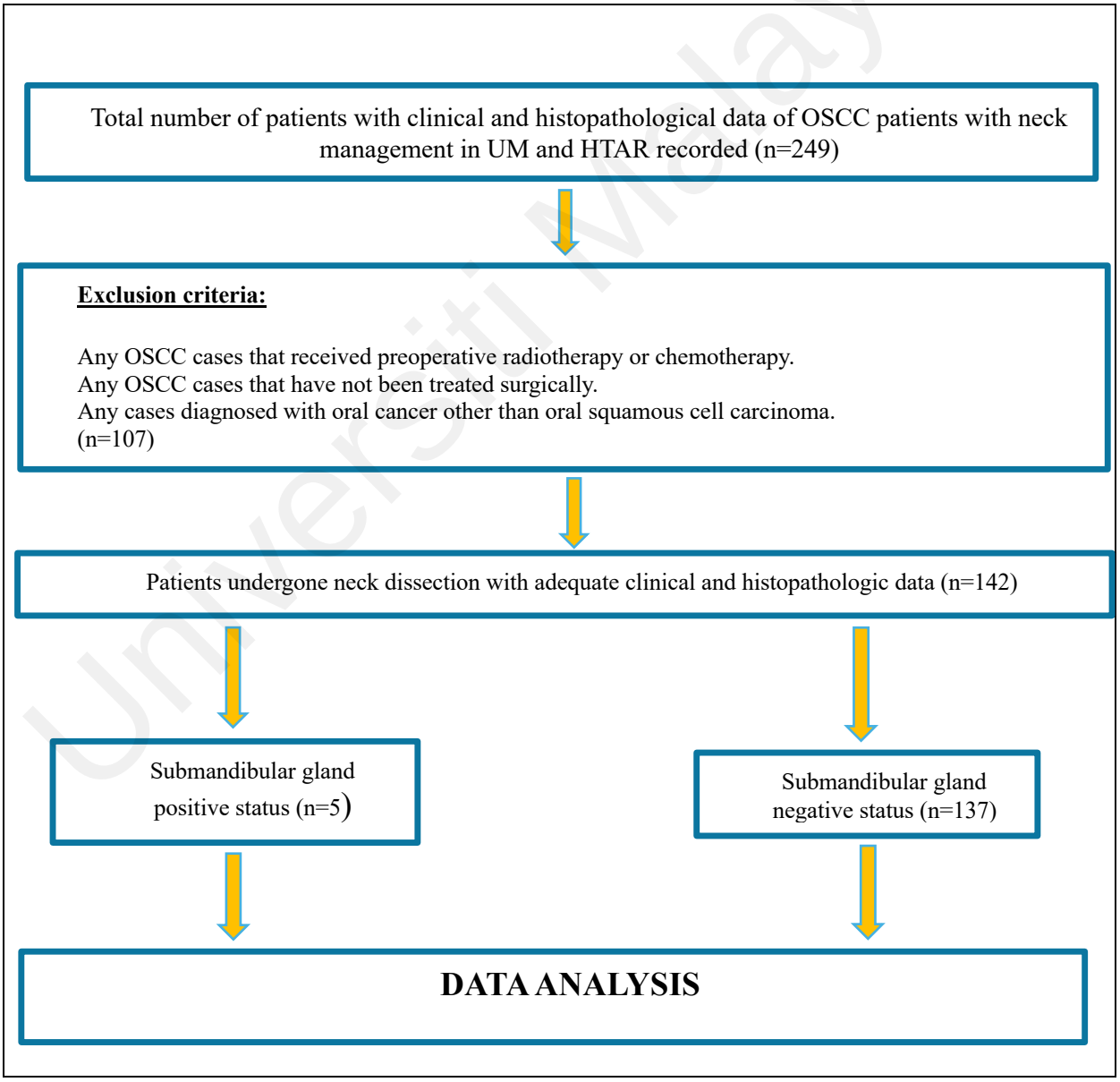

Figure 3.1: Illustrates the selection criteria of cases in this study.

3.4 Statistical Analysis

Data entry and data analysis were done using the Statistical Package for the Social Sciences (SPSS) software. Analysis was done according to the specific objectives of the study.

The prevalence of SMG involvement was statistically analyzed using descriptive statistics. Frequency and percentages were calculated for the categorical variables. To analyze the association between the involvement of the SMG and cases with level Ib lymph nodes Chi-square test was used. This statistical test allowed for the evaluation of the independence of these categorical variables and the determination of any significant relationships between them. Fisher exact test was used where applicable.

The association of the overall survival and disease-free survival of patients with SMG and level Ib involvement respectively were analyzed using the Kaplan-Meir test. This non-parametric approach enabled the estimation of survival probabilities and the generation of survival curves, providing insights into the time-to-event outcomes for the study population. In addition, the log-rank test was conducted to assess the significant differences in survival time for SMG status and level Ib lymph node status.

CHAPTER 4: RESULTS

A total of 249 OSCC cases were identified from the medical records of the Department of Oral & Maxillofacial Clinical Sciences, Faculty of Dentistry, UM and Department of Oral and Maxillofacial Surgery, HTAR. Based on the inclusion and exclusion criteria of the study, 107 cases were eliminated. A total of 142 samples were included in this study and analyzed.

4.1 Demographic characteristic

Table 4.1 shows the demographic characteristics of patients with OSCC treated with neck dissection. The mean age (±SD) of the OSCC patients included in this study was 56.07 (±12.61) years old. Most of the patients included in this study were female 76 (53.5%) and 66 (46.5%) were male patients. In this study, Indians were the largest ethnic group 68 patients (47.9%) followed by Chinese 47 (33.1%). Others were foreigners, accounting for the minority group of 3.5%.

Table 4.1: Demographic characteristics of patients with oral squamous cell carcinoma (OSCC) included in this study (n=142).

Demographic characteristics	**n (%)**
Age in mean (SD)	56.07 (±12.61)
Gender	
Female	76 (53.5)
Male	66 (46.5)
Ethnicity	
Malay	22 (15.5)
Chinese	47 (33.1)
Indian	68 (47.9)
Others	5 (3.5)

4.2 Clinical characteristics

Table 4.2 shows the clinical characteristics of patients with OSCC treated with neck dissection. The tongue and floor of the mouth accounted for the greatest number of cases (52.1%), followed by buccal mucosa (21.8%) and upper gingiva (17.6%). The least number of cases involved the lip (3.5%).In terms of prognostic staging, most patients were categorized as Stage IV (38.7%) and the least were found to be in Stage III (13.7%).

Table 4.2: Clinical characteristics of patients with oral squamous cell carcinoma (OSCC) included in this study (n=142).

Clinical characteristics	n (%)
Site	
Tongue & Floor of Mouth	74 (52.1)
Lip	5 (3.5)
Buccal Mucosa	31 (21.8)
Upper Gingiva	25 (17.6)
Lower Gingiva	7 (4.9)
Tumor Size	
T1	43 (35.2)
T2	45 (36.9)
T3	4 (3.3)
T4	30 (24.6)
Nodal Status	
N0	66 (52.8)
N1	28 (22.4)
N2	31 (24.8)
N3	0 (0.0)
N4	0 (0.0)
Distant Metastasis	
M0	142 (100.0)
M1	0 (0.0)
Staging	
I	33 (26.6)
II	26 (21.0)
III	17 (13.7)
IV	48 (38.7)

4.3 Histopathological characteristic

Table 4.3 provides information on various variables related to the disease, including the pT, pN, pM, pTNM staging and SMG status, and the status of level Ib nodes.

Based on the findings, pT, T2 had the highest (39.0%), and the least had T3 (10.7%). The highest nodal status, pN were from N0 and the least in N1. There were no cases reported with any distant metastases, M0. The cancer prognostic stage distribution revealed a higher prevalence of stage 4 (41.9%), and stage 3 the least (10.3%). Most patients had a negative status for the involvement of the SMG, with 137 patients (96.5%). According to the level Ib node status, 123 patients (86.6%) had a negative status. Figure 4.1 shows the normal SMG. Figure 4.2 shows the SMG with the invasion of the OSCC destroying the

SMG. Figure 4.3 shows the level Ib lymph node without extracapsular spread (ECS) and Figure 4.4 shows level Ib lymph node with ECS.

Table 4.3: Histopathological characteristics of patients with oral squamous cell carcinoma (OSCC) included in this study (n=142).

Histopathological characteristics	n (%)
Tumor Size	
T1	35 (24.8)
T2	55 (39.0)
T3	15 (10.7)
T4	36 (25.5)
Nodal Status	
N0	86 (61.4)
N1	22 (15.7)
N2	32 (22.9)
N3	0 (0.0)
N4	0 (0.0)
Distant Metastasis	
M0	142 (100.0)
M1	0 (0.0)

Staging	
I	27 (19.9)
II	38 (27.9)
III	14 (10.3)
IV	57 (41.9)
Submandibular Status	
Negative	137 (96.5)
Positive	5 (3.5)
Level Ib lymph node	
Negative	123 (86.6)
Positive	19 (13.4)

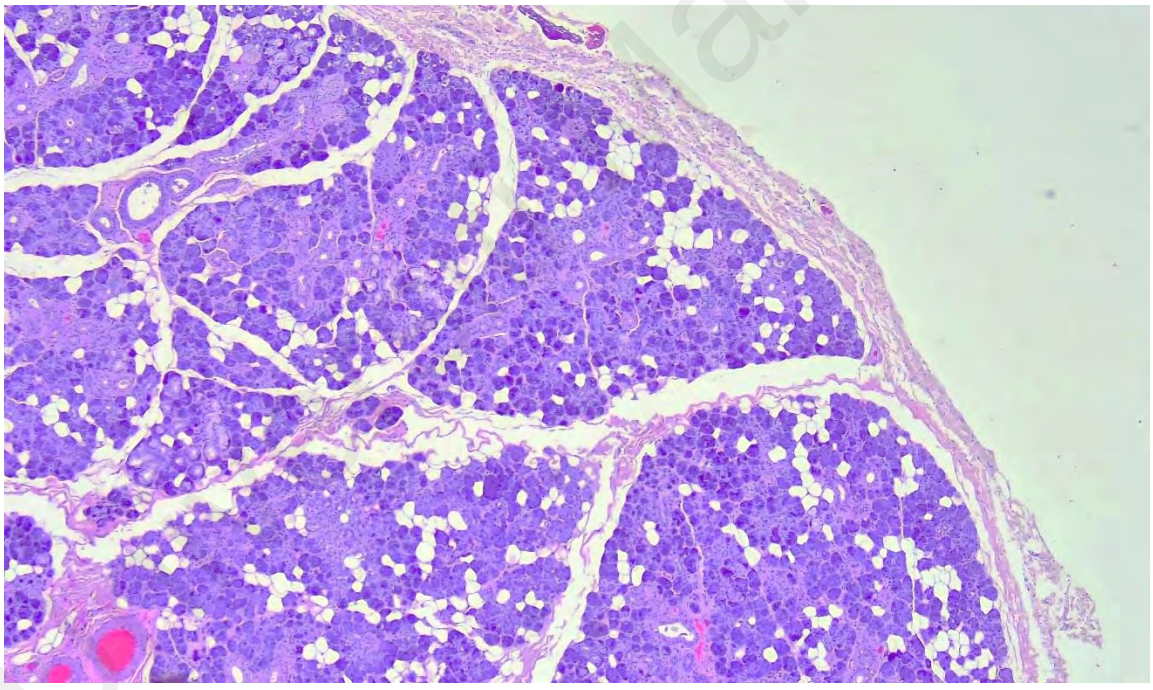

Figure 4.1: Photomicrograph shows normal submandibular gland (Stain: H&E).

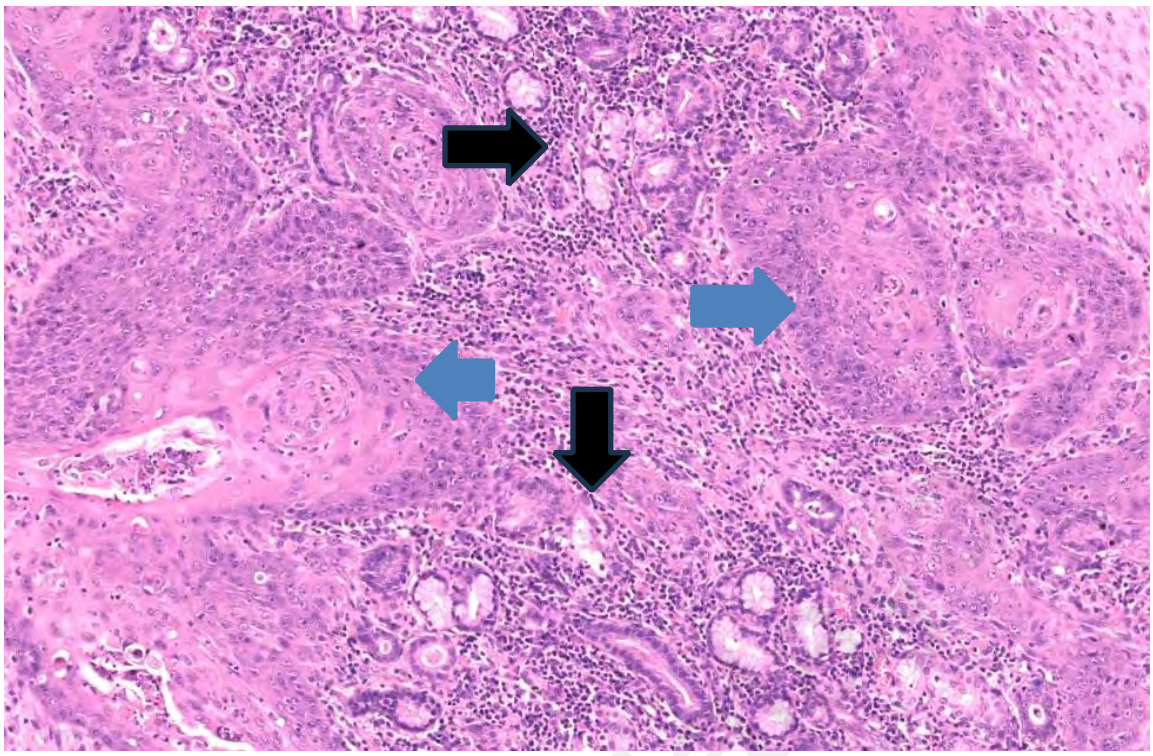

Figure 4.2: Photomicrograph shows submandibular gland (black arrows) with invasion of the oral squamous cell carcinoma (blue arrows) (Stain: H&E).

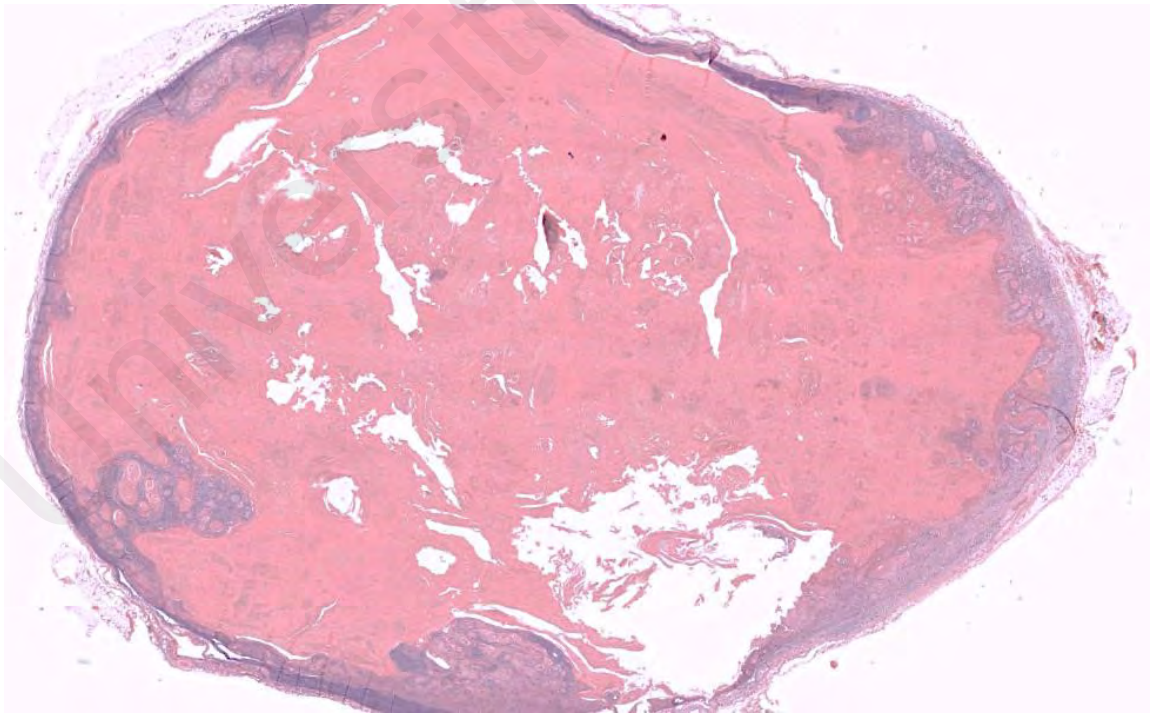

Figure 4.3: Photomicrograph shows level Ib lymph node with invasion of the oral squamous cell carcinoma without extracapsular spread (Stain: H&E).

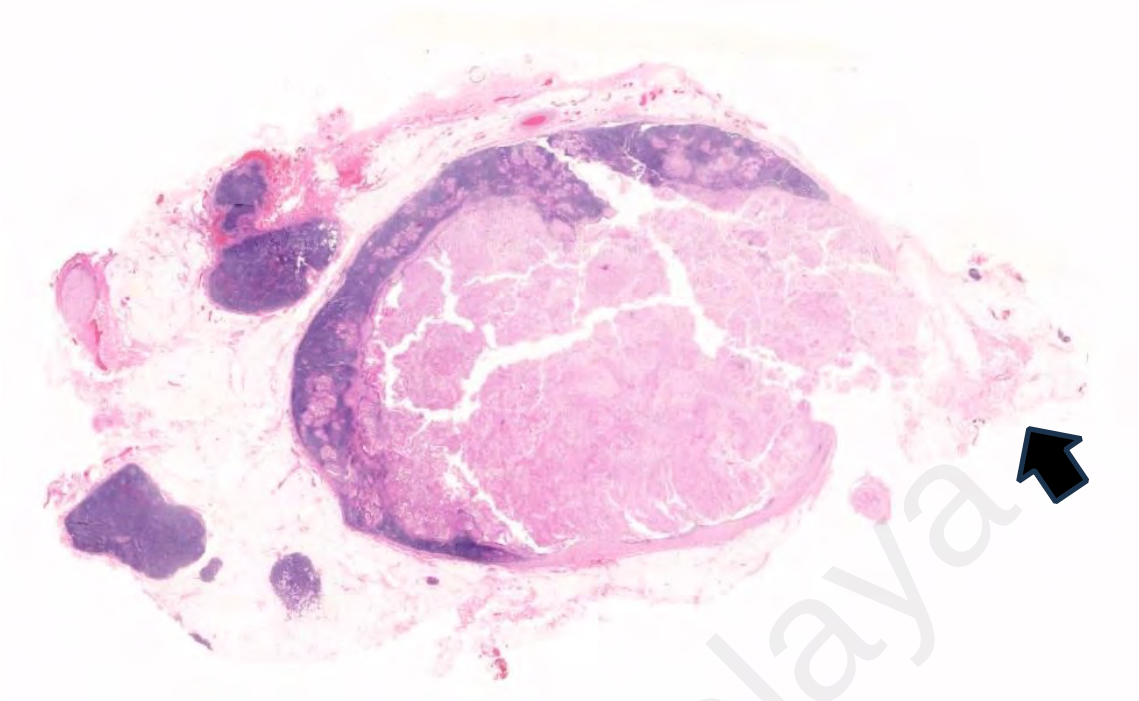

Figure 4.4: Photomicrograph shows level Ib lymph node with invasion of the oral squamous cell carcinoma with extracapsular spread (black arrow) (Stain: H&E).

4.4 Treatment Data

Table 4.4 represents the various treatment modalities undergone by patients diagnosed with OSCC. According to the table, most of the patients underwent surgery only, which is 72.5%. Patients who underwent surgery and radiotherapy account for 22.5%. A minority of 4.9% had surgery and concurrent chemo and radiotherapy.

Table 4.4: Treatment data of patients with oral squamous cell carcinoma (OSCC) included in this study (n=142).

Treatment Data	n (%)
Types of Treatment	
Surgery only	103 (72.5)
Surgery + RT	32(22.5)
Surgery + CCRT	7(4.9)

4.5 Recurrence Data

Table 4.5 describes the details of recurrence among patients in the study. Out of 142 patients, 12 patients were found to have recurrence. Most cases were from Stage IV with prevalence (41.7%). No cases with recurrence were from Stage I.

Table 4.5: Recurrence of patients with oral squamous cell carcinoma (OSCC) included in this study (n=142).

Recurrence	n (%)
Present	12(9.3)
Stage	
I	0 (0.0)
II	4 (33.3)
III	3 (25.0)
IV	5 (41.7)
Absent	117 (90.7)
Stage	
I	26 (22.2)
II	37 (31.6)
III	12 (10.3)
IV	42 (35.9)

4.6 Survival Status

Table 4.6 gives the details on the survival status of the patients in this study. A majority of 73.2% of the study population was still alive at the end of the study period. 26.1% of the study population were deceased and 1 (0.7%) case had a loss of follow-up information then.

Table 4.6: Survival status of patients with oral squamous cell carcinoma (OSCC) included in this Study (n=142).

Survival Status	n (%)
Alive	104 (73.2)
Deceased	37 (26.1)
Lost to follow-up	1 (0.7)

4.7 Association between the Demographic Characteristics and level Ib Node Status

Table 4.7 presents the association between demographic characteristics and level 1b nodal status. There were no statistically significant associations observed between age, gender and ethnicity and the level Ib node status.

Table 4.7: Association between demographic and level Ib lymph node status.

Demographic	Level Ib LN Negative n (%)	Level Ib LN Positive n (%)	Total n (%)	*P*value
Age in mean (SD)	56.26 (12.33)	54.84 (14.59)	56.07 (12.61)	0.650[a]
Gender				
Male	59 (48.0)	7 (36.8)	66 (46.5)	0.366
Female	64 (52.0)	12 (63.2)	76 (53.5)	
Ethnicity				
Malay	19 (15.4)	3 (15.8)	22 (15.5)	0.933
Chinese	40 (32.5)	7 (36.8)	47 (33.1)	
Indian	60 (48.8)	8 (42.1)	68 (47.9)	
Others	4 (2.4)	1 (5.3)	5 (3.5)	

[a]Independent t-test applied; normality and equal variances assumptions were fulfilled.

4.8 Association between the Demographic Characteristics and Submandibular Gland (SMG) Status

Table 4.8 presents the association between demographic characteristics and SMG status. There was no statistically significant association between age, gender, ethnicity, and SMG status.

Table 4.8: Association between demographic characteristics and submandibular gland (SMG)

Sociodemographic	SMG negative	SMG Positive	Total n (%)	*P*-value
Age in mean (SD)	56.10 (12.67)	55.20 (12.09)	56.07 (12.61)	0.876[a]
Gender				
Male	66 (48.2)	0 (0.0)	66 (46.5)	0.061[b]
Female	71 (51.8)	5 (100.0)	76 (53.5)	
Ethnicity				
Malay	20 (14.6)	2 (40.0)	22 (15.5)	
Chinese	46 (33.6)	1 (20.0)	47 (33.1)	0.119[b]
Indian	66 (48.1)	2 (40.0)	68 (48.6)	
Others	5 (3.6)	0 (0.0)	5 (2.8)	

[a]Independent t-test applied; normality and equal variances assumptions were fulfilled.

4.9 Association between the Clinical Characteristics and Status of Level Ib Node

Table 4.9 represents the association between clinical characteristics and the status of the level Ib lymph node. No statistically significant association was found between the site, cT, cN, cM and the clinical staging of the lesion with the status of the level Ib node.

Table 4.9: Association between clinical characteristics and status of level Ib lymph nodes.

Clinical characteristics	Level Ib Lymph Node Negative n (%)	Level Ib lymph node Positive n (%)	Total n (%)	*P*value
Site				
Tongue and FOM	63 (51.2)	11(57.9)	74 (52.1)	0.783
Lip	5 (4.1)	0 (0.0)	5 (3.5)	
Buccal mucosa	26 (21.1)	5 (26.3)	31(21.8)	
Upper gingiva	23 (18.7)	2 (10.5)	25 (17.6)	
Lower gingiva	6 (4.9)	1 (5.3)	7 (4.9)	
Tumour Size				
T1	38 (35.2)	5 (35.7)	43 (35.2)	0.297
T2	42 (38.9)	3 (21.4)	45 (36.9)	
T3	4 (3.7)	0 (0.0)	4 (3.3)	
T4	24 (22.2)	6 (42.9)	30 (24.6)	

Nodal Status				
N0	61(55.0)	5 (35.7)	66 (52.8)	0.068
N1	26 (23.4)	2 (14.3)	28 (22.4)	
N2	24 (21.6)	7 (50.0)	31 (24.8)	
Staging				
I	30 (27.3)	3 (21.4)	33 (36.6)	0.190
II	25 (22.7)	1 (7.1)	26 (21.0)	
III	16 (14.5)	1 (7.1)	17 (13.7)	
IV	39 (35.5)	9 (64.3)	48 (38.7)	

4.10 Association between the Clinical Characteristics and Submandibular Gland (SMG) Status

Table 4.10 presents the association between clinical characteristics and SMG status. There was no statistically significant association found between the site, cT, cN, cM and the staging of the lesion with the submandibular gland status.

Table 4.10: Association between the clinical characteristics and submandibular gland (SMG) status.

Clinical characteristics	Submandibular gland Negative n (%)	Submandibular gland Positive n (%)	Total n (%)	*P*-value
Site				
Tongue and FOM	74 (54.0)	0 (0.0)	74 (52.1)	0.089
Lip	5 (3.6)	0 (0.0)	5 (3.5)	
Buccal mucosa	28 (20.4)	3 (60.0)	31 (21.8)	
Upper gingiva	23 (16.8)	2 (40.0)	25 (17.6)	
Lower gingiva	7 (5.1)	0 (0.0)	7 (4.9)	
Tumor Size				
T1	41(34.7)	2 (50.0)	43(35.2)	0.39
T2	45(38.1)	0 (0.0)	45 (36.9)	
T3	4 (3.4)	0 (0.0)	4 (3.3)	
T4	28(23.7)	2 (50.0)	30 (24.6)	

Nodal Status				
N0	66 (54.5)	0 (0.0)	66 (52.8)	
N1	26 (21.5)	2 (50.0)	28 (22.4)	0.098
N2	29 (24.0)	2 (50.0)	31 (24.8)	
Staging				
I	33 (27.5)	0 (00.0)	33 (26.6)	0.289
II	26 (21.7)	0 (0.0)	26 (21.0)	
III	16 (13.3)	1 (25.0)	17 (13.7)	
IV	45 (37.5)	3 (75.0)	48 (38.7)	

4.11 Association between the Histopathological Characteristic and Level Ib Nodal Status

Table 4.11 presents the association between the pT, pN, pM and pathological staging with the level Ib lymph node status. There was a significant association between the pN and the level Ib lymph node status. Most of the cases with positive level Ib status were found to have node status of N2. Many cases with positive level Ib lymph nodes were from Stage 4, followed by Stages I and III equally.

Table 4.11: Association of histopathologic characteristics and status of level Ib lymph node.

Histopathological characteristics	Level Ib Lymph Node Negative n (%)	Level Ib lymph node Positive n (%)	Total n (%)	*P*-value
Tumor Size				
T1	30 (24.6)	5 (26.3)	35 (24.8)	0.706
T2	50 (41.0)	5 (26.3)	55 (39.0)	
T3	12 (9.8)	12 (9.8)	15 (10.6)	
T4	30 (24.6)	30 (24.6)	25.5 (25.5)	
Nodal Status				
N0	84 (69.4)	2 (10.5)	86 (61.4)	
N1	17 (14.0)	5 (26.3)	22 (15.7)	<0.001
N2	20 (16.5)	12 (63.2)	32 (22.9)	

Staging				
I	25 (20.7)	2(10.5)	27 (19.3)	
II	42 (34.7)	1 (5.3)	43 (30.7)	0.007
III	13 (10.7)	2 (10.5)	15 (10.7)	
IV	41 (33.9)	14 (73.7)	55 (39.3)	

4.12 Association between the Histopathological Characteristic and Submandibular Gland (SMG) Status

Table 4.12 presents the association between the pT, pN and staging with the submandibular gland status. No statistically significant association was found. Most cases with positive submandibular gland status were found in stage IV.

Table 4.12: Association of histopathological characteristics and submandibular gland (SMG) status.

Histopathological characteristics	**Submandibular Gland Negative n (%)**	**Submandibular Gland Positive n (%)**	**Total n (%)**	***P*-value**
Tumour Size				
T1	34 (25.0)	1(20.0)	35 (24.9)	
T2	54 (39.7)	1(20.0)	35 (39.0)	0.471
T3	15 (11.0)	0 (0.0)	15 (10.6)	
T4	33(24.3)	3 (60.0)	36(25.5)	
Nodal Status				0.573
N0	84 (62.2)	2 (40.0)	86 (61.4)	
N1	21 (15.6)	1 (20.0)	22 (15.7)	
N2	30 (22.2)	2 (40.0)	32 (22.9)	
Staging				
I	27 (20.6)	0 (0.0)	27 (19.9)	0.324
II	37 (28.2)	1 (20.0) 0	38 (27.9)	
III	14 (10.7)	(0.0)	14 (10.3)	
IV	53 (40.5)	4 (80.0)	57 (41.9)	

4.13 Association between the Submandibular Gland Status and the Level Ib Lymph Node Status

Table 4.13 presents the data on the association of the SMG status and level Ib lymph node. A total of 3.5 % of the cases had positive SMG involvement. There were 10.5% of the positive level Ib lymph node patients with positive SMG involvement. A majority of 120 (97.6) patients had both SMG and level Ib lymph node status negative.

Table 4.13: Association between level Ib Lymph node status and submandibular gland (SMG) status.

Submandibular gland status	Level IB lymph node Status Negative n(%)	Level IB lymph node Status Positive n (%)	Total n (%)	*P*-value
Submandibular gland Negative	120 (97.6)	17 (89.5)	137 (96.5)	0.075
Submandibular gland Positive	3(2.4)	2 (10.5)	5 (3.5)	

Pearson chi-square test applied; less than 20% of expected count<5.

4.14 Association between the Treatment and Level Ib Lymph Node Status

Table 4.14 describes the association of the treatment modalities with the level Ib lymph node status. It is found that there is no significant association between the level Ib and the various treatment modalities. Most of the patients with positive level Ib lymph nodes had undergone surgery only. Surgery and radiotherapy were the next

most common treatment option, accounting for 31.6% of the positive level Ib lymph node patients. The least common treatment modality was surgery and CCRT.

Table 4.14: Association between treatment data and level Ib lymph node status.

Treatment Data	Level Ib lymph node Negative n (%)	Level Ib lymph node Positive n (%)	Total n (%)	*P*-value
Surgery only	91 (74.0)	12 (63.2)	103 (72.5)	
Surgery + RT	26 (21.1)	6 (31.6)	32 (22.5)	0.587
Surgery + CCRT	6 (4.9)	1 (5.3)	7 (4.9)	

4.15 Association between the Treatment Data and Submandibular Gland (SMG) Status

Table 4.15 presents the association between the treatment modalities and the SMG status. More than half of the patients, (72.5%) have undergone surgery alone. In patients with positive SMG, 40% of the patients underwent surgery alone and 40% had surgery and radiotherapy. Only a minority of 1% had surgery and CCRT.

Table 4.15: Association between the treatment data and submandibular gland (SMG) status.

Treatment Data	Submandibular gland Negative n (%)	Submandibular gland Positive n (%)	Total n (%)	*P*-value
Surgery only	101(73.7)	2 (40.0)	103(72.5)	
Surgery + RT	30 (21.9)	2 (40.0)	32 (22.5)	0.146
Surgery+CCRT	6 (4.4)	1 (20.0)	7 (4.9)	

Pearson chi-square test applied; less than 20% of expected count<5.

4.16 Association between the recurrence and level Ib lymph node status

Table 4.16 presents the association between the recurrence and the level Ib lymph node status of the study population. It was found that there is no statistically significant

association between the recurrence and the status of the level Ib lymph node. 13.3 percent of the cases with positive level Ib node had a recurrence.

Table 4.16: Association between recurrence and level Ib lymph node status.

Recurrence	Level Ib lymph node Negative n (%)	Level Ib lymph node Positive n (%)	Total n (%)	*P*value
Present	10 (8.8)	2 (13.3)	12 (9.3)	0.631[b]
Absent	104 (91.2)	13 (86.7)	117 (90.7)	

[b]Fisher-exact test applied; more than 20% of expected count<5.

4.17 Association between the Recurrence and Submandibular Gland (SMG) Status

Table 4.17 presents the association between the rate of recurrence and submandibular gland status. It was found that most patients with negative submandibular glands did not have a recurrence (91.2%). However, 40% of the patients with positive SMG have recurrence.

Table 4.17: Association between recurrence and submandibular gland (SMG) status.

Recurrence	Submandibular Gland Negative n (%)	Submandibular Gland Positive n (%)	Total n (%)	*P*-value
Present	11 (8.8)	2(40.0)	13 (9.3)	0.327[b]
Absent	114 (91.2)	3(60.0)	117 (90.7)	

[b]Fisher-exact test applied; more than 20% of expected count<5

4.18 Association between Overall Survival (OS) and Level Ib Lymph Node Status.

Figure 4.5 represents the curve of association between the overall survival and the level Ib status of patients in this study. The patients with negative level Ib lymph

nodes have statistically significantly better survival status (88.2%) than those with positive level Ib lymph node status (77.8%).

4.19 Association between Overall Survival (OS) and Submandibular Gland (SMG) Status

Figure 4.6 shows the association between the SMG status and the OS survival of patients in the study. The OS of patients with positive and negative SMG status are 60% and 88.8% respectively. The result is statistically significant.

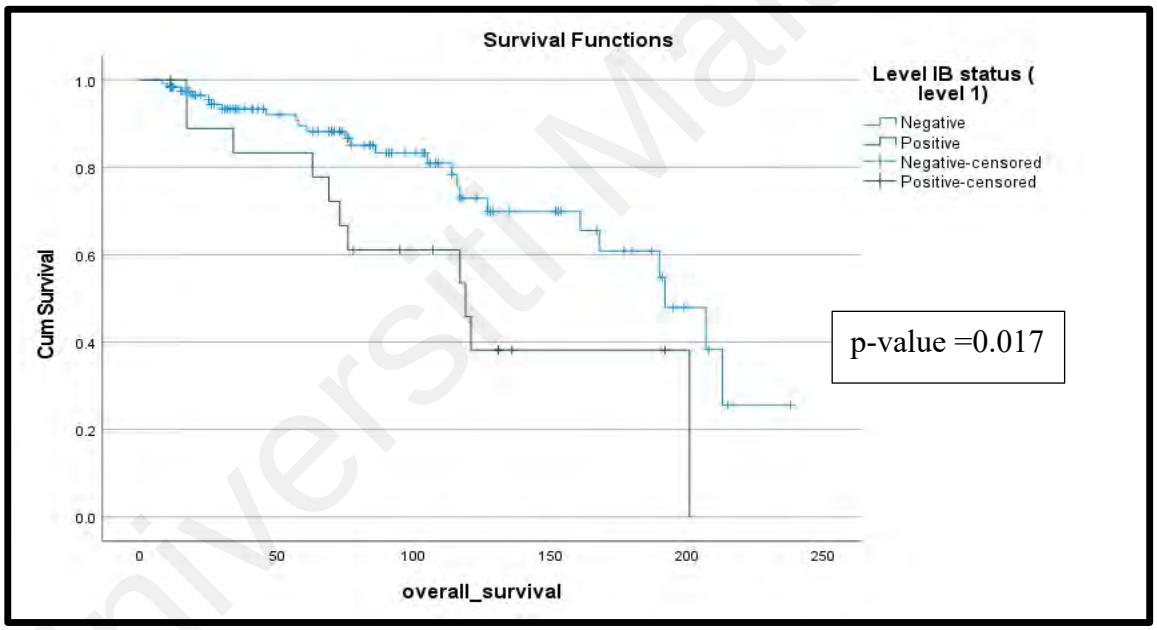

Figure 4.5 Association between the overall survival (OS) and level Ib lymph node status.

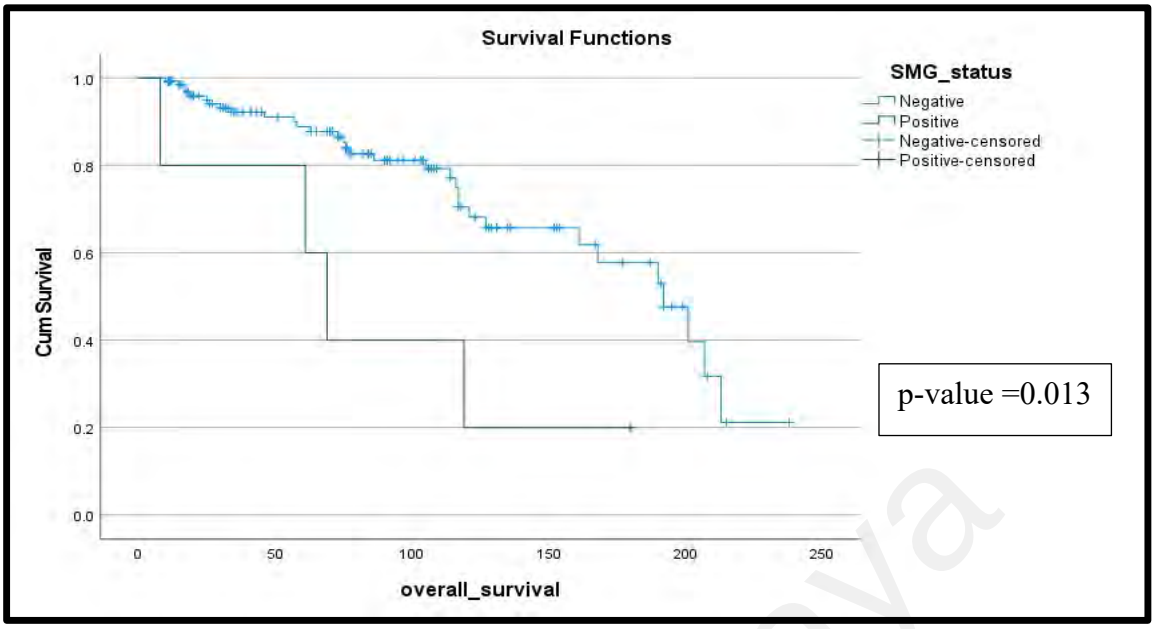

Figure 4.6: Association between the overall survival (OS) and submandibular gland (SMG) status.

4.20 Association between Disease-Free Survival and Level Ib Lymph Node Status

Figure 4.7 shows the association between the level Ib lymph node status and the disease-free survival of patients in the study. The disease-free survival period does not have a significant difference.

4.21 Association between Disease-Free Survival (DFS) and Submandibular Gland (SMG) Status.

Figure 4.8 represents the curve of association between the DFS and the SMG status. It shows a significant difference, the SMG-negative patients having a longer disease-free period (95%) compared to those with SMG involvement (80%).

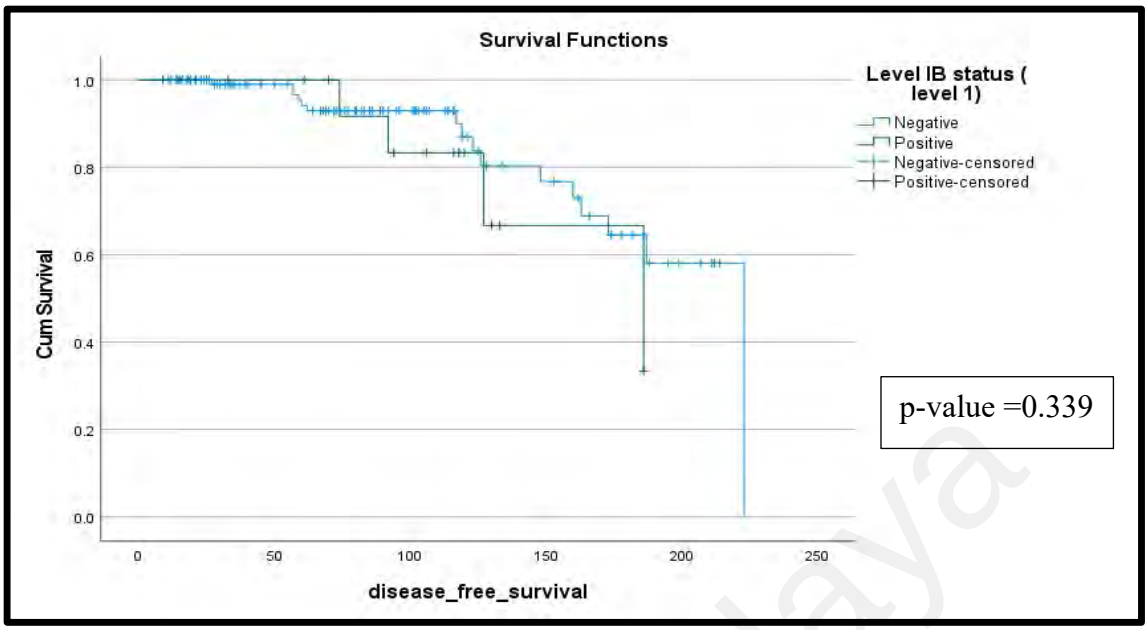

Figure 4.7: Association between disease-free survival (DFS) and level Ib lymph node status.

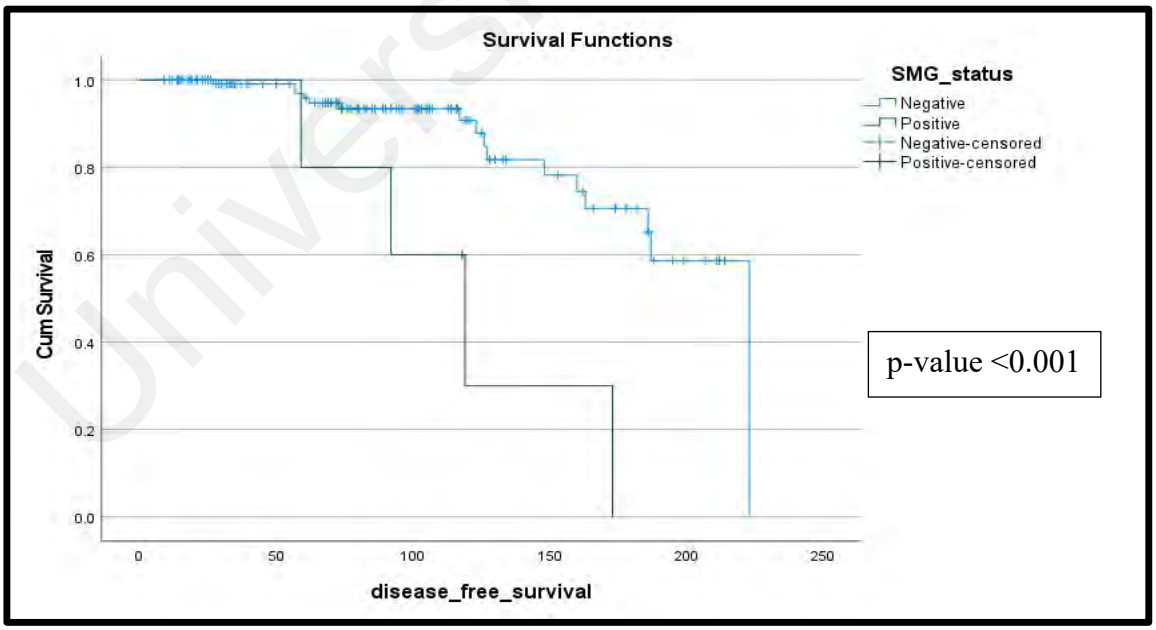

Figure 4.8 Association between the disease-free survival (DFS) and submandibular gland (SMG) status

4.22 Demographic & Clinicopathological Characteristics of Positive Submandibular Gland (SMG) Cases

Table 4.18 represents the demographic and clinicopathological characteristics of all the patients found to have SMG status in this study. Only five cases (3.5%) out of the 142 cases had SMG involvement with tumour. The first case was a Malay woman of 49year-old, who underwent neck dissection and had OSCC of the buccal mucosa with a pathological staging of T1N2bM0 (stage 4) with a poorly differentiated SCC. The lymph nodes at level 1b were involved. Surgery was used to treat the patient and no recurrence was seen in this patient. However, there was a close inferior surgical margin reported in the outcome. According to records, this patient had a 118-month disease-free survival span and a 119-month overall survival with no recurrence.

In the second case, OSCC of the gingiva was diagnosed in a 51-year-old Chinese lady.

With a moderately differentiated tumour and negative level 1b lymph node involvement, the pTNM staging for this instance was pT4aN1M0 (stage 4). She was exclusively treated with surgery and had multiple surgical margins involvement (inferior, posterior, and deep). There was Rrecurrence noted in this case 8 months postoperatively. The DFS and OS, in this case, were 8 and 119 months, respectively.

The third case involved a 64-year-old Indian woman identified as having buccal mucosal OSCC. The pT1N2bM0 staging (stage 4) for a poorly differentiated tumour with positive level IB lymph node involvement. In this instance, the treatment plan comprised both surgery and radiotherapy. There were 69 and 86 months of DFS and OS, respectively with recurrence noted at how many months post-treatment completion.

The fourth case was also an Indian female of 71 years of age diagnosed with OSCC of the lower gingiva. The tumour was poorly differentiated and staged as pT4N0M0 (stage 4). There was no lymph node involvement identified in this case. Treatment modalities were surgery and adjuvant radiotherapy, and no recurrence was noted. Histopathology evaluation was reported positive involvement at the inferior surgical margin. The patient had a 173-month DFS and 174-month OS.

The fifth case of the SMG being positively involved was with a Malay woman, aged forty-one. She had a moderately differentiated tumour of buccal mucosa at stage 2 (pT2N0M0) that was free of cervical lymph node involvement. Surgery was the only treatment given to this patient and was reported to have superior surgical margin involvement. Notably, the patient had recurrence 2 years postoperatively. This patient had a 26-month OS and a 24-month DFS.

Table 4.18: Demographic and Clinico-pathological characteristics of Positive Submandibular Gland Cases.

Case	Age	Gender	Ethnicity	Site	cTNM	Staging	pTNM	Staging	Grading	Level IB node status	SMG involvement
1	49	Female	Malay	Buccal mucosa	T4N2cM0	4	T4aN2bM0	4	Moderate	Positive	Ipsilateral
2	51	Female	Chinese	Lower Gingiva	T4N1M0	4	T4aN1M	4	Moderate	Negative	Ipsilateral
3	64	Female	Indian	Buccal mucosa	T1N2bM0	4	T1N2bM0	4	Poorly	Positive	Ipsilateral
4	71	Female	Indian	Lower Gingiva	T1N1Mx	3	T4N0M0	4	Poorly	Negative	Ipsilateral
5	41	Female	Malay	Buccal Mucosa	T2N0M0	2	T2N0M0	2	Moderately	Negative	Ipsilateral

4.23 Treatment, Recurrence, Overall and Disease-Free Survival of Positive Submandibular Gland Cases.

Table 4.19 shows the treatment, recurrence, and OS and DFS of patients with positive submandibular gland status. According to the table, 3 out of the 5 patients had recurrence postoperatively. The second patient had surgery only but with poor surgical margin clearance and succumb to recurrence 8 months postoperatively. The patient, however, had an OS period of 119 months. In the third case, the patient was treated with surgery and postoperative radiotherapy. The patient had a 69-month DFS and 86 OS. The fourth patient had surgery and postoperative radiotherapy. This patient recorded a 180month OS and 173 months DFS rate. In the last case, the patient underwent surgery only and succumbs to the recurrence of the lesion after 24 months. The OS of this patient was 26 months.

Table 4.19: Treatment, recurrence, overall survival (OS) and disease-free survival (DSF) of the positive submandibular gland (SMG) cases.

Case	Treatment	Surgical Margin clearance	Recurrence	Disease free survival(months)	Overall survival (months)
1	Surgery only	Close inferior margin	No	118	119
2	Surgery only	Posterior, Deep, and inferior margins involved	Yes, 8 months post treatment	8	119
3	Surgery + RT	Close inferior margin	Yes, 69 months post treatment	69	86
4	Surgery + RT	Inferior Margin involved	No	173	180
5	Surgery only	Superior Margin involved	Yes,24 months post treatment	24	26

4.24 Demographic and Clinicopathological Characteristics of Positive Level Ib Lymph Nodes

Table 4.20 presents the sociodemographic and clinicopathological characteristics of cases with positive level Ib lymph nodes. The age range of patients with positive level Ib was wide, from 33 years old to 87 years old. Half of the patients were females, and the more commonly involved ethnicity included Indians and Chinese. Fifty-two percent the cases involved the tongue, and one case involved the floor of the mouth. Almost 60%of the cases were in Stage IV and no cases were reported in Stage II. Moderately differentiated tumours were noted in almost 60% of the cases. Submandibular gland involvement was seen only in 2 cases.

4.25 Treatment, Recurrence, Overall and Disease-Free Survival of Positive Level Ib Lymph Nodes.

Table 4.21 represents the treatment modalities, presence of recurrence and survival status including disease-free and overall survival of patients with positive level Ib lymph nodes. Surgery was the only treatment modality. Three out of 19 cases were noted with recurrence which accounts for 15.8 % of the cases.

Table 4.20: Demographic and clinico-pathological characteristics of positive level Ib lymph nodes.

Case	Age	Gender	Ethnicity	Site	cTNM	Staging	pTNM	Staging	Grading	SMG status
1	48	Male	Others	Tongue	T2N2cM0	IV	T3N1M0	III	Moderate	Negative
2	33	Male	Chinese	Tongue	T4N0M0	IV	T4N0M0	IV	Moderate	Negative
3	55	Male	Chinese	Lower Gingiva	T4N0M0	IV	T4aN2bM0	IV	Well	Negative
4	49	Female	Malay	Buccal Mucosa	T4N2cM0	IV	T4aN2bM0	IV	Moderate	Positive
5	73	Female	Chinese	Tongue	T4N2cM0	IV	T4aN2cM0	IV	Well	Negative
6	87	Male	Indian	Floor of Mouth	T4bN2cM0	IV	T2N2bM0	IV	Moderate	Negative
7	56	Female	Chinese	Lower Gingiva	T4aN2bM0	IV	T4aN2bM0	IV	Well	Negative
8	56	Male	Malay	Tongue	T1N0M0	I	T2N2bM0	IV	Moderate	Negative
9	37	Female	Chinese	Tongue	T1N0M0	I	T1N1M0	III	Poor	Negative
10	70	Male	Malay	Tongue	T2N0M0	II	T3N2cM0	IV	Moderate	Negative
11	64	Female	Indian	Buccal Mucosa	T1N2bM0	IV	T1N2bM0	IV	Poor	Positive
12	52	Female	Chinese	Tongue	T1N1M0	III	T1N2bM0	IV	Well	Negative
13	65	Male	Chinese	Tongue	T1N2M0	IV	T2N2M0	IV	Well	Negative
14	59	Female	Indian	Buccal Mucosa	T2N1M0	III	T2N2bM0	IV	Moderate	Negative
15	49	Female	Indian	Buccal Mucosa	T1N0M0	I	T1N1M0	III	Moderate	Negative
16	70	Female	Indian	Lower Gingiva	T4aN1M0	IV	T4aN1M0	IV	Moderate	Negative
17	52	Female	Indian	Buccal Mucosa	T2N2Mx	IV	T2N2M0	IV	Moderate	Negative
18	34	Male	Indian	Tongue	T3N1M0	III	T3N1M0	III	Moderate	Negative
19	34	Male	Malay	Tongue	T1N0M0	I	T1N1M0	III	Well	Negative

Table 4.21: Treatment, recurrence, overall survival (OS) and disease-free survival (DFS) of positive level Ib lymph nodes.

Case	Treatment	Recurrence	Disease free survival (months)	Overall Survival (months)
1	Surgery + Radiotherapy	Yes	70	78
2	Surgery only	No	106	107
3	Surgery only	No	116	117
4	Surgery only	No	118	119
5	Surgery only	No	33	73
6	Surgery only	No	120	121
7	Surgery + Radiotherapy	No	70	76
8	Surgery only	No	16	17
9	Surgery + Radiotherapy	No	186	201
10	Surgery only	No	15	17
11	Surgery + Radiotherapy	Yes	88	102
12	Surgery only	No	130	131
13	Surgery + Radiotherapy	No	70	75
14	Surgery + CCRT	No	192	186
15	Surgery only	No	134	136
16	Surgery only	No	34	35
17	Surgery + Radiotherapy	No	128	132
18	Surgery only	No	94	95
19	Surgery + Radiotherapy	No	17	22

CHAPTER 5: DISCUSSION

5.1 Study findings

Globally, oral squamous cell carcinoma (OSCC) is acknowledged as a significant contributor to head and neck malignancies (Panda et al., 2015). Current management recommendations for OSCC call for surgical removal of the primary tumour and appropriate neck dissection dependent on the tumour stage (Malgonde & Kumar, 2015). The purpose of neck dissection is to remove cervical lymph nodes that have metastatic disease. Over the years neck dissections have been improvised to suit a more conservative approach, reducing post-operative functional compromise and providing a better quality of life for the patient (G. Agarwal et al., 2016). The submandibular gland (SMG) has been routinely removed as part of the neck dissection due to its anatomical position at level Ib, as it is considered close to the primary tumour and afferent cervical nodes (Malgonde & Kumar, 2015). But does this anatomical position alone support its removal during neck dissections? This question remains unanswered.

The purpose of this study was to investigate the frequency of SMG involvement in OSCC patients. Current literature states that SMG involvement in OSCC cases is rare. The findings of this study are in favour of this literature. Only 3.5% of the 142 study participants who underwent neck dissections had positive SMG involvement, which suggests that SMG involvement in OSCC cases is uncommon.

A study conducted found that six out of 163 analyzed glands showed glandular involvement, accounting for 3.68% of the study population (Panda et al., 2015). In a

study, the author reported only one (0.76%) out of 131 patients had positive SMG involvement (Javadi et al., 2021). Agarwal et al studied 112 cases and found no cases with positive SMG involvement. Demonstrating that SMG involvement in OSCC patients is rare (G. Agarwal et al., 2016). This is an intriguing discovery that persuaded us to advocate for SMG preservation but with caution.

Across the world, literature states OSCC affects both males and females. A study reported that in general, OSCC affects more males compared to females. The authors reported a male-to-female ratio of 2:1 in the United States and 7:1 in Spain, based on demographic profiles. However, found slight female predominance in the Mexican population with a ratio of 1:1.1 (Gaitán-Cepeda et al., 2011). Okoturo et al, in their study on the evaluation of SMG involvement in oral cavity cancers, reported a majority of males in their study population (Okoturo et al., 2012b). Yang et al conducted a study on the clinicopathological involvement of the SMG in OSCC, which also had a majority of male patients (Yang et al., 2020). Contrary to those findings, the patients with SMG involvement in the current study were mostly females. This could be because almost half of the cases (43%) were removed from this study due to incomplete data and those that did not satisfy the criteria during the recruitment process.

Oral SCC is seen to affect people around the world and Asia and Southeast Asia have been identified as a region with a high incidence rate for oral cancers (Warnakulasuriya, 2009). Unlike most studies in literature, that only include one ethnicity, this study population was a multiracial Asian population inclusive of Malays, Chinese and Indians. Hence, we have no doubt our findings have a better representation of the local population.

The average age of 56.07 years old as found in this study, was in keeping with the average range quoted in the literature (Basha et al., 2021; Malgonde & Kumar, 2015, Sancatkar et al., 2019)

Cancer prognosis is often associated with clinical and histopathological features based on TNM staging. Common sites for OSCC reported, include the lip, tongue, buccal region, floor of mouth and alveolus of the maxilla and mandible and the hard palate (Iocca et al., 2023; M. Kalloli et al., 2022). The lateral border of the tongue and the gingivobuccal sulcus were reported to have the second-highest number of cases demonstrating SMG involvement in a study conducted (G. Agarwal et al., 2016). Similar to previous studies, the most frequent sites in this study were determined to be the tongue and the buccal mucosa. The proximity of the SMG to the primary tumour has been identified as the reason for its removal in neck dissections. Amongst the common sites identified to have a higher risk of SMG involvement is the floor of the mouth (Iocca et al., 2023; Takes et al., 2011). Alternatively, Ahmed et al, in their study on the metastasis to a SMG in patients with OSCC, reported that the cases involving positive SMG status had primary tumours in the lips or mandible (Ahmed et al., 2020). One common finding of the literature is that cases with positive SMG involvement are often associated with ipsilateral primary tumours. As reported by Byeon et al, lymph node metastasis to the SMG is highly uncommon and to date, there have been no cases of contralateral SMG involvement reported in head and neck cancer cases (Byeon et al., 2009). In this study, we found most cases with positive SMG status had primary tumours in the lower gingiva or the buccal mucosa. Comparable with other studies, this study also found all ipsilateral gland involvement. No contralateral SMG involvement identified.

Level Ib in the cervical region is also known as the submandibular region. These lymph nodes of level Ib are found to occupy the space close to the SMG (Chong 2004). In oral cavity tumours, metastasis to level Ib is common, whereas metastasis to the SMG is found to be uncommon. This is a result of the poorly developed or possibly even absent lymphatic structures in the SMG parenchyma (Gu et al., 2020; Okoturo et al., 2012a). Contrary to popular belief, the SMG's parenchyma is not at risk of being involved in metastasis-induced tumour seeding, as shown by various retrospective studies (Dhiwakar et al., 2011).

According to the literature, despite being uncommon, SMG metastases have three mechanisms of involvement. One, via direct invasion from the main tumour. The second involves metastases to a lymph node at Level Ib. The third is metastases' invasion of an intraglandular lymph node (Alharbi et al., 2019).

A study found that the primary tumour outside of the head and neck region or the hematogenous route nearly never metastasized to SMG (Sancatkar et al., 2019). In this study, we found 13.38% (19) of the entire sample population had positive nodes at level Ib. 15.8% of the positive level Ib cases were found to have positive SMG involvement. These cases had primary tumours in the buccal mucosa and were of advanced staging.

In this study, no metastatic spread was seen in the SMG. This complements the findings of a study by Okoturo et al., which also discovered that the absence of intracapsular SMG lymph nodes may be supported by the lack of SMG metastasis despite extracapsular spread (Okoturo et al., 2012a). According to a review of the literature, the majority of the more than one hundred cases of metastasizing to SMG were caused by hematogenous spread from distant primary tumours like those of the

breast, lung, and genitourinary system. The investigation of SMG-related patterns in level 1b lymph nodes could theoretically promote SMG preservation (Vessecchia et al., 1995). Due to the rarity of the SMG being involved in metastatic disease, it seems plausible to preserve the SMG unless the initial tumour is immediately adjacent to a metastatic lymph node or extends directly from it (Malgonde & Kumar, 2015).

Management of OSCC includes surgical resection of the primary tumour and neck dissection is performed based on the prognostic TNM staging. Adjuvant therapy is advised based on the prognosis of the cancer (NCCN, 2023). Although neck dissection is decided based on the nodal status of the neck, there are centres across the globe that advise neck dissection even in the N0 status (Mundo, 2020). In a study by Cruz et al. comparing elective and therapeutic neck dissections in cases of N0 oral cancer, the researchers concluded that the latter procedure was superior in terms of OS for patients with early-stage oral cancer (D'Cruz et al., 2015). The SMG being in the submandibular region of level Ib is routinely removed during neck dissection to get better surgical clearance. However, a study conducted had proven that it is possible to ensure the total clearance of cervical nodes at level Ib while preserving an intact SMG (Dhiwakar et al., 2011). In this study, most of the patients (72.5%) underwent surgery only and 22.5 % underwent both surgery and postoperative radiotherapy.

Post-operative adjuvant therapy administered in the management of OSCC includes radiotherapy, chemotherapy and concurrent chemo and radiotherapy, depending on the post-operative findings. Although these modalities aid in the control of the disease, side effects include damage to structures like the salivary gland. The SMG, being in the area of concern, is certainly subjected to the direct effects of these adjuvant therapy, mainly radiotherapy. One of the main consequences of SMG damage

is xerostomia, which then leads to other complications such as osteoradionecrosis, periodontitis, and dental caries because of salivary flow depletion. It is found that post radiotherapy exposure, for radiation at 60Gy, the effects may be reversible over time. However, the complete excision of the gland will not have reversible consequences (Malgonde & Kumar, 2015).

A common reservation in preserving the SMG in neck dissections is the possibility of the gland being subjected to radiotherapy, post-operatively, which then results in xerostomia. However, with advancements in modern medicine, advanced options of radiotherapy, such as the Intensity Modulated Radiotherapy (IMRT) have been proven to improve the salivary flow rate. Studies have also reported that SMG is less sensitive to radiotherapy, hence preserving the gland's relative function despite exposure to radiotherapy (M. Kalloli et al., 2022)

Based on our findings, most cases with SMG involvement belong to the prognostic stage of Stage 4, suggesting involvement is more common in advanced cancer cases. Tumor staging of T1 and T4, and nodal status of N2 were seen in most of our cases with positive SMG involvement. However, out of the cases with positive SMG, only two cases had level Ib lymph node involvement. Okoturo et al reported in their study that most T1-T2 cases had nodal metastasis than late cancer cases of T3 and T4 staging, which was in variance with the literature (Okoturo et al., 2012a). This finding was like those reported by Basha et al in their study. Basha et al suggested the presence of level Ib lymph nodes, does not ascertain the involvement of the SMG, and hence does not require excision in the neck dissection (Basha et al., 2021). In a study conducted, the authors recommended that the SMG and the duct be removed together during neck dissection for oncological safety in advanced cases of SCC if there is a

suspicion of SMG or its ductal involvement. The authors instead proposed gland preservation efforts to be implemented in cases of early T staging as they found no significant difference in the cases treated with and without Tumour-Node block resection, in terms of their DFS (Iocca et al., 2023).

Most studies advocating for SMG preservation in neck dissections claim that preserving the SMG in the absence of a level Ib lymph node is considered oncologically safe (Panda et al., 2015). Subramaniam et al in their study on the determinants of level Ib lymph node involvement in OSCC and implications on SMG sparing neck dissection found no positive SMG involvement in the pN0 cases.

There are not many studies on survival analyses related to SMG preservation in the literature. 137 individuals with surgically treated T1-T2, N0 buccal SCC participated in a prospective, non-randomized cohort study. SMG-sparing and SMG-excising groups of patients were created. This study found no statistically significant difference between the SMG-sparing and SMG-excision groups for the 5-year DFS rates ($p = 0.709$). The 5year DFS rates were 74 and 69%, respectively. This was the first study to report such patients, and those with SMG preservation in it exhibited comparable LRC and DSS to those without SMG preservation. (Gu et al., 2020).

Similarly, Chen et al.'s study included 408 patients with cT1-T2N0 oral SCC, 33 of whom underwent SMG-preserving neck dissections as part of their therapy. Buccal SCC was identified as the disease in eight of the 33 cases. The 5-year DFS rates for patients with buccal SCC with and without SMG preservation were 75 and 69%, respectively, according to the study, and there was no statistically significant difference between these two groups ($p = 0.83$).The 5-year OS rates for these two groups were 87.5 and 95.6%, respectively, and there was no statistically significant

difference between them (p = 0.54). The study's limitations, including the small number of patients who had SMG-sparing neck dissection, were acknowledged by the authors. (Chen et al., 2011).

As a challenge to current literature findings, this study revealed a significant impact on the SMG status on the OS and DFS of OSCC patients. The OS of patients with negative SMG was significantly better than those with positive SMG involvement. Similarly, the 5-year DFS duration of SMG-negative patients is statistically better than those with SMG involvement. This is an intriguing finding that motivates us further to explore the possibilities of preserving the SMG in ensuring a better quality of life for OSCC patients.

As most of the unstimulated saliva production is contributed by the SMG, its role as a functional unit in saliva productivity is critical (Mahesh Kalloli et al., 2022). Aside from keeping the oral cavity moist, saliva also plays a role in swallowing by lubricating food. Saliva also contains the enzyme Amylase which aids in the breakdown of starches and contains bicarbonate, which gives it an alkaline property, buffering the acidic bacterial enzymes in the oral cavity and aiding the mineralization of teeth. Saliva also has antimicrobial properties due to the IgA, lactoferrin and other enzymes found in the saliva (Malgonde & Kumar, 2015). Reduced salivation can cause a variety of problems, such as xerostomia (dry mouth), mucosal and gingival inflammation, dental caries, tongue cracks, altered taste sensation, denture-related soreness, and trouble chewing and swallowing (Sancatkar et al., 2019). In a study, the author stated that OSCC patients that underwent neck dissection with concomitant removal of SMG experienced xerostomia with an increased risk of dental caries (Chen et al., 2011).

A prospective study in Brazil studying the impact of SMG excision on salivary function based on salivary flow rate and salivary gland scintigraphy in head and neck cancer patients. From their study, they found that the compensatory mechanism of the remaining SMG does not perform satisfactorily (Jaguar et al., 2010). New drugs have been developed because of medical advancements, which may enhance the functional capacity of the remaining gland. However, the bulk of these have instead produced disconcerting negative effects rather than considerably enhancing postoperative quality of life. There is currently no therapeutic procedure that can fully restore saliva flow after the SMG has been sacrificed. (Chen et al., 2009).

Aside from the physiologic benefits of preserving the SMG in neck dissections, it has been reported that the risk of an iatrogenic injury to the marginal mandibular branch of the facial nerve, the lingual nerve and the hypoglossal nerve can also be avoided.

Reconstruction of the post-resection defect would certainly benefit from the preserved facial vessels at the site (Iocca et al., 2023). Despite all the positive significance, the myth of the complications of remaining still weighs in on the judgement of the operator. The anatomical location of the gland, close to the primary tumour and the proximity to vascular structures like the facial artery and vein, certainly makes preserving the gland while removing the lymph nodes at level Ib a challenge. However, it is a mission that can be accomplished. Preserving the gland while achieving complete removal of the level Ib lymph nodes has been proven (Dhiwakar et al., 2011). The author and his team conducted a prospective study to challenge this myth that the SMG indefinitely must be sacrificed in a neck dissection to achieve surgical clearance. The authors described the steps of the procedure, which in addition

to the standard neck dissection procedure included the use of lymphazurin blue dye, which was injected in the quadrants around the primary tumour before starting the dissection to look for uptake of the dye at the sites of tumour involvement.

In addition, a thorough dissection of the fibro adipose tissues surrounding the submandibular triangle and examination and palpation of the four lymph node groups, the pre-glandular, pre-vascular, post-glandular and post-vascular, at level Ib of the submandibular triangle by stripping the investing fascia. This was accomplished while protecting the SMG's parenchyma, and its blood supply (the facial artery, facial vein, and visible branches supplying and draining the gland parenchyma) (Dhiwakar et al., 2011).

The aponeurotic envelope that shields the SMG is composed of two layers. A surface layer plus a deeper layer makes up this. Between these two layers are the face artery, vein, and lymphatics. As a result, it is possible to remove the complete aponeurotic and cellular block from the submandibular area while still protecting the SMG and its vascularity (Guney & Yigitbasi, 2004).

The field of Surgery has evolved over the years. Surgeons across the globe have improvised surgical techniques and approaches, including neck dissection. That said, knowledge and skills in preserving the SMG in neck dissection can certainly be attained.

5.2 Limitations of the study

We acknowledge there are several limitations in this study. The medical records of patients from two centres were used as the source of convenience sampling

for this investigation, which was planned as a retrospective study. As a result, this study's limitations were encountered. We had to remove several cases from the study since there were multiple instances of missing data in the records. The p-value employed in this study may be misleading because there was no random sampling. The given information from the histological investigation was not standardized because this is a retrospective study with patients gathered over 20 years. The SMG's histopathological characteristics were not documented in detail to further imply a correlation of the gland involvement in specific patients. We were unable to learn whether any further comorbid conditions or risk behaviours existed. This could influence the patient's OS status.

5.3 Recommendation of the study

Based on the findings of this study, we recommend the decision for SMG preservation be considered on a case-to-case basis. A few criteria should be taken into consideration for preserving the SMG in cases:

(i) in tongue and floor of the mouth OSCC with

(ii) cT1-cT2 cases having

(iii) N0 nodal status which would be (iv) stage 1 and stage 2 SCCs.

Therefore, not all cases of tongue and FOM need to have resection of the SMG.

We do not recommend SMG preservation in cases with the following criteria:

(i) in tongue and floor of the mouth OSCC with

(ii) cN1 and above being involved at level Ib, and

(iii) advance stage such as stage 3 and 4

OR

(i) in buccal mucosa and lower gingiva SCC

(ii) with stage 2 and above tumours

OR

(i) cases with evidence of SMG involvement from tumour extension clinically.

OR

(i) when the preservation of SMG does not permit the resection with a clear safe margin.

To further support the basis of evaluating the oncological safety of SMG preservation in OSCC management, we encourage future prospective studies to be conducted to bridge the gap in the literature.

CHAPTER 6: CONCLUSION

The goal of managing oral cancer patients is to help patients survive cancer and live a life of quality. Neck dissection techniques have evolved over the years to aim to preserve more functional capabilities of patients postoperatively.

In line with recent literature, this study found that SMG is rarely involved in OSCC patients. This study reported the prevalence of SMG involvement as only 3.5% in OSCC patients. This finding is reassuring in encouraging the preservation of the SMG in neck dissection.

Despite the proximity of the level Ib lymph nodes and the SMG, this study reports an insignificant association between the positive status of the SMG and the level Ib lymph nodes.

The OS and DFS of OSCC patients with SMG involvement are significantly impacted. Patients with negative SMG status have a significantly higher overall survival period compared to those who had SMG involvement. Similarly, the DFS of patients with no SMG involvement was significantly greater than those with SMG involvement.

The findings of this study strongly suggest the preservation of the SMG in selected OSCC cases. Nevertheless, to learn more about the oncological safety and actual impact of SMG preservation on quality of life, prospective research in the future is warranted.

CHAPTER 7: REFERENCES

Agarwal, G., Nagpure, P. S., & Chavan, S. S. (2016). Questionable Necessity for Removing Submandibular Gland in Neck Dissection in Squamous Cell Carcinoma of Oral Cavity. *Indian J Otolaryngol Head Neck Surg*, *68*(3), 314-316. https://doi.org/10.1007/s12070-016-0966-4

Agarwal, S. K., Arora, S. K., Kumar, G., & Sarin, D. (2016). Isolated perifacial lymph node metastasis in oral squamous cell carcinoma with clinically node-negative neck. *Laryngoscope*, *126*(10), 2252-2256. https://doi.org/10.1002/lary.25954

Ahmed, S., Salim, Z., hafeez Shaikh, A., Iqbal, S. N., & Ali, A. (2020). Metastasis to The Submandibular Gland In Patients Presenting With Oral Squamous Cell Carcinoma.

AJCC. (2010). AJCC Cancer Staging Manual *Seventh Edition* https://www.facs.org/media/j30havyf/ajcc_7thed_cancer_staging_manual.pdf

Akshat Malik, P. J., Aseem Mishra, Apurva Garg, Manish Mair, Swagnik Chakrabarti, Sudhir Nair, Deepa Nair, Pankaj Chaturvedi,. (2016). Prospective study of the pattern of lymphatic metastasis in relation to the submandibular gland in patients with carcinoma of the oral cavity. *Wiley Online Library (2016*. https://doi.org/DOI 10.1002/hed.24508

Alharbi, J., Sebeih, H., Alshahrani, M., Algarni, M., Al-Hakami, H., Alnemare, A., Assiri, A., Islam, T., & Alqahtani, K. (2019). Risk of submandibular gland metastasis in early-stage oral cavity cancer: A national multicentric study [Original Article]. *Saudi Journal of Otorhinolaryngology Head and Neck Surgery*, *21*(2), 37-39. https://doi.org/10.4103/sjoh.Sjoh_3_19

Almangush, A., Mäkitie, A. A., Triantafyllou, A., de Bree, R., Strojan, P., Rinaldo, A., Hernandez-Prera, J. C., Suárez, C., Kowalski, L. P., Ferlito, A., & Leivo, I. (2020).
Staging and grading of oral squamous cell carcinoma: An update. *Oral Oncology*,
107, 104799. https://doi.org/https://doi.org/10.1016/j.oraloncology.2020.104799

Amr Bugshan , I. F. (2020). Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. https://doi.org/doi.org/10.12688/f1000research.22941.1

Andisheh-Tadbir, A., Mehrabani, D., & Heydari, S. T. (2008). Epidemiology of squamous cell carcinoma of the oral cavity in Iran. *J Craniofac Surg*, *19*(6), 1699-
1702. https://doi.org/10.1097/SCS.0b013e31818c04cc

Anneroth, G., & Hansen, L. S. (1984). A methodologic study of histologic classification and grading of malignancy in oral squamous cell carcinoma. *Scand J Dent Res*, *92*(5), 448-468. https://doi.org/10.1111/j.1600-0722.1984.tb00915.x

Attar, E., Dey, S., Hablas, A., Seifeldin, I. A., Ramadan, M., Rozek, L. S., & Soliman, A. S. (2010). Head and neck cancer in a developing country: a population-based perspective across 8 years. *Oral Oncol*, *46*(8), 591-596. https://doi.org/10.1016/j.oraloncology.2010.05.002

Bagan, J., Sarrion, G., & Jimenez, Y. (2010). Oral cancer: Clinical features. *Oral Oncology*, *46*(6), 414-417. https://doi.org/https://doi.org/10.1016/j.oraloncology.2010.03.009

Basha, S. S., Nayak, V., Goel, A., Panda, S. K., Sharma, T. P., Pande, P. K., & Kumar, K. (2021). Predictive Factors for Submandibular Gland Involvement in Oral Cavity Squamous Cell Carcinoma-a Prospective Study from a Tertiary Cancer Center. *Indian J Surg Oncol*, *12*(4), 737-744. https://doi.org/10.1007/s13193-02101414-5

Bialek, E. J., Jakubowski, W., Zajkowski, P., Szopinski, K. T., & Osmolski, A. (2006). US of the major salivary glands: anatomy and spatial relationships, pathologic conditions, and pitfalls. *Radiographics*, *26*(3), 745-763. https://doi.org/10.1148/rg.263055024

Bo Gu, Q. F., Yao Wu, Wei Du, Xu Zhang and Defeng Chen. (2020). Impact of submandibular gland preservation in neck management of early stage buccal squamous cell carcinoma on locoregional control and disease-specific survival. https://doi.org/doi.org/10.1186/s12885-020-07534-5

Bocca, E., & Pignataro, O. (1967). LXXXI A Conservation Technique in Radical Neck Dissection. *Annals of Otology, Rhinology & Laryngology*, *76*(5), 975-987. https://doi.org/10.1177/000348946707600508

Broders, A. C. (1920). Squamous -cell Epithelioma of the lip: A Study of Five Hudred and thirty-seven Cases. *Journal Of the American Medical Association*, *74*(10), 656-664. Https://Doi.Org/10.1001/Jama.1920.02620100016007

Bryne, M., Koppang, H. S., Lilleng, R., & Kjaerheim, A. (1992). Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognosticvalue.*JPathol*,*166*(4),375-381. https://doi.org/10.1002/path.1711660409

Byeon, H. K., Lim, Y. C., Koo, B. S., & Choi, E. C. (2009). Metastasis to the submandibular gland in oral cavity squamous cell carcinomas: pathologic analysis.*ActaOtolaryngol*,*129*(1),96-100. https://doi.org/10.1080/00016480802032801

Cakir Cetin, A., Dogan, E., Ozay, H., Kumus, O., Erdag, T. K., Karabay, N., Sarioglu, S., & Ikiz, A. O. (2018). Submandibular gland invasion and feasibility of gland sparing neck dissection in oral cavity carcinoma. *J Laryngol Otol*, *132*(5), 446-451. https://doi.org/10.1017/S0022215118000592

Capote, A., Escorial, V., Munoz-Guerra, M. F., Rodriguez-Campo, F. J., Gamallo, C., & Naval, L. (2007). Elective neck dissection in early-stage oral squamous cell carcinoma--does it influence recurrence and survival? *Head Neck*, *29*(1), 3-11. https://doi.org/10.1002/hed.20482

Chen, T. C., Lo, W. C., Ko, J. Y., Lou, P. J., Yang, T. L., & Wang, C. P. (2009). Rare involvement of submandibular gland by oral squamous cell carcinoma. *Head Neck*, *31*(7), 877-881. https://doi.org/10.1002/hed.21039

Chen, T. C., Lou, P. J., Ko, J. Y., Yang, T. L., Lo, W. C., Hu, Y. L., & Wang, C. P. (2011). Feasibility of preservation of the submandibular gland during neck dissection in patients with early-stage oral cancer. *Ann Surg Oncol*, *18*(2), 497-504. https://doi.org/10.1245/s10434-010-1294-7

Chinn, S. B., & Myers, J. N. (2015). Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions. *J Clin Oncol*, *33*(29), 3269-3276. https://doi.org/10.1200/JCO.2015.61.2929

Cuffari, L., Tesseroli de Siqueira, J. T., Nemr, K., & Rapaport, A. (2006). Pain complaint as the first symptom of oral cancer: a descriptive study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, *102*(1), 56-61. https://doi.org/10.1016/j.tripleo.2005.10.041

D'Cruz AK, Vaish R, Kapre N, et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *N Engl J Med* 2015; 373: 521-529. 20150531 DOI: 10.1056/NEJMoa1506007.

P., Pantvaidya, G., Chaukar, D., Deshmukh, A., Kane, S., Arya, S., Ghosh-Laskar, S., Chaturvedi, P., Pai, P., Nair, S., Nair, D., Badwe, R., Head, & Neck Disease Management, G. (2015). Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *N Engl J Med*, *373*(6), 521-529. https://doi.org/10.1056/NEJMoa1506007

Dayanand, S. M., Desai, R., & Reddy, P. B. (2010). Efficiency of ultrasonography in assessing cervical lymph node metastasis in oral carcinoma. *Natl J Maxillofac Surg*, *1*(2), 117-122. https://doi.org/10.4103/0975-5950.79212

Dhiwakar, M., Ronen, O., Malone, J., Rao, K., Bell, S., Phillips, R., Shevlin, B., & Robbins, K. T. (2011). Feasibility of submandibular gland preservation in neck dissection: A prospective anatomic-pathologic study. *Head Neck*, *33*(5), 603-609. https://doi.org/10.1002/hed.21499

DiNardo, L. J. (1998). Lymphatics of the submandibular space: an anatomic, clinical, and pathologic study with applications to floor-of-mouth carcinoma. *Laryngoscope*,*108*(2),206-214. https://doi.org/10.1097/00005537-199802000-00009

Du, W., Fang, Q., Liu, S., Chen, D., Luo, R., & Zhang, X. (2020). Feasibility of Submandibular Gland Preservation in cT1-2N0 Squamous Cell Carcinoma in the Floor of the Mouth. *Front Oncol*, *10*, 579. https://doi.org/10.3389/fonc.2020.00579

Dundar, Y., Mandle, Q., Raza, S. N., Lin, H. S., Cramer, J., & Hotaling, J. M. (2019). Submandibular Gland Invasion by Oral Cavity Cancers: A Systematic Review. *Otolaryngol Head Neck Surg*, *161*(2), 227-234. https://doi.org/10.1177/0194599819838475

Effiom, O., Adeyemo, W., Omitola, O., Ajayi, O., Emmanuel, M., & Gbotolorun, O. (2008). Oral squamous cell carcinoma: a clinicopathologic review of 233 cases in Lagos, Nigeria.

El-Naggar, A. K., Chan, J. K. C., Takata, T., Grandis, J. R., & Slootweg, P. J. (2017). The fourth edition of the head and neck World Health Organization blue book: editors' perspectives. *Hum Pathol*, *66*, 10-12. https://doi.org/10.1016/j.humpath.2017.05.014

Fábio Ramôa Pires, A. B. R., Jade Bittencourt Coutinho de Olivera, Amanda Serra Tavares, Priscilla Silva Ribeiro da LUZ, Teresa Cristina Ribeiro Bartholomeu dos SANTOS. (2013). Oral squamous cell carcinoma: clinicopathological features from 346 cases from a single Oral Pathology service during an 8-year period. *br jaos* https://doi.org/doi.org/10.1590/1679-775720130317

Farah, C. S., Woo, S. B., Zain, R. B., Sklavounou, A., McCullough, M. J., & Lingen, M. (2014). Oral cancer and oral potentially malignant disorders. *Int J Dent*, *2014*, 853479. https://doi.org/10.1155/2014/853479

Feller, L., & Lemmer, J. (2012). Oral Squamous Cell Carcinoma: Epidemiology, Clinical Presentation and Treatment. *Journal of Cancer Therapy*, *03*. https://doi.org/10.4236/jct.2012.34037

Ferlito, A., Rinaldo, A., Devaney, K. O., MacLennan, K., Myers, J. N., Petruzzelli, G. J., Shaha, A. R., Genden, E. M., Johnson, J. T., de Carvalho, M. B., & Myers, E. N. (2002). Prognostic significance of microscopic and macroscopic extracapsular spread from metastatic tumor in the cervical lymph nodes. *Oral Oncol*, *38*(8), 747-751. https://doi.org/10.1016/s1368-8375(02)00052-0

Ferlito, A., Rinaldo, A., Silver, C. E., Shah, J. P., Suárez, C., Medina, J. E., Kowalski, L. P., Johnson, J. T., Strome, M., Rodrigo, J. P., Werner, J. A., Takes, R. P., Towpik, E., Robbins, K. T., Leemans, C. R., Herranz, J., Gavilán, J., Shaha, A. R., & Wei, W. I. (2006). Neck dissection: then and now. *Auris Nasus Larynx*, *33*(4), 365-374. https://doi.org/10.1016/j.anl.2006.06.001

Fives, C., Feeley, L., Sadadcharam, M., O'Leary, G., •, & Sheahan, P. (2016). Incidence of intraglandular lymph nodes within submandibular gland, and involvement by floor of mouth cancer. *Eur Arch Otorhinolaryngol*. https://doi.org/DOI 10.1007/s00405-016-4205-0

Fuentes, B., Duaso, J., Droguett, D., Castillo, C., Donoso, W., Rivera, C., Venegas, B., & Kemmerling, U. (2012). Progressive extracellular matrix disorganization in chemically induced murine oral squamous cell carcinoma. *International Scholarly Research Notices*, *2012*.

Gaitán-Cepeda, L. A., Peniche-Becerra, A. G., & Quezada-Rivera, D. (2011). Trends in frequency and prevalence of oral cancer and oral squamous cell carcinoma in Mexicans. A 20-year retrospective study. *Med Oral Patol Oral Cir Bucal*, *16*(1), e1-5. https://doi.org/10.4317/medoral.16.e1

Grimm, M. (2012). Prognostic value of clinicopathological parameters and outcome in 484 patients with oral squamous cell carcinoma: microvascular invasion (V+) is an independent prognostic factor for OSCC. *Clin Transl Oncol (2012)*. https://doi.org/DOI 10.1007/s12094-012-0867-2

Gu, B., Fang, Q., Wu, Y., Du, W., Zhang, X., & Chen, D. (2020). Impact of submandibular gland preservation in neck management of early-stage buccal squamous cell carcinoma on locoregional control and disease-specific survival.
BMC Cancer, *20*(1), 1034. https://doi.org/10.1186/s12885-020-07534-5

Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell*, *100*(1), 57-70. https://doi.org/10.1016/s0092-8674(00)81683-9

Huang, S. F., Chang, J. T., Liao, C. T., Kang, C. J., Lin, C. Y., Fan, K. H., Wang, H. M., & Chen, I. H. (2015). The role of elective neck dissection in early-stage buccal cancer. *Laryngoscope*, *125*(1), 128-133. https://doi.org/10.1002/lary.24840

Ibrahim, S. A., Ahmed, A. N. A., Elsersy, H. A., & Darahem, I. M. H. (2020). Elective neck dissection in T1/T2 oral squamous cell carcinoma with N0 neck: essential or not? A systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*, *277*(6),
1741-1752. https://doi.org/10.1007/s00405-020-05866-3

[1]Iocca, O., Copelli, C., Garzino-Demo, P., Ramieri, G., Rubattino, S., Sedran, L., Volpe,
F., Manfuso, A., Longo, F., Sanchez-Aniceto, G., Rivero-Calle, Á., GarcíaSánchez, A., Pellini, R., Petruzzi, G., Moretto, S., Al-Qamachi, L., Aga, H., Ridley, S., & Di Maio, P. (2023). Submandibular gland involvement in oral cavity squamous cell carcinoma: a retrospective multicenter study. *Eur Arch Otorhinolaryngol*. https://doi.org/10.1007/s00405-023-08007-8

Jaguar, G., Lima, E., Kowalski, L., Pellizon, A., Carvalho, A., & Alves, F. (2010). Impact of submandibular gland excision on salivary gland function in head and neck cancer patients. *Oral Oncology*, *46*(5), 349-354. https://doi.org/10.1016/j.oraloncology.2009.11.018

Jainkittivong, A., Swasdison, S., Thangpisityotin, M., & Langlais, R. P. (2009). Oral squamous cell carcinoma: a clinicopathological study of 342 Thai cases. *The journal of contemporary dental practice*, *10*(5), E033-040. Retrieved 2009/09//, from http://europepmc.org/abstract/MED/19838608

Janotha, B. L., & Tamari, K. (2017). Oral squamous cell carcinoma: Focusing on interprofessional collaboration. *Nurse Pract*, *42*(4), 26-30. https://doi.org/10.1097/01.NPR.0000513340.69567.4e

Javadi, S., Khademi, B., Mohamadianpanah, M., Shishegar, M., & Babaei, A. (2021). Elective Submandibular Gland Resection in Patients with Squamous Cell Carcinomas of the Tongue. *Iran J Otorhinolaryngol*, *33*(114), 23-29. https://doi.org/10.22038/ijorl.2020.44283.2463

Johnson, N. W., Jayasekara, P., & Amarasinghe, A. A. (2011). Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology. *Periodontol 2000*, *57*(1), 19-37. https://doi.org/10.1111/j.1600-0757.2011.00401.x

Kalloli, M., Patil, R. S., Singh, R., Prabhu, N., & Issrani, R. (2022). Submandibular gland extirpation during neck dissection, is it truly justified? *Indian J Cancer*, *59*(4),
591-596. https://doi.org/10.4103/ijc.IJC_68_21

Keski-Santti, H., Atula, T., Tornwall, J., Koivunen, P., & Makitie, A. (2006). Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol*, *42*(1), 96-101. https://doi.org/10.1016/j.oraloncology.2005.06.018

Kramer, D., Durham, J. S., Jackson, S., & Brookes, J. (2001). Management of the neck in N0 squamous cell carcinoma of the oral cavity. *J Otolaryngol*, *30*(5), 283-288. https://doi.org/10.2310/7070.2001.19563

Kruse, A. L., Bredell, M., & Grätz, K. W. (2011). Oral cancer in men and women: are there differences? *Oral Maxillofac Surg*, *15*(1), 51-55. https://doi.org/10.1007/s10006-010-0253-6

Locatello, L., & Gallo, O. (2018). Elective neck dissection in clinically node-negative oral cavity carcinoma. https://doi.org/B-ENT 14(4):281-286

Lanzer, M., Gander, T., Lübbers, H. T., Metzler, P., Bredell, M., & Reinisch, S. (2014). Preservation of ipsilateral submandibular gland is ill advised in cancer of the floor of the mouth or tongue. *Laryngoscope*, *124*(9), 2070-2074. https://doi.org/10.1002/lary.24672

Larsen, S. R., Johansen, J., Sorensen, J. A., & Krogdahl, A. (2009). The prognostic significance of histological features in oral squamous cell carcinoma. *J Oral Pathol Med*, *38*(8), 657-662. https://doi.org/10.1111/j.1600-0714.2009.00797.x

Loree, J. T., Popat, S. R., Burke, M. S., Frustino, J., Grewal, J. S., & Loree, T. R. (2019). Sentinel lymph node biopsy for management of the N0 neck in oral cavity squamous cell carcinoma. *J Surg Oncol*, *120*(2), 101-108. https://doi.org/10.1002/jso.25494

Malgonde, M. S., & Kumar, M. (2015). Practicability of submandibular gland in squamous cell carcinomas of oral cavity. *Indian J Otolaryngol Head Neck Surg*, *67*(Suppl 1), 138-140. https://doi.org/10.1007/s12070-014-0803-6

Mallet, Y., Avalos, N., Le Ridant, A. M., Gangloff, P., Moriniere, S., Rame, J. P., Poissonnet, G., Makeieff, M., Cosmidis, A., Babin, E., Barry, B., & Fournier, C. (2009). Head and neck cancer in young people: a series of 52 SCCs of the oral tongue in patients aged 35 years or less. *Acta Otolaryngol*, *129*(12), 1503-1508. https://doi.org/10.3109/00016480902798343

Massano, J., Regateiro, F. S., Januario, G., & Ferreira, A. (2006). Oral squamous cell carcinoma: review of prognostic and predictive factors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, *102*(1), 67-76 https://doi.org/10.1016/j.tripleo.2005.07.038

Mundo, A. Q. Y. P. J. a. D. A. A. d. (2020). The Role of Neck Dissection in Oral Cavity Carcinoma. https://doi.org/.doi.org/10.5772/intechopen.90925

NCCN. (2019). NCCN Guidelines for Head and Neck Cancers V1.2019. https://www.nccn.org/guidelines/guidelines-process/transparency-process-andrecommendations/GetFileFromFileManagerGuid?FileManagerGuidId=7a8a0e9c -e4b8-4b8b-87da-1786c9806d4e

NCCN. (2023). *National Comprehensive Cancer Network Head and Neck Cancers V1*.

https://www.nccn.org/guidelines/guidelines-process/transparency-process-andrecommendations/GetFileFromFileManagerGuid?FileManagerGuidId=c4edff60 -3e93-45d9-8503-5892d71ea8be

Neville, B. W., & Day, T. A. (2002). Oral cancer and precancerous lesions. *CA Cancer J Clin*, *52*(4), 195-215. https://doi.org/10.3322/canjclin.52.4.195

Okoturo, E. M., Trivedi, N. P., Kekatpure, V., Gangoli, A., Shetkar, G. S., Mohan, M., & Kuriakose, M. A. (2012a). A retrospective evaluation of submandibular gland involvement in oral cavity cancers: a case for gland preservation. *Int J OralMaxillofacSurg*,*41*(11),1383-1386. https://doi.org/10.1016/j.ijom.2012.07.016

Okoturo, E. M., Trivedi, N. P., Kekatpure, V., Gangoli, A., Shetkar, G. S., Mohan, M., & Kuriakose, M. A. (2012b). A retrospective evaluation of submandibular gland involvement in oral cavity cancers: a case for gland preservation. *International Journal of Oral and Maxillofacial Surgery*, *41*(11), 1383-1386. https://doi.org/https://doi.org/10.1016/j.ijom.2012.07.016

Olajumoke Ajibola Effiom, B., FMCDS, Wasiu Lanre Adeyemo, B., FMCDS, DMD, Olufemi Gbenga Omitola, B., FMCDS, Oluseyi Folake Ajayi, B., FMCDS, Mubarak M. Emmanuel, B., FMCDS, & and Olalekan Micah Gbotolorun, B., FMCDS¶. (2008). Oral Squamous Cell Carcinoma: A Clinicopathologic Review of 233 Cases in Lagos, Nigeria. *J Oral Maxillofac Surg 66:1595-1599, 2008*(.). https://doi.org/doi:10.1016/j.joms.2007.12.025

Ota, Y., Noguchi, T., Ariji, E., Fushimi, C., Fuwa, N., Harada, H., Hayashi, T., Hayashi, studies on oral cancer (2nd edition): a synopsis. *Int J Clin Oncol*, *26*(4), 623-635. R., Honma, Y., Miura, M., Mori, T., Nagatsuka, H., Okura, M., Ueda, M., Uzawa, N., Yagihara, K., Yagishita, H., Yamashiro, M., Yanamoto, S., & Kirita, T. (2021). General rules for clinical and pathological, https://doi.org/10.1007/s10147-020-01812-9

Panda, N. K., Patro, S. K., Bakshi, J., Verma, R. K., Das, A., & Chatterjee, D. (2015). Metastasis to submandibular glands in oral cavity cancers: Can we preserve the gland safely? *Auris Nasus Larynx*, *42*(4), 322-325. https://doi.org/10.1016/j.anl.2015.02.006

Peng, K. A., Chu, A. C., Lai, C., Grogan, T., Elashoff, D., Abemayor, E., & St John, M. A. (2014). Is there a role for neck dissection in T1 oral tongue squamous cell carcinoma? The UCLA experience. *Am J Otolaryngol*, *35*(6), 741-746. https://doi.org/10.1016/j.amjoto.2014.06.019

Petti, S. (2009). Lifestyle risk factors for oral cancer. *Oral Oncol*, *45*(4-5), 340-350. https://doi.org/10.1016/j.oraloncology.2008.05.018

Pires, F. R., Ramos, A. B., Oliveira, J. B., Tavares, A. S., Luz, P. S., & Santos, T. C. (2013). Oral squamous cell carcinoma: clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. *J Appl Oral Sci*, *21*(5), 460-467. https://doi.org/10.1590/1679-775720130317

Ranganathan, K., & Kavitha, L. (2019). Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol*, *23*(1), 19-27. https://doi.org/10.4103/jomfp.JOMFP_13_19

Rapidis, A. D., Gullane, P., Langdon, J. D., Lefebvre, J. L., Scully, C., & Jatin P. Shah *, Z. G. (2009). Major advances in the knowledge and understanding of the epidemiology, aetiopathogenesis, diagnosis, management and prognosis of oral cancer. *Oral Oncology 45*. https://doi.org/doi:10.1016/j.oraloncology.2009.04.001

Razfar, A., Walvekar, R. R., Melkane, A., Johnson, J. T., & Myers, E. N. (2009). Incidence and patterns of regional metastasis in early oral squamous cell cancers: feasibility of submandibular gland preservation. *Head Neck*, *31*(12), 1619-1623. https://doi.org/10.1002/hed.21129

Ren, Z.-H., Xu, J.-L., Li, B., Fan, T.-F., Ji, T., & Zhang, C.-P. (2015). Elective versus therapeutic neck dissection in node-negative oral cancer: Evidence from five randomized controlled trials. *Oral Oncology*, *51*(11), 976-981. https://doi.org/https://doi.org/10.1016/j.oraloncology.2015.08.009

Ribeiro, A. C., Silva, A. R., Simonato, L. E., Salzedas, L. M., Sundefeld, M. L., & Soubhia, A. M. (2009). Clinical and histopathological analysis of oral squamous cell carcinoma in young people: a descriptive study in Brazilians. *BrJOralMaxillofacSurg*,*47*(2),95-98. https://doi.org/10.1016/j.bjoms.2008.05.004

Robbins, K. T., Shaha, A. R., Medina, J. E., Califano, J. A., Wolf, G. T., Ferlito, A., Som, P. M., Day, T. A., Committee for Neck Dissection Classification, A. H., & Neck, S. (2008). Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg*, *134*(5), 536-538. https://doi.org/10.1001/archotol.134.5.536

S. Yang, J.-Z. S., Y. Gaob, G.-Y. Yua, ∗. (2019). Clinicopathological study of involvement of the submandibular gland in oral squamous cell carcinoma. *Journal of Oral and Maxillofacial Surgery 58*. https://doi.org/doi.org/10.1016/j.bjoms.2019.11.016

Sancatkar,M.E.,Çelebi,M.,Ağri,İ.,Akgül,G.,&Bakirtaş,M.SubmandibularGland Involvement In Patients Who Underwent Level 1b Neck Dissection For Oral Cavity Cancers.

Sankaranarayanan, R., Fernandez Garrote, L., Lence Anta, J., Pisani, P., & Rodriguez Salva, A. (2002). Visual inspection in oral cancer screening in Cuba: a case- control study. *Oral Oncol*, *38*(2), 131-136. https://doi.org/10.1016/s13688375(01)00033-1

Scully, C., & Bagan, J. (2009). Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical implications. *Oral Dis*, *15*(6), 388-399. https://doi.org/10.1111/j.1601-0825.2009.01563.x (.)

Shah, J. P. (1990). Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. *Am J Surg*, *160*(4),405-409. https://doi.org/10.1016/s0002-9610(05)80554-9 (.)

Sharma, A., Kim, J. W., & Paeng, J. Y. (2018). Clinical analysis of neck node metastasis in oral cavity cancer. *J Korean Assoc Oral Maxillofac Surg*, *44*(6), 282-288. https://doi.org/10.5125/jkaoms.2018.44.6.282

Shingaki, S., Takada, M., Sasai, K., Bibi, R., Kobayashi, T., Nomura, T., & Saito, C. (2003). Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg*, *185*(3), 278-284. https://doi.org/10.1016/s00029610(02)01378-8

Shuang Yang, R., Xiao Wang, Resident, Jia-Zeng Su, & Yu, G.-Y. (2018). The Rate of Submandibular Gland Involvement in Oral Squamous Cell Carcinoma. *JournalofOralandMaxillofacialSurgery*. https://doi.org/doi.org/10.1016/j.joms.2018.12.011

Singh, J. (2014). Histopathology of oral squamous cell carcinoma - A review *TMU J Dent ,1(4), 141-4*

Spoerl, S., Gerken, M., Mamilos, A., Fischer, R., Wolf, S., Nieberle, F., Klingelhöffer, C., Meier, J. K., Spoerl, S., Ettl, T., Reichert, T. E., & Spanier, G. (2021). Lymph node ratio as a predictor for outcome in oral squamous cell carcinoma: a multicenter population-based cohort study. *Clin Oral Investig*, *25*(4), 1705-1713. https://doi.org/10.1007/s00784-020-03471-6

Takes, R. P., Robbins, K. T., Woolgar, J. A., Rinaldo, A., Silver, C. E., Olofsson, J., & Ferlito, A. (2011). Questionable necessity to remove the submandibular gland in neck dissection. *Head Neck*, *33*(5), 743-745. https://doi.org/10.1002/hed.21451

Vessecchia, G., Di Palma, S., & Giardini, R. (1995). Submandibular gland metastasis of breast carcinoma: a case report and review of the literature. *Virchows Arch*, *427*(3), 349-351. https://doi.org/10.1007/bf00203404

Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology 45*. https://doi.org/doi:10.1016/j.oraloncology.2008.06.002

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

Wierzbicka, M., & Napierała, J. (2017). Updated National Comprehensive Cancer Network guidelines for treatment of head and neck cancers 2010-2017. *Otolaryngol Pol*, *71*(6), 1-6. https://doi.org/10.5604/01.3001.0010.7193

Woolgar, J. A., & Triantafyllou, A. (2009). Pitfalls and procedures in the histopathological diagnosis of oral and oropharyngeal squamous cell carcinoma and a review of the role of pathology in prognosis. *Oral Oncol*, *45*(4-5), 361-385. https://doi.org/10.1016/j.oraloncology.2008.07.016

Yang, S., Su, J. Z., Gao, Y., & Yu, G. Y. (2020). Clinicopathological study of involvement of the submandibular gland in oral squamous cell carcinoma. *Br J Oral Maxillofac Surg*, *58*(2), 203-207. https://doi.org/10.1016/j.bjoms.2019.11.016

Yang, S., Wang, X., Su, J. Z., & Yu, G. Y. (2019). Rate of Submandibular Gland Involvement in Oral Squamous Cell Carcinoma. *J Oral Maxillofac Surg*, *77*(5), 1000-1008. https://doi.org/10.1016/j.joms.2018.12.011

Yuen, A. P., Ho, C. M., Chow, T. L., Tang, L. C., Cheung, W. Y., Ng, R. W., Wei, W. I., Kong, C. K., Book, K. S., Yuen, W. C., Lam, A. K., Yuen, N. W., Trendell-Smith,
N. J., Chan, Y. W., Wong, B. Y., Li, G. K., Ho, A. C., Ho, W. K., Wong, S. Y., & Yao, T. J. (2009). Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck*, *31*(6), 765772. https://doi.org/10.1002/hed.21033

Yusuf Dundar, Q. M., Syed N. Raza, Ho-Sheng Lin, J. C., & Jeffrey M. Hotaling. (2019). Submandibular Gland Invasion by Oral Cavity Cancers: A Systematic Review. *Otolaryngology–Head and Neck Surgery*. https://doi.org/DOI: 10.1177/0194599819838475

Zeng, W., Qiu, C. Y., Liu, J. F., Pan, Y., Li, R., Luo, K., Tian, K. Q., Xiao, F. F., Xie, J. H., & Zhang, X. (2019). The preservation and application of the submandibular gland in oral squamous cell carcinoma (STROBE). *Medicine (Baltimore)*, *98*(52), e18520. https://doi.org/10.1097/md.0000000000018520

Zhen-Hu Ren a, J.-L. X. b., Bo Li c, Teng-Fei Fan d, Tong Ji a,1, Chen-Ping Zhang. (2015). Elective versus therapeutic neck dissection in node-negative oral cancer:

Evidence from five randomized controlled trials. *Oral Oncology*, *2015*. https://doi.org/.doi.org/10.1016/j.oraloncology.2015.08.009