SURVIVAL OF PATIENTS WITH FLOOR OF MOUTH SQUAMOUS CELL CARCINOMA TREATED WITH SURGICAL RESECTION AND RECONSTRUCTION AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Nishat Thokan

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MMED Otorhinolaryngology

Johannesburg 2020-11-25

Declaration

I Nishat Thokan declare that this Research Report is my own work. It is being submitted for the Degree of MMED Otorhinolaryngology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____

(Signature of candidate)

25th day of November 2020 in Johannesburg

Abstract

Introduction. The aims of this study were to assess survival rate of patients who underwent surgical treatment for squamous cell carcinoma (SCC) that involved the floor of mouth, as well as identify predictors of survival in patients with floor of mouth SCC.

Methods. A clinical audit was undertaken by means of a retrospective record review of patients who underwent surgical treatment for floor of mouth SCC at Charlotte Maxeke Johannesburg Academic Hospital. Patient data were collected and analysed with respect to age, sex, race, tobacco usage, alcohol usage, tumour stage and postoperative chemo-radiation. Five-year recurrence and overall survival rates were evaluated.

Results. Of 60 patients identified, only 20 were included in the study. The five-year overall recurrence rate was 25%. The five-year overall survival was 55%. Regular alcohol consumption and advanced disease stage were found to be significant predictors of high recurrence and low survival rates.

Conclusion. Floor of mouth SCC has a low five-year survival rate which might be improved by attending to habits such as smoking as well as early disease detection.

Acknowledgements

I would like to thank my supervisor Dr. Shivesh Maharaj for his tireless efforts in guiding me through this endeavour.

I would like to thank Mazvita Sengayi, a statistician from the National Health Laboratory Service, for her assistance with the statistical analysis in this project.

Lastly, I would like to thank my husband Muhammad Bobat for his patience and support during this endeavour.

Financial support

No financial support was required for the conduction of this study. This study was self-funded.

Contents Page

Declaration……...ii
Abstract……..……iii
Acknowledgements……iv
Financial support……iv
Nomenclature/List of Abbreviations and Symbols……..……vii
List of Figures……viii
List of Tables……...ix

Chapter 1: Introduction and literature review..……..…..1
1.1 Introduction……...……1
1.2 Literature review……..…...2
1.2.1 Regional anatomy……..2
1.2.2 Causes of malignancy……..……3
1.2.3 Staging of oral squamous cell carcinoma……..…...4
1.2.4 Surgical management……6
1.2.5 The role of neck dissection……...7
1.2.6 Histological features affecting survival…...……...……8
1.2.7 Reconstruction of tumour defects……..10
1.2.8 Adjuvant Therapies – Chemo and radiation therapy……..10
1.2.9 Survival rates of oral SCC……..11
1.2.10 Other factors affecting survival outcomes……..12
1.2.11 Summary……13
1.3 Aims and objectives……...14
1.3.1 Aims……....14
1.3.2 Objectives……..14
1.3.2.1 Primary Objectives……14
1.3.2.2 Secondary Objectives……14

Chapter 2: Materials and methods……...…..…..15
2.1 Ethics approval……..15

2.2 Study design……..……..15
2.3 Study Population……..…….……15
2.4 Inclusion criteria……..…….……..15
2.5 Exclusion criteria……..…….15
2.6 Data collection……....16
2.7 Recorded variables……..……..……16
2.8 Statistical analysis……..…..……17

Chapter 3: Results……..……..19
3.1 Study size……..……..19
3.2 Patient Demographics and overall data……..……19
3.3 Bivariate analysis - Factors associated with recurrence...……....19
3.4 Bivariate analysis - Factors associated with death…….……20
3.5 Recurrence analysis……20
3.6 Survival analysis……..….20
3.7 Predictors of mortality……20

Chapter 4: Discussion……33
4.1 Patient data……..……33
4.2 Factors associated with recurrence……..34
4.3 Factors associated with poor survival rates……35

Chapter 5: Conclusion……37
5.1 Conclusion……37
5.2 Recommendations……..…….38
5.3 Limitations……....38
5.4 Conflict of interest……39
5.5 Ethical standards……..39

References……...41
Appendix 1: Staging…….....…….…….49
Appendix 2: Data sheet……52
Plagiarism declaration……53
Ethics clearance……..54

Nomenclature/List of Abbreviations and Symbols

SCC: Squamous Cell Carcinoma

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

ICU: Intensive Care Unit

TNM: Tumour, Node, Metastases

AJCC: American Joint Committee of Cancer

NCDB: National Cancer Database

SEER: Surveillance, Epidemiology, and End Results

List of Figures

Figure 3.1: Overall recurrence……....23

Figure 3.2: Recurrence by gender…….23

Figure 3.3: Recurrence by race……..24

Figure 3.4: Recurrence by tobacco use……24

Figure 3.5: Recurrence by stage…..…….25

Figure 3.6: Recurrence by alcohol use …….....25

Figure 3.7: Recurrence by chemoradiation……..26

Figure 3.8: Overall survival…….29

Figure 3.9: Survival by gender……...29

Figure 3.10: Survival by race……..30

Figure 3.11: Survival by tobacco use…….30

Figure 3.12: Survival by alcohol use……..…31

Figure 3.13: Survival by stage…….....31

Figure 3.14: Survival by chemoradiation……..32

List of Tables

Table 3.1: Overall characteristics of patients with floor of mouth SCC……...21

Table 3.2: Factors associated with recurrence at 1 year and 5 years……..……22

Table 3.3: Cumulative survivor function for recurrence…….26

Table 3.4: Factors associated with death at 1 year and 5 years……..27

Table 3.5: Predictors of mortality……..….28

Table 3.6: Cumulative survival in patients……28

Chapter 1

Introduction and Literature review

1.1 Introduction

Oral cavity malignancies are the most common condition admitted to the otolaryngology wards at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). They are the eighth most common cancer worldwide and the most common malignancy in the head and neck (Ferlay *et al*.,2015). Floor of mouth malignancies are the second most common sub-site in the oral cavity after oral tongue malignancies (Farhood *et al*., 2019). More than 90% of oral cavity malignancies are squamous cell carcinoma (SCC) in South Africa as well as globally (Ferlay *et al*., 2015; Abram, 2012).

CMJAH is a tertiary institution with a multi-disciplinary approach to management patients with oral cavity SCC especially in advanced stages of the disease as these cases often require larger and more complicated resection and reconstruction procedures. The treating teams are variously comprised of otorhinolaryngology surgeons, plastic surgeons, maxillofacial surgeons, prosthodontists, radiation oncologists as well as various allied disciplines such as speech therapy and dietetics. Besides the personnel requirements, these cases often require prolonged theatre times, prolonged Intensive Care Unit (ICU) stay and prolonged hospital admission. They also frequently require post-operative adjuvant radiation therapy. Therefore, the management of these cases places a significant time, resource and financial burden on the hospital system.

This study will add value to this resource limited institution by guiding treatment decisions so that patient outcomes and valuable resources can be used more efficiently.

1.2 Literature Review

1.2.1 Regional Anatomy

Anatomically, the oral cavity can be divided into subsites; oral tongue (anterior two-thirds), floor of mouth, upper and lower alveolar ridges, right and left buccal mucosa, hard palate, and retromolar trigone. These subsites tend to have relatively unique lymphatic drainage pathways as shown by Shah (1990) and they also require varied surgical and reconstructive approaches. Subsites classically have varying propensities for locoregional spread. Furthermore, anatomic location predisposes certain tumours to more advanced tumour staging and bone invasion (Su *et al*., 2019).

Floor of mouth SCC presents unique challenges in treatment when compared with other sites in the oral cavity. The floor of mouth is defined as the mucosal surface below the tongue bordered by the alveolar ridge laterally and anteriorly, and the oral tongue posteriorly and medially (Wein, 2015). The lingual frenulum divides it in the midline. Its deep margin is the mylohyoid muscle. The contents include the sublingual glands, the deep portion of the submandibular glands, and the sub-epithelial minor salivary glands, deep lingual artery and veins, Wharton's duct and the lingual nerve (Wein, 2015). Due to the close proximity to the mandibular midline, alveolar ridge and tongue, the floor of mouth is positioned in an area with limited surgical access, higher risk of positive margins, and a propensity for bilateral cervical metastases (Hicks *et al*.,1997; Luryi *et al*, 2014).

The arterial supply to the floor of the mouth is from the dorsal lingual, sublingual, and deep lingual branches of the lingual artery. The venous drainage is into the lingual veins, which drain into the facial and retromandibular veins, which join to form the common facial vein (Wein, 2015). The lingual nerve provides general sensory innervation to the floor of the mouth and tongue as well as special taste sensation through the accompanying chorda tympani branch of the facial nerve (Wein, 2015).

The oral cavity has rich lymphatic drainage, and regional nodal metastasis occurs early and consistently in oral SCC. Lymphatic drainage of the floor of mouth is via cervical lymph nodes. The first echelon lymph nodes of the floor of mouth are located in the supra-omohyoid triangle (levels I to III). The lymphatic channels accompany the lingual venous system, and their density increases from the anterior to the posterior. Lymphatic metastases generally occur in a predictable fashion, but lymph nodes at level IV may be involved directly without involvement of level II nodes (Shah, 1990). The central portions toward the midline may drain bilaterally; those from the anterior midline portion pass to the submental and submandibular triangles (Wein, 2015).

1.2.2 Causes of malignancy

Primary neoplasms may arise from the mucosa, salivary glands, muscle or neurovascular tissues (Wein, 2015). Squamous cell carcinoma arises from the epithelial tissue of the mucosal lining of the oral cavity.

Malignant transformation is caused by genetic changes that progress as sequential series of somatic mutations in specific genes such as proto-oncogenes and tumour suppressor genes, resulting in malignant cell proliferation. These events can be triggered by extrinsic factors such as smoking and drinking habits as well as environmental factors and immunosuppression. Among the extrinsic factors, tobacco use and alcohol usage represent the highest risk to the emergence of this malignant disease in the oral cavity. Other known risk factors known for development of head and neck SCC are nutritional deficits (carotenoids & vitamin A, C and E), Fanconi anaemia, genetic predisposition, Human Papilloma Virus infection, previous head and neck malignancy and radiation exposure. Betel quid chewing (made of the areca nut wrapped in betel leaf) popularly used amongst the Asian population is also known to be a strong risk factor (Wein, 2015).

There are sixty carcinogens present in tobacco smoke and at least sixteen carcinogens in unburned tobacco. Smokers with a pack year history of more than thirty, have a four-fold greater risk of getting Oral SCC (Wein, 2015; Centers, 2010).

Alcohol use is another important risk factor in the development of Oral SCC however the synergistic effect of alcohol and tobacco consumption is believed to play a greater role than either agent alone as alcohol inhibits DNA repair from cellular injury due to nitrosamines found in cigarette smoke and may also act as a solvent that facilitates the passage of carcinogens through cellular membranes. In a large prospective study by Bao *et al*. (2020) who looked at 1165 patients with oral SCC, comparing users of alcohol and tobacco with those who did not use alcohol and tobacco, it was found that smoking and drinking was associated younger age group of oral SCC patients, the patients had a worse nutritional status and had poorer survival outcomes. Another large single institution retrospective study by Zanoni *et al*. (2019), who looked at data of 2082 patients that underwent resection for oral SCC, found that a history of regular alcohol consumption was an independent prognostic factor for poor five-year survival outcomes.

The chewing of betel quid in South Asian populations is a very common practice which can lead to the premalignant lesion oral submucous fibrosis and holds a 7% risk of malignant transformation into SCC (Su *et al*., 2019).

1.2.3 Staging of oral squamous cell carcinoma

The eighth edition of the Tumour, Node, Metastases (TNM) staging system devised by the American Joint Committee of Cancer (AJCC) is used to stage malignancies of the oral cavity (Appendix 1). The staging assists with assessment of disease status, prognosis and management (Pollaers *et al*., 2018). All available clinical findings may be used in staging including physical exam, radiologic, intraoperative, histopathology and biomarkers. Stage of disease at time of treatment initiation is a very important predictor of survival in oral

squamous cell carcinoma (Ong *et al*., 2017; Shin et al., 2018). It is widely accepted that the advanced stage (Stage III and IV) cancers of the oral cavity have lower disease free and overall survival rates compared to early stage cancers (Ong *et al*., 2017; Saggi *et al*., 2018; Su et al., 2019; Zanoni *et al*., 2019).

Stage I and II disease are associated with smaller tumours and smaller depth of invasion with no nodal or distant metastases (Appendix 1). Pollaers *et al*. (2018) reports the five-year survival for stage I is 84,6%, and for stage II 70,2%. Luryi *et al.* (2014) used the National Cancer Database (NCDB) data in the United Kingdom to study patients with exclusively early stage (stage I and II) oral SCC. Overall survival at five years for early stage (I and II) was 69.7% in this study that analysed 6830 cases.

Stage III disease is associated with a larger tumour and/or nodal metastases in a single ipsilateral node (Appendix 1). Pollaers *et al*. (2018) report the five-year survival for stage III disease to be 63.5%.

Stage IVa disease is associated with tumours that invade adjacent structures such as bone and skin or multiple lymph node metastases. Pollaers *et al*. (2018) reported the five-year survival for stage IVa disease to be 66%. Stage IVb oral SCC is advanced disease where the tumour is deemed irresectable due to tumour invasion of the masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery. Stage IVb also encompasses nodal metastases where the node is very large, six centimetres (cm) or more, or there is clinically overt extra nodal extension where the node is found to be fixed to the underlying structures or overlying skin (Appendix 1). Pollaers *et al*. (2018) reports five-year survival for stage IVb disease to be around 25%. Stage IVc disease is when there are distant metastases.

Cervical lymph node metastasis is an important prognostic factor in patients with oral SCC. 30% of patients with floor of mouth SCC present with regional metastases to lymph nodes and the overall five-year survival varies from 30-76% (Hicks *et al*., 1997; le Campion *et al*., 2017; Mashberg *et al*., 1976; Saggi *et al*., 2018; Sessions *et al*., 2000).

1.2.4 Surgical management

The goal of oral cavity SCC treatment is to eradicate the cancer, preserve or restore form and function of the oral cavity, minimize the sequelae of treatment and also to prevent locoregional recurrence. Treatment strategies are aimed at tumour control, restoration of function and prevention of recurrence. The tumour factors that affect the choice of initial treatment of oral cancer are primary site, size (T Stage), location (anterior versus posterior), proximity to bone (mandible or maxilla), status of cervical lymph nodes and previous treatment. Stage IVA disease indicates moderately advanced disease but is still considered to be surgically resectable. Stage IV B and stage IV C disease is very advanced disease and is considered to be unresectable. Good treatment outcomes for oral cavity SCC can be achieved by complete tumour resection with wide free margins (Shin *et al*., 2018). An adequate margin is the one of the most important prognostic factors (Amit *et al*., 2016).

The mandible is considered at risk when the primary tumour invades, is adherent to, or is adjacent to the mandible. Treatment options for suspected bony involvement of the mandible are segmental mandibulectomy or marginal mandibulectomy. A segmental mandibulectomy is indicated when there is gross invasion of cancellous bone, invasion of inferior alveolar nerve or canal or massive soft tissue disease adjacent to the mandible. A marginal mandibulectomy is indicated when tumour that involves only the periosteum and cortical bone. It is therefore mandible sparing. A review by Fives *et al*. (2016), they found that patients with T1 floor of mouth tumours with bony involvement had survival outcomes similar to those with more advanced tumours and no bone involvement, and those who had post-operative adjuvant therapy for bone involvement had better local disease control but the overall survival was not significantly improved.

Appropriate management of neck nodes is necessary to maximize locoregional control of disease and overall survival. Oral cavity cancers are treated primarily by surgery, followed by adjuvant therapy, depending upon their stage and

histopathological characteristics. Neck dissection, therefore, has an important role in management of oral cancers, not only as a part of treatment, but also for determining adjuvant therapy. In a large study by Zhan *et al*. (2018) who looked for predictors of occult nodal disease in a cohort of 2623 patients with Stage I oral SCC who underwent elective neck dissections, the incidence of occult pathological nodes was 15%. The incidence was found to be significantly higher in moderately differentiated (17.4%) and poorly differentiated tumours (28.5%) than well-differentiated disease (5.9%).

At the Department of Otorhinolaryngology at the CMJAH, primary surgical treatment is advocated for oral SCC. Resection of the primary tumour, with reconstruction by free tissue transfer where indicated, and a selective neck dissection when there are clinically palpable lymph nodes or an elective neck dissection if there are no palpable lymph nodes but the tumour T2/T3. Operations are intended to cure with resection of a margin of normal tissue of at least 0.5 cm.

1.2.5 The role of neck dissection

A systematic review and meta-analysis published by Massey *et al*. (2019) looking at management of N0 neck in early oral SCC included 39 publications of studies that looked at occult nodal metastases in patients with stage I and II disease, yielding a review of 4300 patients. The incidence of occult metastasis for stage I disease was 11.5% and for stage II disease was 24.5%.

In a prospective randomized control trial by D'Cruz *et al*. (2015) looking at elective neck dissection for node-negative T1/T2 oral SCC at the same time of surgery versus at the time of the primary surgery) versus therapeutic node dissection (watchful waiting followed by neck dissection for nodal relapse). There was a disease-free survival (three-year 69.5% versus. 45.9%) and overall survival benefit for the elective neck dissection group (three-year overall survival 80% vs. 67.5%).

Rodrigo *et al*. (2018) published a systematic review and meta-analysis which included studies of patients with clinically positive neck nodes N1 and N2 that received selective or comprehensive neck dissections. Four of the studies that looked at oral cavity only showed regional disease control rates of 86% in patients that received neck dissections and adjuvant radiation therapy.

In 2014, Ebrahimi *et al*. (2014), in a multicentric international study on 1567 patients with oral SCC and clinical N0 classification, demonstrated that the extent of regional lymph node dissection, namely nodal yield, is a strong independent prognostic factor. They found that lymphadenectomy of 18 nodes could be used as a cut off value for significant differences in prognosis and loco-regional recurrences rates for patients with oral SCC treated with elective neck dissection. These findings were supported by Safi *et al*. (2017).

1.2.6 Histological features affecting survival

The presence of extra-capsular nodal spread is an important prognostic factor significantly upstaging the tumour to a stage IVb (Shaw *et al.*, 2010; Shin *et al.*, 2018). Extracapsular spread correlates with the size of metastatic lymph nodes smaller nodes would have less probability of extracapsular spread compared with larger nodes (Shaw *et al*., 2010). Lopez- Cedrún and de Llano, (2015) observed correlation between the extracapsular nodal spread and the number of metastatic nodes. They found capsular invasion of 26.5% of patients with one or two involved nodes versus 55.5% when three or more nodes were involved. They also showed a significantly higher mortality rate in patients with node capsular invasion and in patients with two or more involved nodes. The significance of the number of affected nodes in correlation with prognosis has also been shown in a study by Ebrahimi *et al*. (2014).

While histological grade of the lesion reflects the aggressiveness of the tumour, it has not always been shown to be an independent parameter of prognosis (Okamoto *et al*., 2002; Woolgar and Triantafyllou, 2009) The most important histologic feature of the primary tumour which heavily impacts upon

selection of treatment and eventual prognosis is its depth of invasion. Depth of invasion and tumour thickness are not the same, and a distinction has to be made, even though many authors use these two terms synonymously. Tumour thickness was first demonstrated by Spiro *et al*. (1986) to be an important factor for nodal metastases and thus prognosis. In situ and superficially invasive lesions have a lower risk of regional lymph node metastases. Thicker lesions which are deeply infiltrating the underlying soft tissues have a significantly increased risk of lymph node metastases with its adverse impact on prognosis.

Depth of invasion is defined as the distance from the adjacent basement membrane to the deepest part of the primary tumour. It is now incorporated as part of the T staging of oral cavity SCC (Appendix 1). The depth of invasion takes into account the amount of tumour adjacent to the blood vessels and lymphatics which is what determines an increased risk of nodal metastases developing. Kane *et al*. (2006) reviewed 48 previously untreated patients with a T1/T2 N0 SCC of the oral cavity who underwent a primary excision of the tumour and elective neck node dissection and concluded that depth of invasion was the most significant histologic predictor of subclinical nodal metastasis. Brockhoff *et al*. (2017) published a review of 303 patients with a diagnosis of oral SCC who underwent primary excision and elective or selective neck dissection. They correlated the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck. They concluded that for floor of mouth SCC a neck dissection should be done for any tumour with a DOI of more than two millimetres.

Various studies have demonstrated a significant association between perineural invasion and cervical lymph node metastasis, poor locoregional control, and poor overall survival (Liebig *et al*., 2009; Brandwein-Gensler et al., 2005; Subramanium *et al*., 2018; Zanoni *et al*., 2019; Lopez-Cedrún and de Llano, 2015). Perineural invasion is present in up to 52% of head and neck carcinomas (Fagan *et al*.,1998). Perineural invasion is defined as tumour in close proximity to a nerve involving at least 33% of its circumference, or existence of tumour cells within any of the three layers of the nerve sheath

(Liebig *et al*., 2009). Safi *et al*. (2017) found that perineural invasion was associated with higher nodal yield (percentage of positive nodes found on a neck dissection).

Lymphovascular invasion is an important marker for tumour aggressiveness and poorer outcome in terms of locoregional control and overall survival (Beggan 2016; Fives, 2015; Subramanium, 2018).

1.2.7 Reconstruction of tumour defects

T4a tumours that are treated surgically often result in large composite tissue defects that need to be reconstructed for functional and aesthetic outcomes (Salvatori *et al*., 2014). The use of tissue-flaps for reconstruction improves resection margins. Reconstructive options include grafts, local or regional flaps as well as free tissue transfers from different sites, most commonly the leg, thigh and forearm (Salvatori *et al*., 2014; Sarafoleanu *et al*., 2017).

1.2.8 Adjuvant Therapies – Chemo and radiation therapy

Primary treatment with radiotherapy is not favoured due to the close proximity of the oral cavity sub-sites to bony structures such as the mandible and maxilla, which can lead to complications such as osteoradionecrosis of these structures (Farhood *et al*., 2019; Roland, 2011; Ong *et al*., 2017). Various studies have shown poorer outcomes in patients treated with radiotherapy; thus, surgical resection has been advocated as the primary treatment for most oral cavity malignancies, with reconstruction for large defects only (Nandakumar *et al*., 2016).

Adjuvant radiotherapy has been advocated for advanced tumours stage (III/IV), positive post-surgical margins, multiple positive neck nodes, extracapsular extension, perineural or intravascular invasion, and bone, cartilage and soft tissue invasion (Ong *et al*., 2017; Roland, 2011; Saggi *et al*., 2018; Shin *et al*.,

2018). Shin *et al*. (2018), investigated the impact of adjuvant radiotherapy on overall survival in patients with locoregionally advanced squamous cell carcinoma of the oral cavity. In their cohort of 3946 patients with oral SCC who had surgery, 50% received adjuvant radiotherapy. The five-year overall survival was 47.9% versus 39.4% in those who did not receive adjuvant radiotherapy. Similar observations were made by Saggi *et al*. (2018) wherein adjuvant radiotherapy was shown to be an important predictor of improved survival in floor of mouth SCC patients.

Outcomes of two prospective randomized trials both published in 2004 evaluated the addition of concurrent chemotherapy to adjuvant radiotherapy and found that adjuvant chemoradiotherapy for treatment in extracapsular extension of disease in metastatic cervical lymph nodes and those who have positive margins, have a significant improvement in local regional control and disease free survival compared to post-operative radiation therapy alone (Bernier *et al*., 2004; Cooper *et al*., 2004). Both studies demonstrated that for poor prognosis carcinomas, adjuvant postoperative high-dose cisplatin and radiation given concomitantly were more likely to control local-regional disease and yield disease-free survival than postoperative radiotherapy alone. The current practice at CMJAH radiation oncology department is concurrent chemoradiation as adjuvant treatment.

1.2.9 Survival rates of oral SCC

When looking at the literature for survival rates of specific subsites of the oral cavity there are few studies that separate the subsites. For those few studies that do evaluate floor of mouth SCC, the results show uniformly poor survival outcomes. In a very large prospective study by Su *et al*. (2019) undertaken over a nine year period in Taiwan, with a cohort of 27717 cases, the site specific five-year overall survival for floor of mouth SCC was 63%. Saggi *et al*. (2018) in the United States used the Surveillance, Epidemiology, and End Results (SEER) national database to correlate clinicopathologic characteristics and survival outcomes in floor of mouth SCC in order to describe the determinants of survival

for patients with floor of mouth SCC from 1973 to 2013. With their cohort of 14010 they reported an overall survival and disease specific survival of 39% and 59% at 5 years. Lopez- Cedrún and de Llano, (2015), did a long term (22 year) follow-up of 64 patients with advanced floor of mouth SCC who underwent surgical management. Their overall five-year survival rate was 34.4%, and their 22-year overall survival rate was 6.3%. Their median overall survival was 7.2 years.

There have definitely been improvements in the management of oral SCC. In the retrospective review by Zanoni *et al*. (2019) of 2082 patients that underwent resection for oral SCC over a 30-year period, the five-year overall survival and disease specific survival were 64.4% and 79.3%.

Schwam *et al*. (2015) also used the NCDB data in the USA to study differences in outcomes for patients treated from 1998 through 2003 and those treated from 2004 through 2006 and found an improvement in five-year overall survival from 50% to 60%. The International Consortium for Outcome Research (ICOR) in Head and Neck Cancer studied 2738 patients treated in seven cancer centres worldwide and reported a change in five-year overall survival from 59% in patients with oral SCC who were treated between the years 1990 and 2000 to 70% in those treated between 2001 and 2011 (Amit *et al*., 2013). These improved survival statistics are most likely owing to improvements in treatment protocols such as early detection and greater use of adjuvant radiation and chemotherapy and support of this was shown by Cheraglou *et al*. (2018).

1.2.10 Other factors affecting survival outcomes

Age on its own is not a contraindication for surgical treatment. Primary surgery in a younger patient with an early tumour would be more appropriate as the patient may develop a second primary later on in life requiring radiotherapy. In the study by Zanoni *et al*. (2019) age over 60 was found to be a poor predictor of survival as also found by other researchers such as Farhood *et al*. (2019), Lopez-Cedrún and de Llano, (2015), *et al*., (2018) and

Shin *et al*., (2018) but other researchers such as Luryi *et al*. (2014) and Moro *et al*. (2018) have found that older age does not significantly affect five-year survival outcomes.

Comorbidities such as cardiac and pulmonary conditions may affect anaesthetic outcomes, patients are at risk of adverse cardiac events on table or immediately post-operative and these comorbidities also affected long term overall survival (Lopez-Cedrún and de Llano, 2015; Piccirillo *et al*., 2002; Shin *et al*., 2018; Zanoni *et al*., 2019). Smoking, poorly controlled diabetes and HIV patients with poor nutritional status associated with a low body mass index may have poor outcomes in terms of wound and flap healing (Schwam *et al*., 2016; Wolfer *et al*., 2018; Zanoni *et al*., 2019).

1.2.11 Summary

Oral SCC is a complex, multifactorial disease that has diagnostic, surgical and reconstructive challenges affecting outcomes.

This study will attempt to identify prognostic and predictive factors that may help in developing improved institution-specific protocols for the management of oral SCC as the hospital is in a resource limited environment with a high burden of malignant disease.

1.3. Aims and Objectives

1.3.1 Aims

The aims of this study were to assess survival rate of patients who undergo surgical treatment for squamous cell carcinoma (SCC) involving the floor of mouth, as well as to identify predictors of survival in patients with floor of mouth SCC.

1.3.2 Objectives

1.3.2.1 Primary Objectives

- To report five-year overall survival rates for each stage of floor of mouth SCC for a period of 10 years from 2008 to 2017.

- To report five-year recurrence rates for each stage of floor of mouth SCC for a period of 10 years from 2008 to 2017.

1.3.2.2 Secondary Objectives

- To report on patient demographic data
- To report on smoking and alcohol use as risk factors
- To report on tumour staging
- To report on the use of adjuvant chemoradiation therapy
- To analyse the relationship between demographics, risk factors, tumour staging, management and survival and recurrence rates

Chapter 2

Materials and methods

2.1 Ethics approval

Ethics clearance certificate was obtained from the University of the Witwatersrand Human Research Ethics Committee**.**

2.2 Study design

The study is a retrospective review of available clinical records. It is a quantitative design looking to correlate clinical findings with survival trends.

2.3 Study Population

Patients diagnosed with squamous cell carcinoma of the floor of mouth who underwent oncological resection and reconstruction at CMJAH between 2008-2017 were included in the study.

2.4 Inclusion criteria

All patients with documented floor of mouth squamous cell carcinoma that underwent surgical resection.

2.5 Exclusion criteria

Patients with inadequate data in their clinical records and patients who could not be contacted or traced in order to determine survival were excluded from the study.

2.6 Data Collection

Data was collected from theatre records-all patients that underwent the procedure were identifiied. Hospital file records for the identified patients were procured to document age at diagnosis, gender, race, tobacco use, regular alcohol use, clinical stage at diagnosis and adjuvant chemoradiation received. Alcohol and tobacco use was not quantified, hospital notes were searched for a history of regular alcohol and tobacco use which was regarded as sufficient. National Health Laboratory System records were also procured where histopathalogical diagnosis was confirmedd as SCC and date of recurrence specimen documented. ENT out-patient department records of patient contact details were procured. Patient/family telephonic interviews were undertaken to asses patients living status and date of death. Data was recorded on a Microsoft Excel sheet (Appendix 2).

2.7 Recorded variables

Patient Demographics

- age at diagnosis
- gender
- race

Risk Factors

- smoking habit
- alcohol use

Clinical findings

- Tumour staging at diagnosis

Treatment

- Chemo-radiation received

Outcomes

- recurrence at 1 year
- recurrence at 5 years
- death by 1 year
- death by 5 years

2.8 Statistical analysis

All analyses were done using StataCorp. 2017. Stata 15 Base Reference Manual. College Station, TX: Stata Press.

Statistical significance was set at 5%. The overall patient characteristics were tabulated. Frequencies and percentages were used to describe categorical variables; mean and standard deviation were used to describe the age.

In bivariate analysis, characteristics of patients who had recurrence and those who did not were compared. Comparisons of recurrence at one year and 5 years were made using Fisher's exact tests for categorical variables and Student's T-test for age. Similarly, characteristics of patients who died and those who survived at one year and 5 years were compared.

Time-to-event analyses were used to estimate time to recurrence and time to death. For recurrence, time was calculated from date of surgery to date of recurrence or date of death for those who died before recurrence, or date of database closure (30 November 2019) for those who did not die and did not have recurrence. For death, time was calculated from date of surgery to date of death or date of database closure (30 November 2019) for those who did not die.

The number of recurrences and deaths and mean follow-up time was reported. Kaplan Meier cumulative survival curves for death and mortality were plotted and log rank tests were used to compare survivor curves.

Adjusted and unadjusted Cox regression models were fitted to help identify predictors of mortality in patients with floor of mouth SCC post-surgery.

Chapter 3

Results

3.1 Study size

Within the study period, 60 patients were identified who had surgical management for floor of mouth SCC. Thirty-seven patients were excluded from the study as there were inadequate clinical records available requiring clinical information pertinent to the study. A further three patients were excluded as there was no follow up or useable contact details available to determine survival status. Therefore, a total of 20 patients were included in the study that were identified that were treated with resection and reconstruction for floor of mouth SCC (Table 3.1).

3.2 Patient demographics and overall data

Within the study period, 20 patients were included that were treated surgically for floor of mouth SCC (Table 3.1). The mean age at diagnosis was 56.9 years, with 70% of the sample being male and 50% being black. Amongst the sample, 90% of patients used tobacco and 60% were frequent alcohol users. The most common stage at diagnosis was stage IVA which was found in 8 out of 20 patients (40% of the sample). 70% of patients received adjuvant chemoradiation as an adjunct to surgery.

3.3 Bivariate analysis - Factors associated with recurrence

There were no significant factors associated with recurrence at 1 year. At five years, alcohol usage was a significant predictor of recurrence (P=0.044).

3.4 Bivariate analysis - Factors associated with death

There were no significant factors associated with death at one year however tumour stage at five years was a significant predictor (P=0.035).

3.5 Recurrence analysis

Out of 20 patients, five patients had recurrence making the five-year recurrence rate 25%.
Total person-time was 72.9 person-years, with a mean follow-up time of 3.65 (SD 2.04) years per person.

3.6 Survival analysis

Out of 20 patients, nine patients died within five years making the five-year overall survival 55%.

Total person-time was 72.9 person-years, with a mean follow-up time of 3.65 (SD 2.04) years per person.

3.7 Predictors of mortality

Alcohol was the only statistically significant factor associated with increased mortality.

Table 3.1: Overall characteristics of patients with floor of mouth SCC

Variable	**N (%)**
Demographics	
Age(years), *mean (standard deviation)*	56.9 (14.3)
Gender	
Male	14 (70.0)
Female	6 (30.0)
Race	
Black	10 (50.0)
White	8 (40.0)
Coloured	2 (10.0)
Risk Factors	
Tobacco users	18 (90.0)
Alcohol users	12 (60.0)
Clinical findings	
Stage at diagnosis	
Stage I	3 (15.0)
Stage II	3 (15.0)
Stage III	6 (30.0)
Stage IVA	8 (40.0)
Treatment	
Chemo-radiation received	14 (70.0)
Outcomes	
Recurrence at 1 year	1 (5.0)
Recurrence at 5 years	5 (25.0)
Death by 1 year	2 (10.0)
Death by 5 years	9 (45.0)

Table 3.2: Factors associated with recurrence at 1 year and 5 years

Factors	Recurrence at 1 year (N=20)			Recurrence at 5 years (N=15)		
	No recurrence	Recurrence	P value	No recurrence	Recurrence	P value
Age, *mean (standard deviation)*	57.63 (14.22)	42	-	55.4 (12.28)	58 (11.55)	0.0702
Gender						
Male	13 (92.86)	1 (7.14)		5 (50.0)	5 (50.0)	
Female	6 (100.0)	0 (0.0)	1.000	5 (100.0)	0 (0.0)	0.101
Race						
Black	9 (90.0)	1 (10.0)		3 (50.0)	3 (50.0)	
White	8 (100.0)	0 (0.0)		6 (85.71)	1 (14.29)	
Coloured	2 (100.0)	0 (0.0)	1.000	1 (50.0)	1 (50.0)	0.336
Tobacco						
Non-users	2 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Tobacco users	17 (94.44)	1 (5.56)	1.000	9 (64.29)	5 (35.71)	1.000
Alcohol						
Non-users	8 (100.0)	0 (0.0)		6 (100.0)	0 (0.0)	
Alcohol users	11 (91.67)	1 (8.33)	1.000	4 (44.44)	5 (55.56)	**0.044**
Stage at diagnosis						
Stage I	3 (100.0)	0 (0.0)		3 (100.0)	0 (0.0)	
Stage II	3 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)	
Stage III	6 (100.0)	0 (0.0)		2 (40.0)	3 (60.0)	
Stage IVA	7 (87.50)	1 (12.50)	1.000	3 (60.0)	2 (40.0)	0.384
Chemo-radiation received						
No	6 (100.0)	0 (0.0)		5 (83.33)	1 (16.67)	
Yes	13 (92.86)	1 (7.14)	1.000	5 (55.56)	4 (44.44)	0.580

KAPLAN MEIER CURVES FOR RECURRENCE

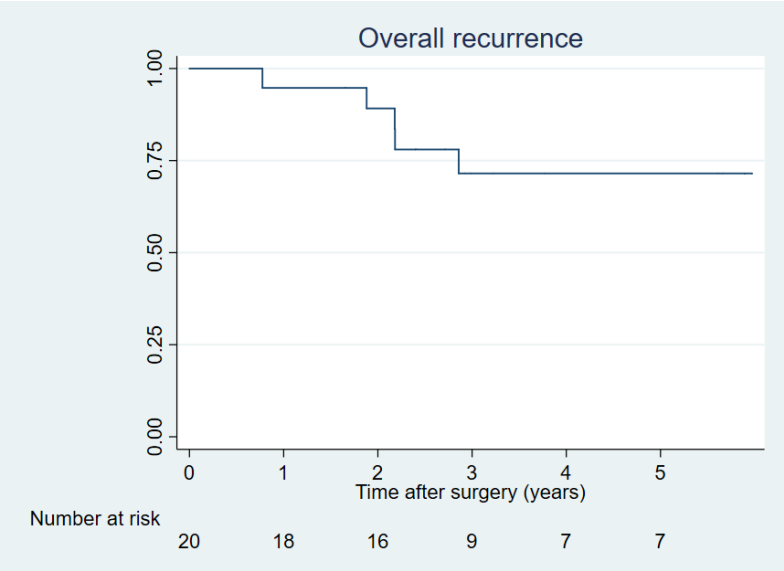

Figure 3.1: Overall recurrence

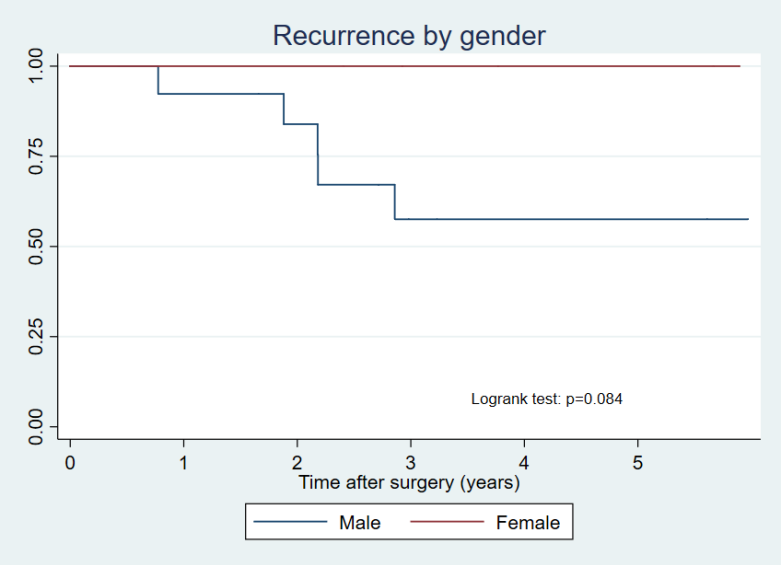

Figure 3.2: Recurrence by gender

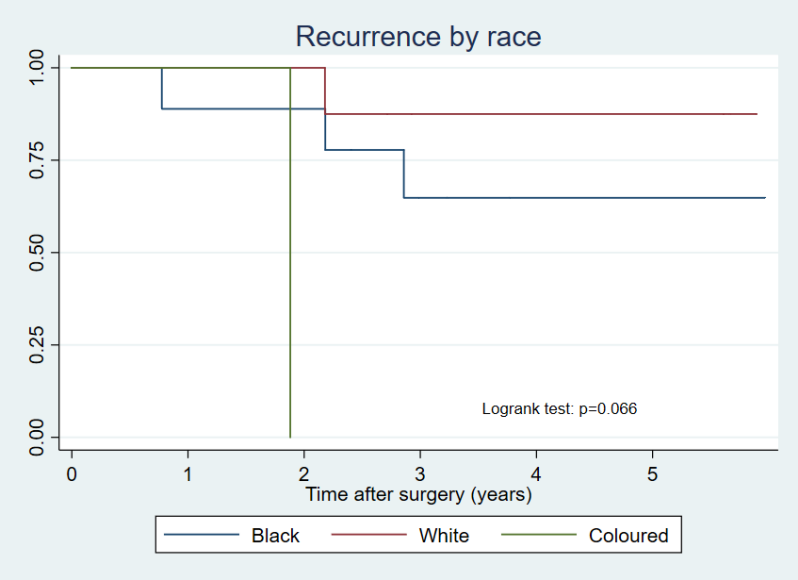

Figure 3.3: Recurrence by race

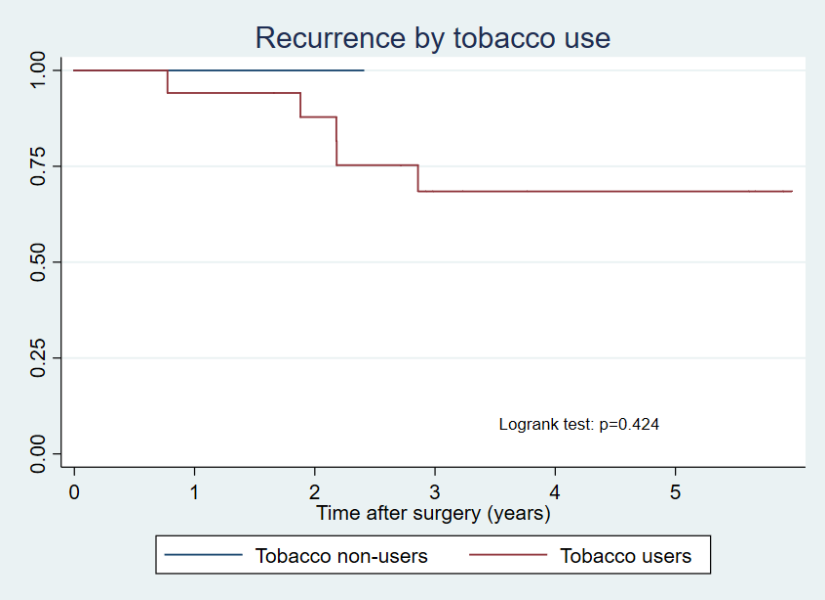

Figure 3.4: Recurrence by tobacco use

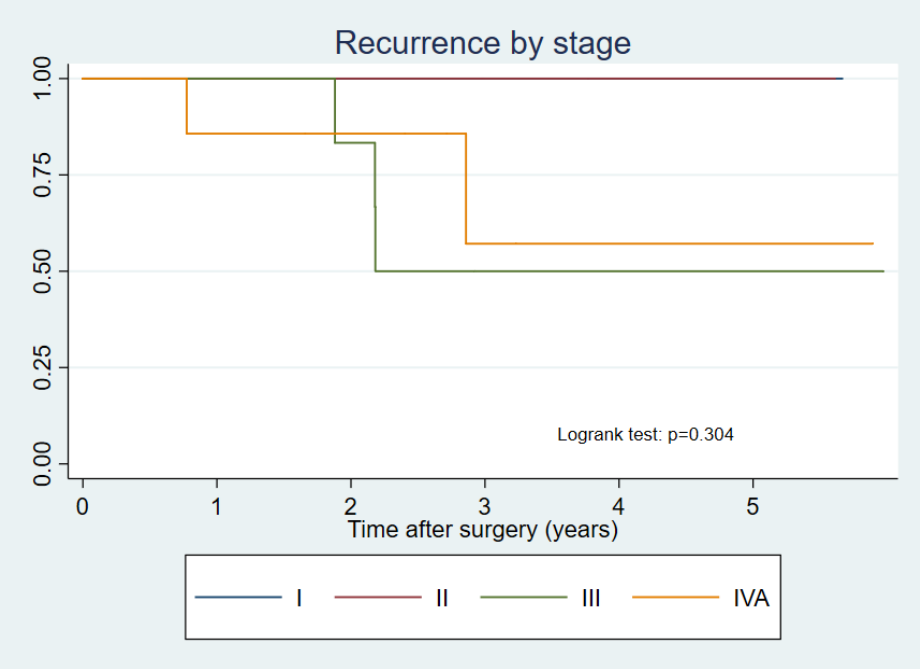

Figure 3.5: Recurrence by stage

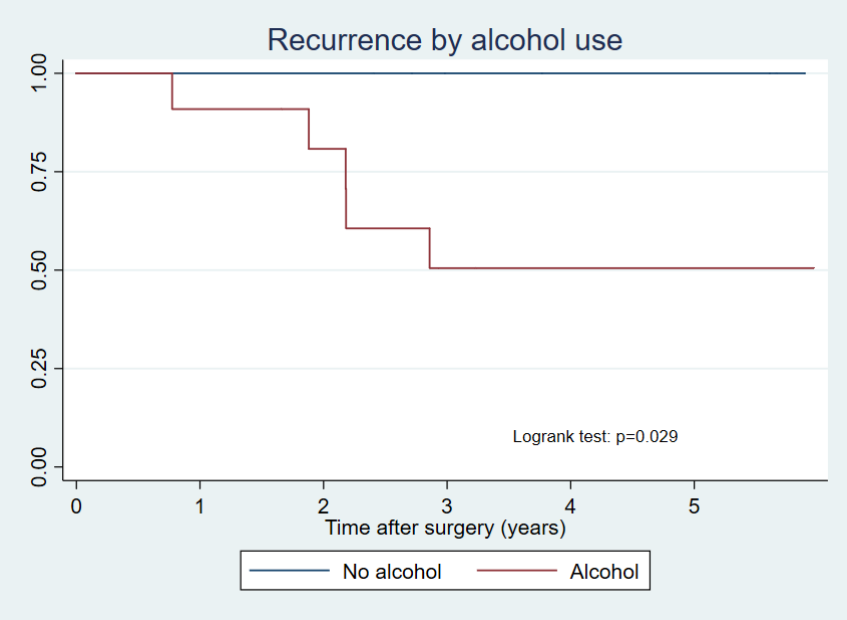

Figure 3.6: Recurrence by alcohol use

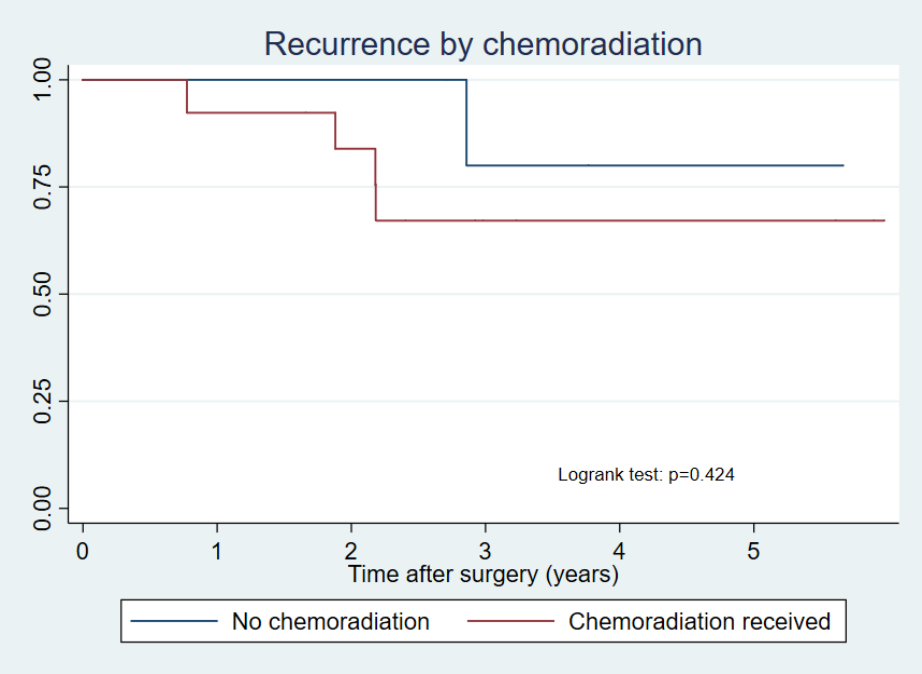

Figure 3.7: Recurrence by chemoradiation

Table 3.3: Cumulative survivor function for recurrence

Time from surgery (in years)	Total at the beginning of period	Number of recurrences	Survivor Function	95% CI	
1	19	1	0.9474	0.6812	0.9924
3	10	4	0.7152	0.4425	0.8712
5	8	0	0.7152	0.4425	0.8712

Table 3.4: Factors associated with death at 1 year and 5 years

Factors	Death at 1 year (N=20)			Death at 5 years (N=17)		
	Alive N (%)	Dead N (%)	P value	Alive N (%)	Dead N (%)	P value
Age, *mean (standard deviation)*	57.78 (14.62)	48.50 (9.19)	0.398	58.25 (17.0)	57.78 (10.05)	0.944
Gender						
Male	12 (84.71)	2 (14.29)		4 (33.33)	8 (66.67)	
Female	6 (100.0)	0 (0.0)	1.000	4 (80.0)	1 (20.0)	0.131
Race						
Black	8 (80.0)	2 (20.0)		3 (42.86)	4 (57.14)	
White	8 (100.0)	0 (0.0)		5 (62.50)	3 (37.50)	
Coloured	2 (100.0)	0 (0.0)	0.579	0 (0.0)	2 (100.0)	0.444
Tobacco						
Tobacco non-users	2 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Tobacco users	16 (88.89)	2 (11.11)	1.000	7 (43.75)	9 (56.25)	0.471
Alcohol						
Alcohol non-users	8 (100.0)	0 (0.0)		5 (83.33)	1 (16.67)	
Alcohol users	10 (83.33)	2 (16.67)	0.495	3 (27.27)	8 (72.73)	0.05
Stage at diagnosis						
Stage I	3 (100.0)	0 (0.0)		3 (100.0)	0 (0.0)	
Stage II	3 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)	
Stage III	6 (100.0)	0 (0.0)		2 (33.33)	4 (66.67)	
Stage IVA	6 (75.0)	2 (25.0)	0.747	1 (16.67)	5 (83.33)	**0.035**
Chemo-radiation received						
No	6 (100.0)	0 (0.0)		4 (66.67)	2 (33.33)	
Yes	12 (85.71)	2 (14.29)	1.000	4 (36.36)	7 (63.64)	0.335

Table 3.5: Predictors of mortality

Factors	**Unadjusted Cox Regression Models**			**Adjusted Cox Regression Model**		
	Hazard Ratios	95% CI	P Value	Hazard Ratios	95% CI	P Value
Age	0.99	0.95 – 1.04	0.955	0.91	0.82 – 1.01	0.096
Gender						
Male	*Reference					
Female	0.21	0.02 – 1.69	0.142	-	-	-
Race						
Black	*Reference			Reference		
White	0.74	0.17 – 3.33	0.700	4.77	0.45 – 50.82	0.196
Coloured	8.71	1.10 – 69.06	**0.040**	9.63	0.88 – 105.46	0.064
Alcohol						
Alcohol non-users	*Reference			Reference		
Alcohol users	7.60	0.95 – 61.03	0.056	44.05	1.59 – 1221.32	**0.026**
Stage at diagnosis						
Stage I - III	*Reference			Reference		
Stage IVA	2.85	0.75 – 10.79	0.122	3.66	0.59 – 22.71	0.164
Chemo-radiation received						
No	*Reference			Reference		
Yes	2.06	0.42 – 9.96	0.370	2.23	0.38 – 12.91	0.371

*Referece = Hazard ratio of 1

Table 3.6: Cumulative survival in patients

Time from surgery (in years)	Total at the beginning of period	Number of deaths	Survivor Function	95% CI	
1	19	2	0.9000	0.6560	0.9740
3	10	7	0.5385	0.2990	0.7280
5	8	0	0.5385	0.2990	0.7280

KAPLAN MEIER CURVES FOR SURVIVAL

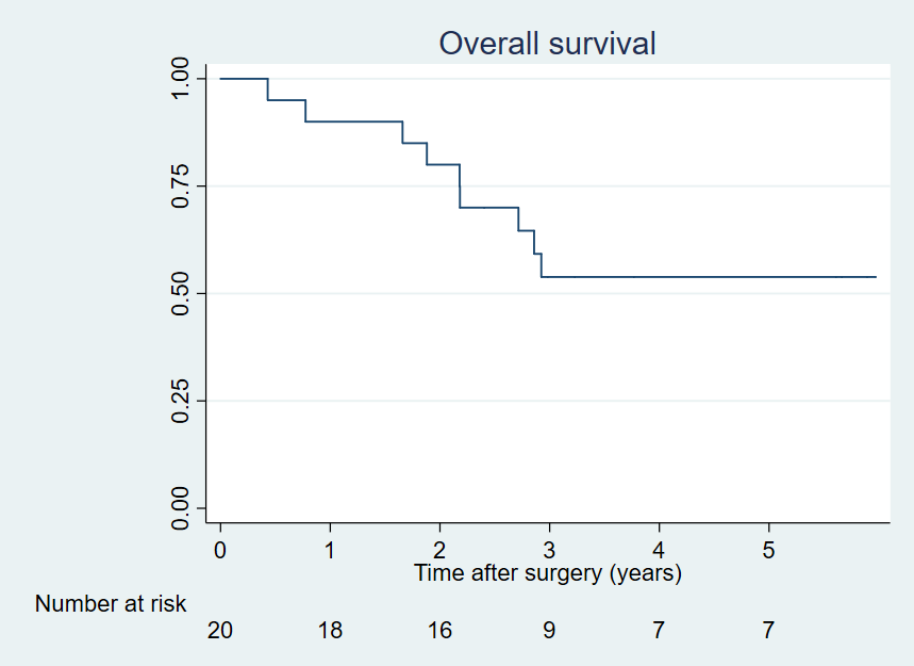

Figure 3.8: Overall survival

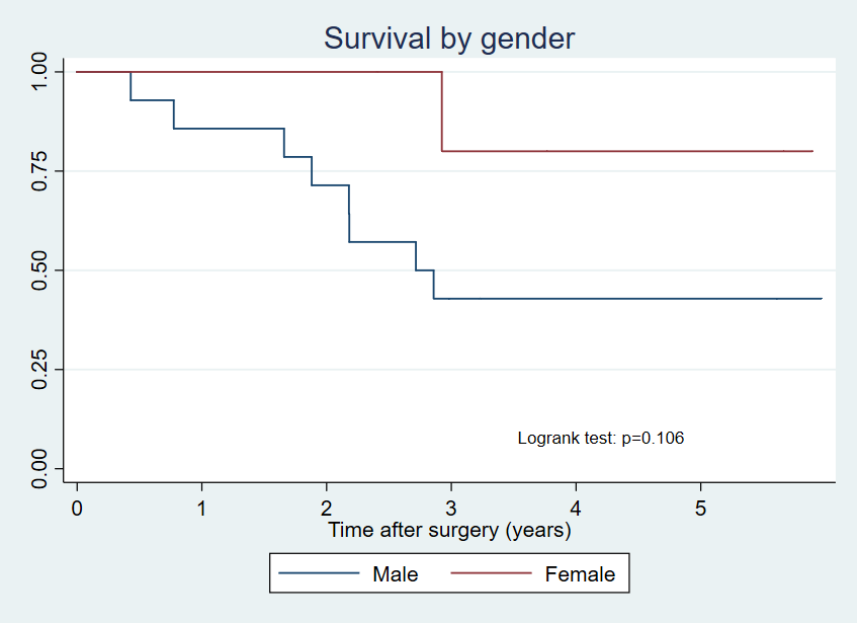

Figure 3.9: Survival by gender

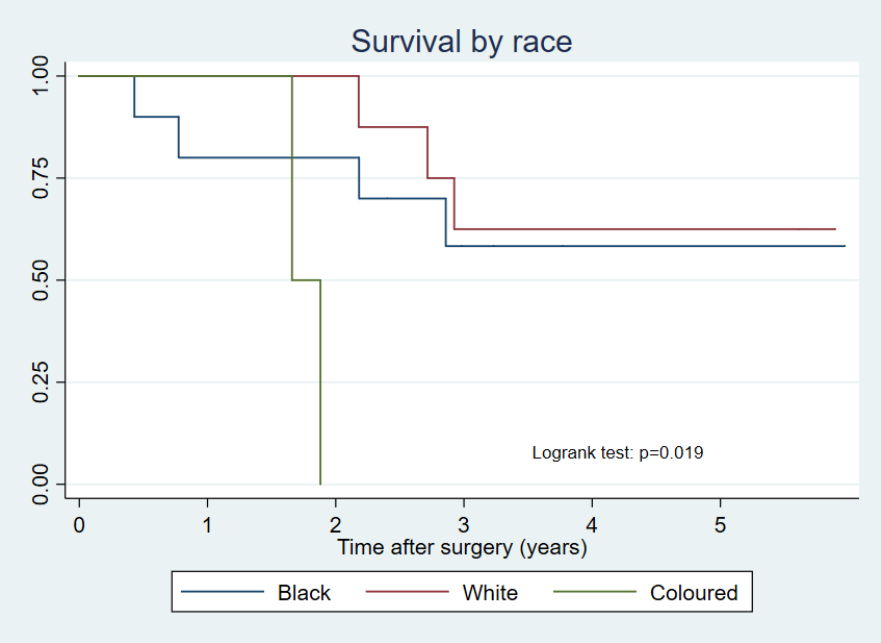

Figure 3.10: Survival by race

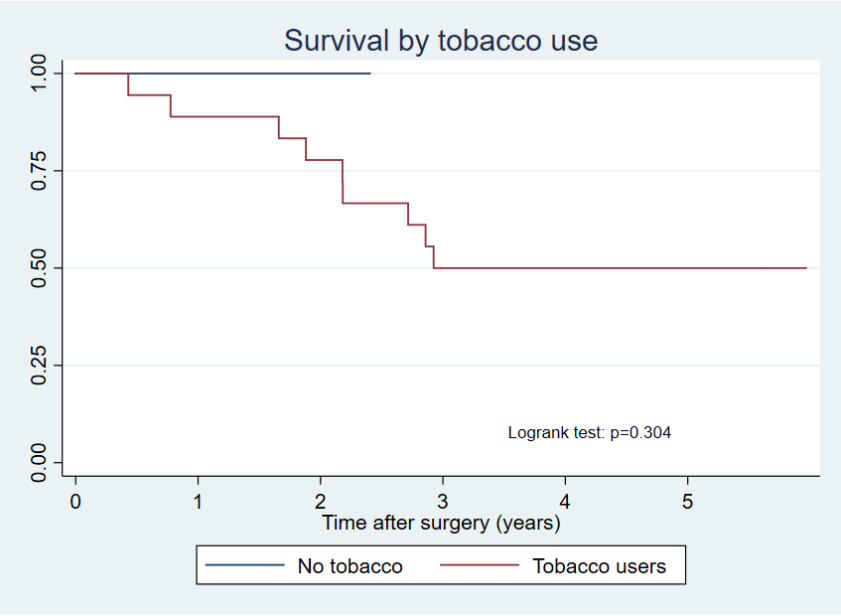

Figure 3.11: Survival by tobacco use

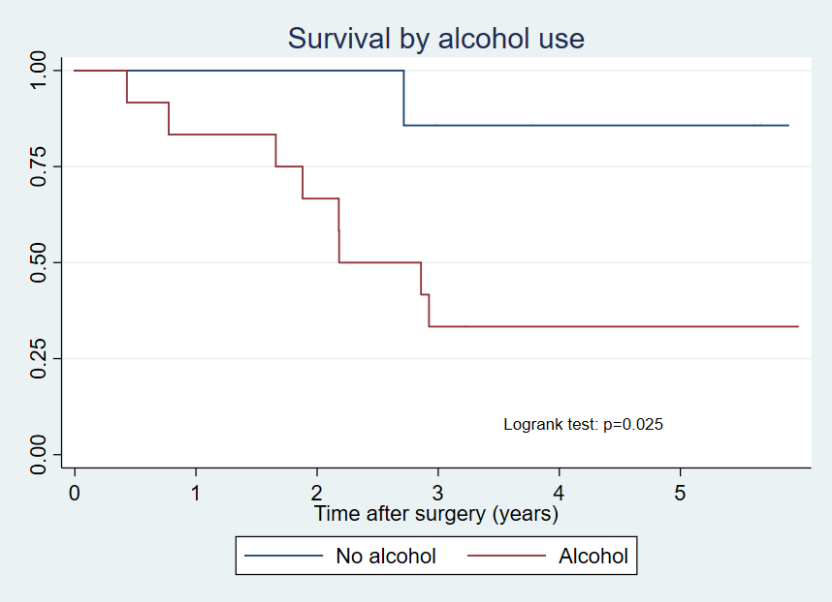

Figure 3.12: Survival by alcohol use

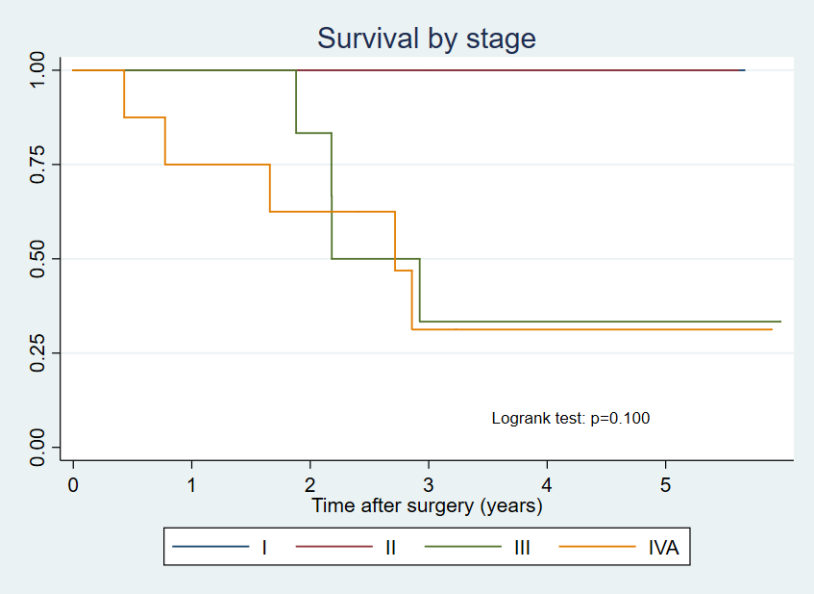

Figure 3.13: Survival by stage

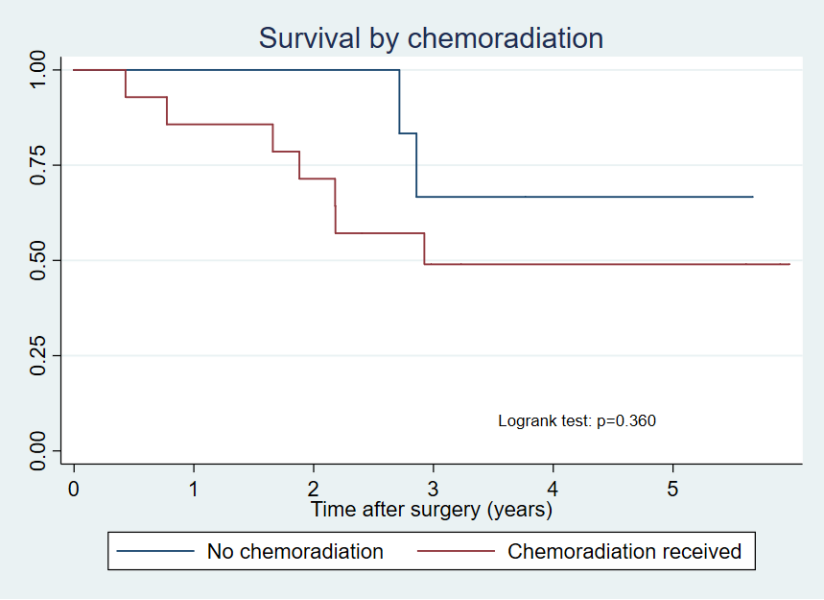

Figure 3.14: Survival by Chemoradiation

Chapter 4

Discussion

4.1 Patient Data

The data collection identified 20 patients who fit the inclusion criteria for the study with complete clinical records treated for floor of mouth cancer from 2008 to 2017.

The mean age range of 56.9 (SD 14.3) years. The age distribution was in keeping with previously reported studies where the peak age range of patients affected with floor of mouth SCC in the literature is 54.4 (SD 11.5) years (Su *et al*., 2019).

Floor of mouth SCC has historically affected males more frequently than females, however, there is an increasing incidence in females due to the rise in smoking and alcohol consumption rates in females (Sarafoleanu *et al*., 2017). In this study 70% of patients were male and 30% female in keeping with the male predominance reported in the literature (Ong *et al*., 2017).

In South Africa, oral SCC predominates in black males followed by Caucasian males (Abram, 2012). Racial demographics were the same as other studies done in South Africa for oral SCC, with black predominance, followed by white then coloured (Abram, 2012; Altini and Kola,1985).

In this study the stage of tumour at presentation was more advanced with 40% presenting with stage IV disease which is in keeping with findings from other third world centres such as Brazil and India where the most frequent stage of presentation is stage IV disease (le Campion *et al*., 2017; Coelho, 2012). This is in contrast to reports from first world countries such as the USA where patients most commonly present at early stages (I and II) of disease (Saggi *et al*., 2017). This could be due to delays in appropriate referral of patients or due to delays in

seeking treatment by patients due to social, educational and economic factors that are prevalent in third world countries.

4.2 Factors associated with recurrence

The five-year recurrence rate of 25% which is lower than that reported by Masoudi *et al*. (2017) who had a 41% five-year recurrence rate. There was also a higher number of recurrences (1 versus 5) as well as deaths (2 versus 9) from the study sample at five years compared to one year, which is in keeping with data reported by Ong *et al*. (2017).

This study showed that overall risk for recurrence increased from year one to three then stabilized (Figure 3.1). The survivor function for recurrence remained the same between years three and five (Table 3.3).

The risk of recurrence was more likely in males over females (Figure 3.2), coloured people over black people and black people over white people (Figure 3.3).

Tobacco users carried a higher risk of recurrence over non–tobacco users (Figure 3.4). Those patients with stage III and stage IVA disease had a higher risk of recurrence (Figure 3.5). This finding is in keeping with the findings in the study by Bao *et al*. (2020).

An interesting observation is that patients who received adjuvant chemo-radiation had a higher risk of recurrence than those who had surgery only (Figure 3.7). However, these risks were not statistically significant and were possibly due to the small sample size and the fact that advanced stage patients receive adjuvant chemoradiotherapy at this institute.

Bivariate analysis showed no significant risks factors to predict recurrence at one year, however there was a significant association of recurrence (P=0.044) at five years with alcohol use (Figure 3.6). Perhaps the continued use of alcohol post

treatment or the oncogenic effects of synergistic alcohol and tobacco use allow for greater field mutations which, in turn, increase the risk of recurrence compared to non-alcohol users.

4.3 Factors associated with poor survival rates

The survival rate was 90% at one year and 55% at five years. The five-year overall survival of 55% is higher than floor of mouth SCC survival of 39% and 34% reported by Saggi *et al*. (2018) and Lopez-Cedrún *et al*. (2015), but lower than Su *et al*. (2019) who reported a 64% five year overall survival. Other researchers published higher five-year overall survival rates for oral SCC between 60-71% (Amit *et al*., 2013; Garzino-Demo *et al*., 2016; Ong *et al*., 2017; Schwam et al., 2015; Zanoni *et al*., 2019). The study analysis also found that patient survival decreased to nearly half from time of surgery to 3 years then stabilized (Figure 3.8).

Males were found to have a higher risk of death than females (Figure 3.9), In the literature, gender has not been shown to have a statistically significant difference in survival rates (Cheraglou *et al*., 2018; Honorato *et al*., 2015).

Coloured people had a higher risk of death than black and white people (hazard ratio of 8) but this was not found to be statistically significant.

The findings show no statistical differences in survival based on age in keeping with some studies in the literature (Cheraglou *et al*., 2018).

In the study there found that tobacco use carried a higher risk of death over non-tobacco users although this was not statistically significant (P=0.304) in keeping with findings by Bao *et al*. (2018).

The study also found that alcohol use carried a statistically significant (P=0.026) risk of death compared to non-alcohol users (Figure 3.12). This finding is in

keeping with other studies that found alcohol usage as a significant predictor of low survival rates (Bao *et al*., 2020, and le Campion *et al*., 2017).

As with recurrence there were no significant risk factors for predicting patient death at one year. At five years advanced stages had a higher number of deaths (Figure 3.13). Floor of the mouth SCC has a high risk of regional lymph node metastases with an adverse impact on prognosis (Brockhoff *et al*., 2017; Farhood *et al*., 2019). Patients with lymph node metastases are staged as Stage III or IV. Stage IV disease has been shown to have a five-year survival rate of 23-58%, stage III disease 41-66%, stage II disease 59-80% and stage I disease 86-94%. In this study the five-year survival rates were 65% for Stage IV disease, 80% for Stage III disease and 100% for Stage I and II disease.

The study analysis found that patients that had post-operative chemoradiation had a slightly lower survival rate than those who did not receive it. This was not found to be statistically significant (P=0.36). This finding is similar to findings reported by Chang *et al*. (2015) and Ong *et al*. (2017) It is however conflicting with other literature which shows that concurrent postoperative chemo-radiation improves survival rates (Nandakumar *et al*. 2016 ; Spiotto *et al*., 2017). The findings in this study are most likely due to the small sample size and the fact that advanced stage patients receive adjuvant chemoradiotherapy at this institute.

Chapter 5:

Conclusion

5.1 Conclusion

Oral SCC is a multifactorial disease with a wide range of presentations, staging and prognosis.

From the literature review it is clear that the management choices, made at CMJAH for patients with floor of mouth SCC, are backed up by evidence-based treatment guidelines.

From the data analysis, the regular use of alcohol appear to be significant variable in the risk of recurrence and was the only statistically significant variable identified as a predictor of mortality (Table 3.5).

This study also showed that patients who present with aadvanced stage disease have worse overall survival rates.

The findings from this study suggest that earlier diagnosis and active treatment of early stage disease may be the best means of improving five-year survival rates. Efforts to improve quality of care and manage limited resources should concentrate on choosing the appropriate disease stage for surgical management, improve cancer surveillance and strengthen referral system so as to improve early detection of disease and provide social support and counselling for adjunctive habits such as alcohol and tobacco use cessation, which will improve patient outcomes.

5.2. Recommendations

Through doing this research project based at CMJAH, the need for improving the record keeping and record storage at this institute has been identified, based on the fact that only 20 patients out of 60 identified could be included in the study. An electronic data capturing system could be implemented in this department in order to improve data recovery for future similar projects.

The value of doing this study is that it has provided motivation to improve the record keeping system at this institution. CMJAH provides services to such a large volume of head and neck cancer patients and the small sample size that has been yielded is a testament to the problems with the current record keeping system. The information and potential data that could potentially be recorded for future studies will be much more significant if a better system of record keeping could be implemented.

Given the relatively small sample size in single-institution studies of floor of mouth SCC, a larger population-based study would further our understanding of this clinical entity, specifically the effect of patient demographics, patient nutrtional status and comorbidities, quantification of alcohol and tobacco usage, cancer characteristics (size, grade, and stage), and treatment modalities on patient outcomes and survival.

5.3 Limitations of the study

This study is limited by the small sample size which could be due to the selection a single Oral SCC sub-site in order to reduce confounding variables.

Histopathological findings were in the proposal for this study in order to assess impact on survival and recurrence of specific histopathological findings such as lymphovascular invasion, perineural invasion and grading of tumour and depth of invasion. As mentioned in the introduction, these have been found to have significant prognostic markers. However, these findings were not consistently

documented in the histology reports, therefore could not be assessed in this study.

Poor clinical record keeping was the most severe limitation in this study. There were missing theatre records therefore less patients were identified. There was missing clinical information in the patient hospital records. There was inadequate documentation for some patients who therefore had to be excluded due to inability to stage the patient or document smoking and alcohol use. Quantification of alcohol and tobacco use could not be done.

The NHLS data prior to 2014 is no longer stored online therefore histopathology could not be traced on the laboratory system and clinical notes had to be used. In terms of using patients clinical background such as comorbidities and overall nutritional status as predictors of survival this was inconsistently documented. Prospective collection of this data will, in future, allow for a deeper analysis of the factors associated with recurrence and survival of these patients.
Due to inadequate record keeping disease specific survival could not be determined.

5.4 Conflict of interest

There is no conflict of interest.

5.5 Ethical standards

Ethics clearance certificate was obtained from the University of the Witwatersrand Human Research Ethics Committee**.**

There was no human experimentation conducted in this study as it was a retrospective record review.

Data was extracted from hospital records by myself only.

Patients were de-indentiied and given a numbered code on the data collection sheet that was submitted for statistical analysis.

REFERENCES

Abram, MH. Van Heerden, WFP. Rheeder, P. *et al*. (2012). Epidemiology of oral squamous cell carcinoma. *South African Dental Journal,* 67(10), 550-3.

Altini, M. and Kola, A.H. (1985), Age-specific and age-standardised incidence rates for intraoral squamous cell carcinoma in Blacks on the Witwatersrand, South Africa. *Community Dentistry and Oral Epidemiology*, 13, 334-339.

Amit, M. Yen, TC. Liao, CT. *et al*. (2013). Improvement in survival of patients with oral cavity squamous cell carcinoma: An international collaborative study. *Cancer*, 119(24), 4242–8.

Amit, M. Na'ara, S. Leider-Trejo, L. *et al*. (2016). Improving the rate of negative margins after surgery for oral cavity squamous cell carcinoma: A prospective randomized controlled study. *Head & Neck*, 38(S1), 1803-1809.

Bao, X. Liu, F. Chen, Q. *et al*. (2020). Propensity score analysis exploring the impact of smoking and drinking on the prognosis of patients with oral cancer. *Head & Neck,* 42, 1837–1847.

Beggan, C. Fives, C. O'Leary, G. *et al*. (2016). Pattern of invasion and lymphovascular invasion in squamous cell carcinoma of the floor of the mouth: an inter-observer variability study. *Histopathology*, 69, 914-920.

Bernier, J. Domenge, C. Ozsahin, M. *et al*. (2004). Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *New England Journal of Medicine*, 350(19), 1945–1952.

Brandwein-Gensler, M. Teixeira, MS. Lewis, CM. *et a*l. (2005). Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *American Journal of Surgical Pathology,* 29(2),167-178.

Brockhoff, HC. Kim, RY. Braun, TM. *et al*. (2017). Correlating the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck for oral squamous cell carcinoma. *Head & Neck*, 39(5), 974–9.

Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. 5, Cancer. Available from: https://www.ncbi.nlm.nih.gov/books

Chang, E. Yu, P, Skoracki, RJ. *et al*. (2015). Comprehensive Analysis of Functional Outcomes and Survival After Microvascular Reconstruction of Glossectomy Defects. *Annals of Surgical Oncology*, 22(9), 3061–9.

Cheraglou, S. Schettino, A. Zogg, CK. *et al*. (2018). Changing Prognosis of Oral Cancer: An Analysis of Survival and Treatment Between 1973 and 2014. *Laryngoscope,* 128(12), 2762-2769.

Coelho, KR. (2012). Challenges of the oral cancer burden in India. *Journal of cancer epidemiology*, [online] Volume(2012), Article id:701932. Available at: https://doi.org/10.1155/2012/701932. [Accessed 23 Jun. 2020].

Cooper, JS. Pajak, TF. Forastiere, AA. *et al*. (2004). Postoperative concurrent radio-therapy and chemotherapy for high risk squamous cell carcinoma of the head and neck. *New England Journal of Medicine,* 350(19), 1937–1944.

D'Cruz, AK. Vaish, R. Kapre, N. *et al*. (2015). Elective versus therapeutic neck dissection in node-negative oral cancer. *New England Journal of Medicine,* 373, 521–9.

Ebrahimi, A. Clark JR. Amit, M. *et al*. (2014). Minimum nodal yield in oral squamous cell carcinoma: defining the standard of care in a multicenter international pooled validation study. *Annals of Surgical Oncology*, 21(9), 3049-55.

Fagan, JJ. Collins, B. Barnes, L. *et al*. (1998). Perineural invasion in squamous cell carcinoma of the head and neck. *Archives of Otolaryngology Head & Neck Surgery,* 124(6), 637-40.

Farhood, Z. Simpson, M. Ward, G. *et al*. (2019). Does anatomic subsite influence oral cavity cancer mortality?. *Laryngoscope*, 129(6), 1400–1406.

Ferlay, J. Soerjomataram, I. Dikshit, R. *et al*. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*, 136(E3), 59-386.

Fives, C. Feeley, L. O'Leary, G. (2016). Importance of lymphovascular invasion and invasive front on survival in floor of mouth cancer. *Head & Neck*. 38(S1),1528-1534.

Garzino-Demo, P. Zavattero, E. Franco, P. *et al*. (2016). Parameters and outcomes in 525 patients operated on for oral squamous cell carcinoma. Journal of Craniomaxillofacial Surgery, 44(9), 1414–21.

Hicks, WL. Loree, TR. Garcia, RI. *et al*. (1997). Squamous cell carcinoma of the floor of mouth: a 20-year review. *Head and Neck*, 19(5), 400–5.

Honorato, J. Rebelo, MS. Dias, FL. *et al*. (2015). Gender differences in prognostic factors for oral cancer. *International Journal of Oral & Maxillofacial Surgery,* 44(10), 1205–11.

Kane, SV. Gupta, M. Kakade, AC. *et al*. (2006). Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *European Journal of Surgical Oncology,* 32(7), 795-803.

Le Campion, ACOV. Ribeiro, CMB. Luiz, RR. *et al*. (2017). Low Survival Rates of Oral and Oropharyngeal Squamous Cell Carcinoma. *International Journal of Dentistry,* [online] Volume*(*2017), Article ID 5815493, Available at: https://doi.org/10.1155/2017/5815493. [Accessed 7 Apr. 2018].

Liebig, C. Ayala, G. Wilks, J. *et al*. (2009). Perineural invasion is an independent predictor of outcome in colorectal cancer. *Journal of Clinical Oncology,* 27(31), 5131-5137.

Lopez-Cedrún, A. and de Llano, JA. (2015). A 22 years survival and prognostic factors analysis in a homogeneous series of 64 patients with advanced cancer of the tongue and the floor of the mouth. *Journal of Cranio-Maxillofacial Surgery,* 43(3), 376-381.

Luryi, AL. Chen, MM. Mehra, S. *et al*. (2014). Positive surgical margins in early stage oral cavity cancer. *Otolaryngology Head & Neck Surgery*, 151(6), 984-990.

Mashberg, A. and Meyers H. (1976). Anatomical site and size of 222 early asymptomatic oral squamous cell carcinomas: A continuing prospective study of oral cancer. *Cancer*, 37(5), 2149–57.

Massey, C. Dharmarajan, A. Bannuruet, RR. *et al*. (2019). Management of N0 Neck in Early Oral Squamous Cell Carcinoma: A Systematic Review and Meta-analysis. *Laryngoscope*, 129, 284–298.

Masoudi, S. Montazeri, SA. Pourdanesh, F. *et al*. (2017). A new approach to survival analysis of head and neck squamous cell carcinoma. *Archives of Iranian Medicine*, 20(8), 503–10.

Moro, JDS. Maroneze, MC. Ardenghi, TM. *et al*. (2018). Oral and oropharyngeal cancer: epidemiology and survival analysis. *Einstein (Sao Paulo)*, 16(2), 1-5.

Nandakumar, A. Rath, GK. Kataki, CA. *et al*. (2016). Survival in Head and Neck Cancers - Results of A Multi-Institution Study. *Asian Pacific Journal of Cancer Prevention*. 17(4), 1745–54.

Noone, AM. Howlader, N. Krapcho, M. (2018) SEER Cancer Statistics Review,1975-2015. National Cancer Institute. Bethesda, MD, based on November 2017 SEER data submission, posted to the SEER website https://seer.cancer.gov/csr/1975_2015

Okamoto, M. Nishimine, M. Kishi, M. *et al*. (2002). Prediction of delayed neck metastasis in patients with stage I/II squamous cell carcinoma of the tongue. *Journal of Oral Pathology Medicine,* 31(4), 227-233.

Ong, TK. Murphy, C. Smith, AB. *et al*. (2017). Survival after surgery for oral cancer: a 30-year experience. *British Journal of Oral and Maxillofacial Surgery*, 55(9), 911–6.

Piazza, C. Grammatica, A. Montalto, N. *et al*. (2019). Compartmental surgery for oral tongue and floor of the mouth cancer: Oncologic outcomes. *Head & Neck*. 41(1), 110–115.

Piccirillo, JF. Lacy, PD. Basu, A. *et al*. (2002). Development of a new head and neck cancer-specific co- morbidity index. *Archives of Otolaryngology Head & Neck Surg*ery, 128(10), 1172–9.

Pollaers, K. Hinton-Bayreb, A. Friedland PL. *et al*. (2018). AJCC 8th Edition oral cavity squamous cell carcinoma staging – Is it an improvement on the AJCC 7th Edition?. *Oral Oncology*, 82(2018), 23–28.

Rodrigo, JP. Grilli, G. Shah, JP. *et al*. (2018). Selective neck dissection in surgically treated head and neck squamous cell carcinoma patients with a clinically positive neck: Systematic review. *European Journal of Surgical Oncology,* 44(2018), 395–403.

Roland NJ. Head and Neck Cancer: Multidisciplinary Management Guidelines. 4th edition [Internet]. 2011. Available from: http://www.entuk.org/

Safi, AF. Kauke, M. Grandoch, A. *et al*. (2017). Clinicopathological parameters affecting nodal yields in patients with oral squamous cell carcinoma receiving selective neck dissection. *Journal of Cranio-Maxillo-Facial Surgery,* 45 (2017) 2092-2096.

Saggi, S. Badran, KW. Han, AY. *et al.* (2018). Clinicopathologic Characteristics and Survival Outcomes in Floor of Mouth Squamous Cell Carcinoma: A Population-Based Study. *Otolaryngology-Head and Neck Surgery*, 159(1), 51–8.

Salvatori, P. Paradisi, S. Calabrese, L. *et al*. (2014). Patients' survival after free flap reconstructive surgery of head and neck squamous cell carcinoma: a retrospective multicentre study. *Acta Otorhinolaryngologica Italica,* 34(2), 99–104.

Sarafoleanu, C. Vuzitas, A. and Manea, C. (2017). Difficulties in the surgical management of head and neck cancer patient. *Romanian Journal Rhinology,* 7(27), 153–61.

Schwam, ZG. Judson, BL. Sosa, JA. *et al*. (2015). Improved prognosis for patients with oral cavity squamous cell carcinoma: analysis of the national cancer database 1998–2006. *Oral Oncol,* 52, 45–51.

Sessions, DG. Spector, GJ. Lenox, J. *et al*. (2000). Analysis of treatment results for floor of mouth cancer. *Laryngoscope*, 110(10), 1764–72.

Shah, JP. (1990). Cervical lymph node metastases -diagnostic, therapeutic, and prognostic implications. *Oncology*, 4(10), 61–9.

Shaw, RJ. Lowe, D. Woolgar, JA. *et al*. (2010). Extracapsular spread in oral squamous cell carcinoma. *Head & Neck,* 32(6), 714-722.

Shin, JT. Yoon, JK. Shin, AK. *et al*. (2018). Locoregionally advanced oral cavity cancer: A propensity-score matched analysis on overall survival with emphasis on the impact of adjuvant radiotherapy. *Head & Neck*. 40(9), 1934–1946.

Spiotto, MT. Jefferson, G. Wennig, B. *et al*. (2017). Differences in survival with surgery and postoperative radiotherapy compared with definitive chemoradiotherapy for oral cavity cancer: A National Cancer Database Analysis. *JAMA Otolaryngology Head & Neck Surgery*, 143(7), 691–9.

Spiro, RH. Huvos, AG. Wong, GY. (1986). Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *American Journal of Surgery*, 52(4), 345–50.

Su, WWY. Su, CW. Chang, DC. *et al*. (2019). Impact of varying anatomic sites on advanced stage and survival of oral cancer: 9-year prospective cohort of 27 717 cases. *Head & Neck*. 41(5), 1475–1483.

Subramanium, N. Murthy, S. Balasubramanian, D. *et al*. (2018). Adverse pathologic features in T1/2 oral squamous cell carcinoma classified by the American Joint Committee on Cancer eighth edition and implications for treatment *Head & Neck*. 40(10), 2123–2128.

Wein R. (2015). Malignant neoplasms of the oral cavity. In: PW F, editor. Cummings Otolaryngology Head and Neck Surgery. 6th ed. Elsevier Saunders, p.1359–87.

Wolfer, S. Foos, T. Kunlzer, A. *et al*. (2018). Association of the preoperative body mass index with postoperative complications after treatment of oral squamous cell carcinoma. *Journal of Oral and Maxillofacial Surgery,* 76, 1800-1815.

Woolgar, JA. (1997). Detailed topography of cervical lymph-node metastases from oral squamous cell carcinoma. *International Journal of Oral & Maxillofacial Surgery*, 26(1), 3–9.

Woolgar, JA. and 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 Oncology*, 45(4-5), 361-385.

Zanoni, DK. Montero, PH. Shah, JP. *et al*. (2019). Survival outcomes after treatment of cancer of the oral cavity (1985–2015). *Oral Oncology,* 90, 115–121.

Zhan, KY. Morgan, PF. Neskey, DM. *et al*. (2018). Preoperative predictors of occult nodal disease in cT1N0 oral cavity squamous cell carcinoma: Review of 2623 cases. *Head & Neck*, 40(9), 1967–1976.

Appendix 1

American Joint Committee on Cancer (AJCC) Tumor Staging 8th Edition by Site: ORAL CAVITY

PRIMARY TUMOUR (T)

TX Primary tumor cannot be assessed

Tis Carcinoma in situ

T1 Tumor ≤ 2 cm, ≤ 5 mm depth of invasion (DOI)

T2 Tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm;
or tumor > 2 cm but ≤ 4 cm, and DOI ≤ 10 mm

T3 Tumor > 4 cm;
or any tumor with DOI > 10 mm but ≤ 20 mm

T4 Moderately advanced or very advanced local disease

T4a Moderately advanced local disease
Tumor invades adjacent structures (e.g. through cortical bone of the mandible or maxilla, or involves maxillary sinus or skin of the face) or extensive tumor with bilateral tongue involvement and/or DOI > 20 mm
Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.

T4b Very advanced local disease
Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed N0 No regional nodes metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest Dimension

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3a Metastasis in a lymph node more than 6 cm in greatest dimension.

N3b Metastases in any node with clinically overt extra nodal extension

DISTANT METASTASIS (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

TNM Staging, Oral Cavity

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	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Appendix 2

PATIENT CODE	AGE	SEX	RACE	TOBACCO	ALCOHOL	STAGE	CHEMORADIATION	RECURRENCE		DEATH STATUS		DATE OF SURGERY	DATE OF DEATH	RECURRENCE DATE
								1 YEAR	5 YEAR	1 YEAR	5 YEAR			
PT01	64	M	W	Y	Y	II	N	N	N	A	A	05/03/2013	ALIVE	
PT02	28	F	B	N	N	I	N	N	N	A	A	07/05/2013	ALIVE	
PT03	87	M	W	Y	Y	III	Y	N	NA	A	A	21/05/2013	ALIVE	
PT04	64	M	C	Y	Y	III	Y	N	Y	A	D	04/06/2013	22/04/2015	15/12/2014
PT05	73	M	B	Y	Y	III	Y	N	Y	A	D	07/06/2013	13/08/2015	12/11/2014
PT06	70	F	W	Y	Y	III	Y	N	N	A	D	25/06/2013	28/05/2016	
PT07	55	M	B	Y	Y	IV A	Y	N	N/A	D	D	03/09/2013	07/02/2014	
PT08	57	M	W	Y	Y	III	Y	N	Y	A	D	01/10/2013	06/12/2015	26/11/2014
PT09	54	M	B	Y	Y	III	Y	N	N	A	A	10/12/2013	ALIVE	
PT10	55	F	W	Y	N	IVA	Y	N	N	A	A	07/01/2014	ALIVE	
PT11	51	F	W	Y	N	I	N	N	N	A	A	01/04/2014	ALIVE	
PT12	58	M	C	Y	Y	IV A	Y	N	N	A	D	21/06/2016	17/02/2018	
PT13	64	M	B	Y	Y	IVA	Y	N	N/A	A	N/A	06/09/2016	ALIVE	
PT14	54	M	B	Y	Y	IV A	N	N	Y	A	D	21/11/2016	01/10/2019	19/02/2019
PT15	42	M	B	Y	Y	IVA	Y	Y	Y	D	D	29/08/2017	08/06/2018	30/04/2018
PT16	26	F	B	N	N	IVA	Y	N	N/A	A	N/A	05/07/2017	ALIVE	
PT17	61	M	B	Y	N	II	Y	N	N/A	A	N/A	06/12/2016	ALIVE	
PT18	56	F	B	Y	N	I	N	N	N	A	A	23/02/2016	ALIVE	
PT19	71	M	W	Y	N	II	Y	N	N	A	A	21/04/2014	ALIVE	
PT20	47	M	W	Y	N	IV A	N	N	N	A	D	11/11/2014	30/07/2017	

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I, **Nishat Thokan**, (Student number: **0005486V**) am a student registered for the degree of Master of Medicine in Otorhinolaryngology, in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: Date: 25 November 2020

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Nishat Thokan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190527

NAME: (Principal Investigator)	Dr Nishat Thokan
DEPARTMENT:	Neurosciences Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Survival of patients with Floor of mouth Squamous cell carcinoma treated with surgical resection and reconstruction at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	31/05/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Shivesh Maharaj
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/06/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore be due in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Nishat Thokan

SURVIVAL OF PATIENTS WITH FLOOR OF MOUTH SQUAMOUS CELL CARCINOMA TREATED WITH SURGICAL RESECTION AND RECONSTRUCTION AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Submission date: 31-Aug-2020 10:52AM (UTC+0200)
Submission ID: 1191470410 File name: mmednishatthokan.docx (77.67K) Word count: 10562

Character count: 58014

Nishat Thokan

ORIGINALITY REPORT

20%	19%	4%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	hdl.handle.net Internet Source	11%
2	www.coursehero.com Internet Source	2%
3	vtechworks.lib.vt.edu Internet Source	1%
4	www.cureus.com Internet Source	1%
5	cardiothoracicsurgery.biomedcentral.com Internet Source	1%
6	bu.umc.edu.dz Internet Source	1%
7	etd.cput.ac.za Internet Source	1%
8	"UEG Week 2013 Oral Presentations", United European Gastroenterology Journal, 2013. Publication	1%