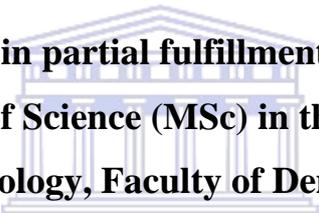


Epidemiological pattern of oral squamous cell carcinoma seen at the Tygerberg academic complex

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A mini-thesis submitted in partial fulfillment of the requirements for the degree of Master of Science (MSc) in the Department of Oral Medicine and Periodontology, Faculty of Dentistry, University of the



Western Cape
UNIVERSITY OF THE
WESTERN CAPE

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September, 2014

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Tygerberg academic complex**

Dr Abdullahi Alhashimi Hamid

Keywords

Epidemiology

Oral

Squamous cell carcinoma

Tygerberg

Cape Town



Abstract

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Background Recent epidemiological reports established that there is an increase in the incidence of oral squamous cell carcinoma in young patients. Some report this to be in the absence of contributing habits such as smoking and alcohol use. Few reports of such a nature have reported a similar trend in South Africa.

Aim Describe the epidemiological pattern of oral squamous cell carcinoma seen at the Tygerberg academic complex.

Method Histopathological biopsy reports of patients diagnosed by the oral pathology department of Tygerberg hospital from 1996 to 2013 were electronically retrieved and included. Patients were grouped by age into two groups, one included patients 40 years and younger, the other included patients older than 40 years. Descriptive analysis was performed for age, sex, smoking and alcohol habits and oral site of tumor. Frequency of OSCC patients was calculated manually from the total number of oral biopsies. Chi-square or Fisher's exact tests were used as appropriate. Probabilities of less than 0.05 were regarded as significant.

Results The total number of OSCC patients over the 18-year period was 2220. The mean age was 57.6 years. The male to female ratio was 2.9:1 for all age groups and 2.2:1 for young patients. The majority of patients (96%) were above 40 years old. Smoking and alcohol were commonly reported for all age groups (91.3%) and (83.8%) for young patients. The tongue was the commonest site for all age groups (30.8%) followed by oropharynx (27.3%) while in younger patients, the oropharynx was the commonest site (30.3%) followed by tongue (29.2%).

Conclusion The study confirmed that OSCC is still an affliction of people older than 40 years and males are predominantly affected. Smoking and alcohol are strong risk

factors for OSCC irrespective of patient's age. OSCC among people older than 40 years may have no great difference from the same disease affecting younger ones in terms of sex, oral habits and tumor site.

16.09.2014



Declaration

I declare that (Epidemiological pattern of oral squamous cell carcinoma seen at the Tygerberg academic complex) is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name Abdullahi Alhashimi Hamid

Date: September, 2014

Signed.....



Acknowledgement

I would like to acknowledge the following people for their support in this project:

Dr. Anthea Jeftha, my supervisor for her invaluable suggestions and her assistance in making this study possible

Professor LXG Stephen, for his expertise, instructive guidance and useful direction.

Dr Esraa Mosalleum and Mr Wessel Kleinhans, for their unlimited help during the phase of data collection for the study

Professor Stefan Maritz, for his assistance with the data analysis and his expert statistical advice.



Dedication

This work is dedicated to my parents,
my brothers and my sisters.



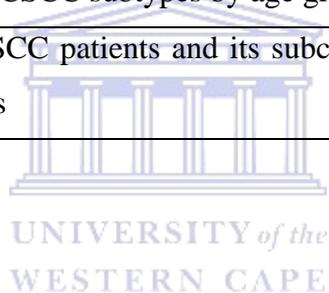
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List of Abbreviations

ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenases
DNA	Deoxyribonucleic acid
FMSCC	Floor of the mouth squamous cell carcinoma
GSCC	Gingival squamous cell carcinoma
HPV	Human papilloma virus
IBM	International Business Machines Corporation
LSCC	Lip squamous cell carcinoma
NosSCC	Not otherwise specified squamous cell carcinoma
(n)	Frequency
%	Proportion
OPSCC	Oropharyngeal squamous cell carcinoma
OCSCC	Oral cavity proper squamous cell carcinoma
PSCC	Palatal squamous cell carcinoma
RSCC	Retromolar squamous cell carcinoma
SPSS	Software package used for statistical analysis
TNM	Tumor, node and metastasis
TSCC	Tongue squamous cell carcinoma
TSGs	Tumor suppressor genes
SCC	Squamous cell carcinoma
UICC	Union for International Cancer Control
UVB	Ultraviolet radiation type B



CHAPTER ONE: INTRODUCTION

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Cancer is one of the most important medical issues in today's world. A great proportion of all deaths are attributed to cancer. Squamous cell carcinoma is among the most common cancers affecting the mouth and the tenth most common cancer afflicting the world population (Scully and Bagan, 2009; Scully, 2013). About three hundred thousand persons are diagnosed each year, representing 3% of the total cancers world-wide (Scully, 2013).

Most oral squamous cell carcinomas (OSCCs) are preventable and the majority of cases share similar risks to those diagnosed in the upper aerodigestive tract (Warnakulasuriya, 2009). Despite this, epidemiological studies showed that the incidence and mortality are increasing and most patients present at a late stage at the time of diagnosis (Scully, 2011).

Research into epidemiology aims to identify the pattern of cancer among populations in order to establish a causative link between the disease and the risk factors at play within specific populations.

This is a descriptive record based study of patients diagnosed with oral squamous cell carcinoma at a referral center in Cape Town from 1996 to 2013.

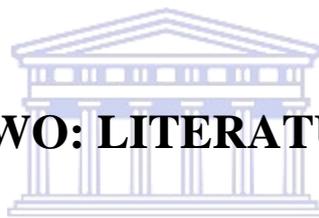
The purpose of the study is to describe the epidemiological pattern of these patients in relation to the oral site affected.

Previous reports have established an increased incidence of OSCC in younger patients with no history of smoking and alcohol exposure (Annertz *et al.*, 2002; Muller *et al.*, 2008; Patel *et al.*, 2011). This study also aims to investigate whether such a trend exists in patients diagnosed at Tygerberg hospital.

Histopathological biopsy reports of patients diagnosed over the past eighteen years were reviewed. Evidence regarding the disease in terms of age, sex, risk factors and oral site of cancer diagnosed was sought, investigated and analyzed.

The dissertation concludes with recommendations for future research required in this field and strategies for disease prevention.

CHAPTER TWO: LITERATURE REVIEW



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2.1 Introduction

OSCC is the commonest malignant neoplasm affecting the oral cavity (Scully, 2011).

The oral cavity is characterized by a complex anatomy and difficulty of precise delineation of its boundaries. As a consequence of this, no single term has been ascribed to oral cancer and therefore, to OSCC (Moore *et al.*, 2000).

Over the past years, the disease was called by several names, including, but not limited to oral cancer, mouth cancer, intraoral cancer, oral cavity cancer, oral cavity and pharyngeal cancer (Moore *et al.*, 2000). However, these terms are frequently used to refer to oral squamous cell carcinoma (Abram *et al.*, 2012).

For the purpose of this study, the term OSCC will indicate squamous cell carcinoma of the lip, oral cavity proper and oropharynx.

The literature reviews OSCC under the headings: epidemiology, risk factors, site and other aspects of OSCC including investigations, diagnosis, management and prognosis.

2.2 Epidemiology

OSCC is the most common head and neck cancer and the tenth most common cancer afflicting world population (Scully and Bagan, 2009; Scully, 2013). About three hundred thousand persons are diagnosed each year, representing 3% of the total cancers world-wide (Scully, 2013).

The incidence and mortality are widely varied with both intra and inter country discrepancies (Scully, 2013).

In Europe, OSCC is the seventh most common cancer with 67,000 patients diagnosed in 2004 (Boyle and Ferlay, 2005). Areas with high incidence rates include Northern France and Hungary (Banoczy and Squier, 2005; Scully, 2013), while Greece, Finland and Sweden are locations with low incidence rates. Portugal, Germany and Switzerland represent areas with intermediate incidence rates (Black *et al.*, 1997; Warnakulasuriya, 2009).

In the United States of America, 27,767 patients were diagnosed with OSCC from 1975 to 1991. The incidence is decreasing in the US at about 1% per year over the past

decade. This is attributed to the effective public health strategies which resulted in a reduction of smoking and alcohol use (Kohler *et al.*, 2011; Linda *et al.*, 2012).

In South America and the Caribbean, OSCC is the fifth most common cancer among males and the sixth most common cancer among females. Countries with high incidence rates include Argentina, Southern Brazil, Uruguay and Puerto Rico (Warnakulasuriya, 2009; Wunsch-Fiho and de Camargo, 2007). In Brazil, OSCC is the seventh most common cancer with 14,160 patients diagnosed in 2008. Brazilian males are the third most common affected after those reported in France and India (Wunsch-Fiho and de Camargo, 2007).

In Asia, countries such India and Sri Lanka have been cited as areas with the highest incidence in the world. In India alone, more than 100,000 persons are diagnosed with OSCC each year (Ferlay *et al.*, 2004; Warnakulasuriya, 2009). A factor contributing to this is the practice of betel chewing habit which makes OSCC the fourth most common cancer in the country (Warnakulasuriya, 2009). OSCC is not commonly encountered in Japan. The incidence rate represents 5.3 per 100,000 adjusted to the world population (Marugame *et al.*, 2007).

In Australia, the incidence of OSCC remains stable with about 2173 patients diagnosed in 1996. A particular trend reported in the Australian population showed that lip cancer accounts for more than half of OSCC patients (Sugerman *et al.*, 2002).

In Africa, the extrapolation of a specific incidence trend is difficult as epidemiological studies concerning the disease are not sufficient (Warnakulasuriya, 2009). Studies from Sudan have indicated that the incidence of OSCC is increasing among males who use Toombak, a form of smokeless tobacco that is mixed with sodium bicarbonate (Idris *et al.*, 1995).

In South Africa, 5396 patients were diagnosed with OSCC from 1988 to 1991. This comprised 3.4% of all cancers diagnosed over this period. The males represented 5% and the females represented 1.8% in relation to all cancers detected in the country. These percentages exclude skin carcinomas (Hille *et al.*, 1996).

Hille *et al.* (1996) found that the females were more affected among the Asian population while the male incidence was high among the white, colored and black population. Among all races, the colored males were mostly affected whereas the

black females were least affected. The authors referred the significant difference in gender between black and colored people to the difference in exposure to tobacco and alcohol carcinogens between these two groups. The paper concluded that the incidence of OSCC was rising, particularly among Indian females and colored males, emphasizing the need to establish a major educative program among these populations.

Similar findings were also reported by Abram et al (2012) and revealed that the colored males and Asian females were mostly affected with OSCC among all races. The authors again attributed this to the exposure to the traditional risk factors of the disease. The study used the data of the National Cancer Registry of South Africa to describe the incidence of OSCC between 1997 and 2001. It revealed that OCSCC represented 1.9% for males and 0.6% for females while OPSCC was estimated as 0.6% for males and 0.1% for females, in relation to all cancers. These percentages exclude skin carcinomas diagnosed as separate entities.

According to literature, the global male to female ratio of OSCC is 1,5:1 for oral cavity squamous cell carcinoma and 2,8:1 for oropharyngeal squamous cell carcinoma (Warnakulasuriya, 2009). The five-year survival rate is estimated at 50% and the delay in diagnosis is directly proportional to a poorer prognosis (Warnakulasuriya, 2009). The survival rate has been observed to be better among those from higher socioeconomic groups (Edwards and Jones, 1999) in intraoral cancer affecting females (Warnakulasuriya, 2009) and for people who are young in age (Annertz *et al.*, 2002; Shiboski *et al.*, 2005). The mortality is about 3–4 per 100,000 for males and 1.5–2.0 per 100,000 for females (Warnakulasuriya, 2009).

The disease has been known as an affliction of old males, but trends reported from later studies confirm that the difference in prevalence between males and females is decreasing (Toner and O'Regan, 2009).

Studies of young patients (arbitrary aged as younger than 40 years old (Annertz *et al.*, 2002; Udeabor *et al.*, 2012) and in other studies as younger than 45 years old (Iamaroon *et al.*, 2004; Shiboski *et al.*, 2005), have shown an increased incidence of the disease in this group. These reported cases are OSCC of the tongue in non-smoking females that are not related to Human papilloma virus. The causative factors for this group are still unknown (Toner and O'Regan, 2009).

In South Africa, Abram et al (2012) reported a higher incidence of OSCC in patients younger than 45 years of age when comparing to the global literature. Abram et al (2012) found that OCSCC was estimated as 7.3% for males and 7.8% for females, while OPSCC represents 5.2% for males and 11.2% for females in relation to all cancers. These percentages excluded skin carcinomas.

Patel et al (2011) noted an increased incidence of tongue squamous cell carcinoma among young white American females who are younger than 44 years. The study covered histopathological biopsy reports between 1975 and 2007 and revealed a decreased incidence of the disease except for young white American females. The authors suggested that this affected group may represent a new emerging entity among people with head and neck cancer.

Annertz et al (2002) reported an increased incidence of tongue squamous cell carcinoma in patients younger than 40 years among a Scandinavian cohort of patients from 1960 to 1994. This study showed an increased incidence of five-fold for males and six-fold for females since 1960. The authors pointed to this rise in frequency as an unexplained finding. The study however, was confined to describe only cancers affecting the tongue and did not include other intraoral sites.

Muller et al (2008) performed a retrospective review to describe OSCC patients who have been diagnosed at Emory University Hospital, USA from 1971 to 2006. They described patients in terms of age, sex, primary site within oral cavity and histologic grading of cancer. Muller and his group proved a greater than fourfold increase in the incidence of tongue squamous cell carcinoma in patients younger than 40 years old. The causes for this were unknown. One of the drawbacks of this study is that it was limited to analyze cases diagnosed at only one center.

Hirota et al (2008) performed a retrospective study to examine risk factors and clinical aspects associated with OSCC in young patients as compared to older ones. The study was conducted in São Paulo, Brazil between 1994 and 2004 and found that there were 13 patients out of 121 who were younger than 40 years of age. This represented 10.7% of all patients diagnosed.

O'Regan et al (2006) analyzed 130 patients with OSCC diagnosed between 1993 and 2003 at St. James's Hospital, Dublin. The study described these patients by age, sex,

risk factors, tumor site, clinical staging and hematological status. The study detected 30 patients (23.1%) as younger than 40 years of age.

These reports, though limited by retrospective design, clearly depict an increasing trend of OSCC incidence in younger patients. The causes for this were unexplained in most of the cases. The scarcity of this entity makes this phenomenon in need of more investigations.

2.3 Risk Factors

The major lifestyle behaviors that place one at risk to the development of OSCC include the use of tobacco and alcohol (Petti, 2009). Other factors such as viruses, micronutrient deficiency and genetic influences can also play a role and predispose to OSCC (Scully and Bagan, 2009).

2.3.1 Tobacco and Alcohol

Internationally, one-fifth of the population chews betel quid, two billion drink alcohol and more than one billion smoke cigarettes (Petti, 2009).

These factors, as can be seen, are lifestyle related, and OSCC therefore, can be largely avoidable (Scully, 2011). All forms of tobacco do predispose to OSCC as well as to other cancers of the body (e.g. lung cancer) (Kumar *et al.*, 2012). Cigarette smoking is the most common form of tobacco used and is thought to be responsible for about one fourth of all OSCC cases that are seen around the world (Hashibe *et al.*, 2007).

Tobacco consists of at least 50 compounds with N-nitrosamines considered as the carcinogenic agent (Scully and Felix, 2006). The carcinogens produced by tobacco are counterbalanced by antioxidant enzymes such as glutathione-S-transferases, glutathione reductase, and glutathione peroxidase (Scully, 2011). Genetic variations in the level of these enzymes may impair this balance and increase the susceptibility to OSCC (Ba'ez, 2008; Toner and O'Regan, 2009).

Betel quid is a leaf of *Piperaceae* plant that is sometimes mixed with tobacco and chewed by the population of South East Asia (Petti, 2009). Betel quid contains a mixture of a betel leaf, areca nut, spices, and slaked lime with or without tobacco (Scully and Felix, 2006).

The main purpose of chewing betel quid is to extract arecoline, a euphoric stimulating substance that reacts with muscarinic receptors in the body to increase the attentiveness and the capacity to work (Petti, 2009). In addition to its carcinogenic effect, betel quid predisposes to many conditions such as submucous fibrosis, erythroplakia and leukoplakia as well as other cancers in the body (e.g. esophageal cancer) (Scully, 2013).

Other forms of smokeless tobacco such as Qat and Toombak are also available and are practiced in different cultures (Scully, 2011; Scully, 2013).

Alcohol is a well-known risk factor for OSCC. It has been also involved in a variety of medical conditions as well as its negative social implications (Scully, 2011). Alcohol is believed to be responsible for about 7–19% of all OSCC cases that are seen globally (Hashibe *et al.*, 2007). Alcohol (ethanol) is metabolized by alcohol dehydrogenase (ADH) into acetyaldehyde, which is degraded by aldehyde dehydrogenases (ALDH) to acetate (Scully, 2011). The genetic variations in these enzymes among individuals may increase the level of acetyaldehyde, which is carcinogenic (Toner and O'Regan, 2009).

Additionally, when smoking and alcohol are practiced concurrently, the latter may facilitate the penetration of the oral mucosa by tobacco carcinogens (O'Regan *et al.*, 2006).

Though smoking and alcohol are strong risk factors for OSCC that affects older people (Hirota *et al.*, 2008; Scully and Felix, 2006), their role has not yet been fully confirmed among younger patients. Authors such as Kuriakose *et al.* (1992), Toner and O'Regan (2009) proposed that habits such as smoking and alcohol use may not be a significant risk factor in young patients with OSCC as a considerable or long period of exposure is needed for malignant transformation to be established. However, reports such as those of Llewellyn *et al.* (2001) indicated that the practice of a smoking habit for more than twenty years is likely to produce damage sufficient to initiate malignant change. Therefore, people who start smoking early during their second decade are the more likely to undergo these changes when they reach forty years of age due to the prolonged exposure to these carcinogens (Llewellyn *et al.*, 2001).

2.3.2. Microorganisms

Certain micro-organisms that infect the oral cavity are responsible for increasing the risk of OSCC (Scully, 2011). *Candida* species produce nitrosamines and acetylaldehyde. These products are thought to be carcinogens (Meurman and Uttamo, 2008; Regezi *et al.*, 2011). However, the presence of traditional risk factors i.e. smoking and alcohol is crucial in malignant transformation (Scully, 2011). Yet, these microorganisms in the oral cavity may add insult to injury and hasten the onset or further complicate the picture.

Among other microorganisms, the infection with human papilloma virus (HPV) is of a particular importance (Feller *et al.*, 2010). HPV is a deoxy ribonucleic acid virus that has an affinity to infect the mucosa of both anogenital and oropharyngeal districts (Rautava and Syrjanen, 2012). More than 70 subtypes of HPV have been identified with type 16 and 18 being mainly implicated in oropharyngeal squamous cell carcinoma (OPSCC) (van Monsjou *et al.*, 2010). HPV acts through an activation of E6 and E7 oncogenes and deactivation of P53 and Rb tumor suppressor genes (Rautava and Syrjanen, 2012; van Monsjou *et al.*, 2010).

Oropharyngeal carcinomas caused by this virus are different from those attributed to the classical risk factors i.e. smoking and alcohol (Rautava and Syrjanen, 2012). HPV associated carcinomas harbor p53 of a wild type, shows less chromosomal alterations, a lower rate of metastasis and a better prognosis (Dahlstrand & Dalianis, 2005; Lindquist *et al.*, 2007). Moreover, these carcinomas might be a sexually shared affliction; since HPV can be transmitted between anogenital and oropharyngeal epitheliums (Scully, 2013; van Monsjou *et al.*, 2010).

Among other types of viruses, the herpes simplex family is possibly implicated in OSCC (Shillitoe, 2009). Herpes simplex nucleic acids were demonstrated among patients with lip squamous cell carcinoma (Eglin *et al.*, 1983) and antibody levels to these viruses were also higher among OSCC patients when comparing to a control group (Shillitoe, 2009).

Though Epstein-Barr virus was detected in some OSCC patients, its role is still unclear as the virus is not oncogenic in itself and can be found in many individuals with healthy oral mucosa as well as in decreased immune defense states (Shillitoe, 2009).

2.3.4 Genetics

As a result of genetic variations between individuals, some mutated genes may fail to carry out their protective role against carcinogens (Scully, 2011). These include for example the DNA repair genes and tumor suppressor genes (TSGs) (Scully, 2011).

For that reason, persons with certain conditions such as Fanconi's anemia and Dyskeratosis congenita are more likely to develop OSCC, especially when the exposure to other lifestyle risk factors is high (Toner and O'Regan, 2009).

OSCC is a consequence of DNA mutation, either spontaneously or because of mutagens (Scully and Bagan, 2009). DNA mutation results in an up-regulation of oncogenes with or without silencing of tumor suppressor genes (Scully, 2011).

Under normal situations, oncogenes are concerned with the control of cell proliferation, while tumor suppressor genes are responsible for the suppression of this proliferation (Scully and Bagan, 2009). The disturbance of these genes via mutation results in a loss of cycle control and unleashes the tumor to grow with inability of the mutated tumor suppressor genes to constrain this release (Regezi *et al.*, 2011).

Mutation of P53 is believed to have a critical role in OSCC pathogenesis as well as the prognosis of the disease (Scully and Bagan, 2009).

Several oncogenes have been recognized in the pathogenesis of OSCC and their mechanism of action is quite complicated (Scully and Bagan, 2009). Epidermal growth factor receptor (EGFR) gene represents a good example of these offenders when they are over-expressed (Scully, 2011).

Angiogenesis is a process where a new blood supply is formed to allow the tumor cells to grow. This occurs via activation of angiogenic proteins such as vascular endothelial growth factor (VEGF), fibroblastic growth factor (FGF), and/or the inhibitions of proteins that suppress angiogenesis (Regezi *et al.*, 2011).

Other important features acquired by the cancer cells include their capability to evade apoptosis, their ability of limitless replication, tissue invasion and metastasis (Kumar *et al.*, 2012).

The extent of the role of genetic influences in young patients is unclear. Majchrzak *et al.* (2014) stated that young patients with no history of smoking or alcohol are assumed

to be more influenced by the genetic factors. This was supported by a study carried out by Kostrzevska-Poczekaj et al (2013) who described the patients below 30 years of age as more prone to be associated with defective repair mechanisms. In contrast, authors such as Gawęcki et al (2005) and Toner and O'Regan (2009) revealed that the genetics may not play a greater role in young patients than old ones in terms of certain phenotypic aberrations.

The history of cancer within a family can also contribute as a risk factor, particularly when the involvement is of a close relative. However, the paucity of documented records about family cancer history makes this assumption in need of more investigations (Toner and O'Regan, 2009).

2.3.5 Diet

A diet lacking in fruits and vegetables has been addressed as a risk factor for cancer (Popkin, 2007). Yet, the exact role of such a diet in the pathogenesis of cancer is not fully understood (Petti, 2009). The protective role depending on the antioxidants it contains was raised by some authors (Boccia *et al.*, 2008; Bosetti *et al.*, 2003), but is still uncertain (Scully, 2011).

Antioxidants which include components such as vitamins, carotenoids, folates and fibers, are believed to act through counterbalancing the harmful effects of other carcinogens such as tobacco and alcohol (petti, 2009). In this respect, the so called Mediterranean diet which contains high proportions of fruits, cereals, olive oil, and vegetables along with moderate quantities of dairy products and low amounts of meat has shown to decrease the risk of cancer (Bosetti *et al.*, 2003). However, more studies are required to evaluate the effectiveness of such diets as a possible protector from OSCC (Scully, 2011).

2.3.6 Other factors

Sun light (mainly UVB) is a well-recognized risk factor for Lip squamous cell carcinoma which mainly affects people of Caucasian decent (Warnakulasuriya, 2009).

Other factors that may predispose to OSCC with scarce or no strong evidence include poor oral hygiene, periodontal diseases and low socioeconomic status (Scully, 2011), ethnicity, reduced immunity and mouthwashes (Warnakulasuriya, 2009), marijuana (Hashibe *et al.*, 2005), HIV (Neville *et al.*, 2009), certain diseases and syndromes

(Toner and O'Regan, 2009) and repeated trauma to the oral mucosa (Piemonte *et al.*, 2010).

2.4 Site

OSCC can affect any part of the mouth. Each site presents with distinct features and different prognoses (Scully, 2013).

The clinical presentation of OSCC may vary depending on the stage of the disease. Early lesions may appear red, white, or mixed red and white with typically indurated mucosa (Bagan *et al.*, 2010; Scully and Felix, 2006).

More advanced cases show a crater-like ulcer with raised margins and an indurated base, a firm exophytic lump, pain and fixation to deeper tissues (Bagan *et al.*, 2010). Other manifestations include jaw numbness, non-healing of an extraction socket, abnormal vessels supplying a lump, dysphagia and lymphadenopathy (Bagan *et al.*, 2010; Scully and Felix, 2006). Loss of weight, cutaneous discharge, periodontal disease, teeth mobility, bleeding, trismus, difficulty in speech, difficulty in breathing and prosthesis related problems are also features that have been noted in OSCC (Haya-Fernández *et al.*, 2004; Scully and Felix, 2006).

2.4.1 Squamous cell carcinoma of the lip

Squamous cell carcinoma of the lip affects mainly fair skinned males and is principally attributed to excessive sun light exposure (mainly UVB) (Moore *et al.*, 1999; Scully, 2013). The disease can also ensue as a result of an existing condition or habit such as actinic cheilitis and pipe smoking (Main and Pavone, 1994; Scully, 2013).

The course of these carcinomas is usually slow in progression and asymptomatic unless they reach a large size or get into a late stage (Vukadinovic *et al.*, 2007). Clinically, there is ulceration, encrustation or an exophytic mass of a non-healing nature and frequent involvement of the vermilion border (Moore *et al.*, 1999; Regezi *et al.*, 2011).

When compared to intra-oral squamous cell carcinoma, lip squamous cell carcinoma has a higher survival rate; and nodal metastasis is not commonly reported (Vukadinovic *et al.*, 2007).



Exophytic squamous cell carcinoma of the lip (Regezi *et al.*, 2011)

2.4.2 Squamous cell carcinoma of the tongue

Squamous cell carcinoma of the tongue is the commonest OSCCs after **that of** the lip and is the most common intraoral squamous cell carcinoma (Regezi *et al.*, 2011).

The disease has been known as an affliction of older men, but cases diagnosed at younger ages are being seen more frequently **now** (Scully, 2013).

The condition presents in many forms such as leukoplakia, erythroplakia, erythroleukoplakia, ulcer, or mass (Regezi *et al.*, 2011). The posterior lateral border of the tongue is the commonest site of involvement. This area of the mouth is difficult for self-examination and thus most patients tend to present at an advanced stage of the disease when they are symptomatic (Regezi *et al.*, 2011). The majority of cases exhibit regional metastasis at the time of diagnosis and hence, the poorer outcome. The submandibular gland is often the first regional area of metastases and distant metastases are not frequent (Regezi *et al.*, 2011).



Squamous cell carcinoma of the tongue

2.4.3 Squamous cell carcinoma of the floor of the mouth

Squamous cell carcinoma of the floor of the mouth is the second most common intraoral carcinoma after the tongue squamous cell carcinoma (Regezi *et al.*, 2011). The frequency is rising among females and lesions are usually seen close to the lingual frenum (Neville *et al.*, 2009).

Squamous cell carcinoma of the floor of the mouth commonly presents as an asymptomatic non healing ulcer that is often preceded by a red or white lesion. Local infiltration may restrict the tongue movement and regional or distant metastasis is usually evident (Regezi *et al.*, 2011).



Squamous cell carcinoma of the floor of the mouth

2.4.4 Squamous cell carcinoma of the gingiva, buccal and alveolar mucosa

Squamous cell carcinoma of the buccal mucosa and the gingiva constitutes about 10% of all OSCC and presents as a white lesion, ulcer or mass (Regezi *et al.*, 2011).

More attention should be directed to the gingival lesions, since they can adopt an innocent appearance and mimic a benign reaction or periodontal disease (Neville *et al.*, 2009). Pain is not a common symptom with these lesions, but teeth mobility and bone involvement are frequent. Of note, the disease is less linked to the classical risk factors and has a female preponderance (Neville *et al.*, 2009).



Carcinoma on the alveolus (Scully, 2013) Carcinoma on the gingiva (Scully, 2013)

2.4.5 Palatal squamous cell carcinoma

Palatal squamous cell carcinomas are encountered in the soft palate and fauces with the hard palate being usually spared (Regezi *et al.*, 2011).

The disease presents typically with an ulcerated mass and red raised borders. More posterior lesions may go unnoticed resulting in a late diagnosis (Neville *et al.*, 2009).

Reverse smoking is a well-known risk factor for this entity. Nodal metastasis and an increased lesion size are indicators of bad prognosis (Regezi *et al.*, 2011).



Palatal squamous cell carcinoma

2.4.6 Squamous cell carcinoma of the oropharynx

Oropharyngeal squamous cell carcinoma (OPSCC) is designated to describe carcinomas that originate at the tonsils, base of the tongue, soft palate and pharyngeal posterior wall (Barnes *et al.*, 2005).

The incidence of these carcinomas is relatively lower compared to OSCC (Ferlay *et al.*, 2010). However, the emergence of Human papilloma virus has been contributed to the recent rising in frequency, especially among young people (van Monsjou *et al.*, 2010).

The clinical presentation of OPSCC shows various features including ulcerations, exophytic growth, ear pain, voice changes, dysphagia, and nodal involvement (Bagan *et al.*, 2010; Neville *et al.*, 2009).

2.5 Other aspects of OSCC

2.5.1 Investigations

Incisional biopsy is the most commonly used investigation in the diagnosis of OSCC (Scully and Felix, 2006). The biopsy should be large enough and well representative to avoid misdiagnosis and request of another specimen (Scully and Felix, 2006).

The diagnosis of OSCC is established when the dysplastic changes overwhelm the epithelium throughout with an encroachment on the underlying connective tissue (Scully *et al.*, 2008).

2.5.2 Diagnosis

Tumor, node and metastasis (TNM) is a globally accepted system that was introduced by the Union for International Cancer Control (UICC) and has been extensively used for the clinical staging of OSCC. The TNM classification system serves to assist with the selection of intervention strategies and allows for standardization of affected patients (Scully, 2013). This standardization makes it easy to correlate results from different studies conducted on this patient group from different parts of the world.

However, one of its drawbacks is that it lacks the histological details (Woolgar, 2006). Relevant combined systems are also available (Scully, 2013).

The histology of OSCC is classified into three grades; well-differentiated (in which the cells show some pleomorphism but with no separations and evident keratin pearls), moderately differentiated (increasing features of pleomorphism with cell separations) and poorly differentiated (which is characterized by marked pleomorphism and atypia, absence of keratin, significant adhesion loss, unevenly invading epithelium sheets that are hardly recognized as squamous cells and discontinuity of the basement membrane) (Regezi *et al.*, 2011; Scully, 2013).

Unlike the TNM classification system, this grading system has proved to be unhelpful when correlating to the management and prognosis of OSCC patients (O-charoenrat *et al.*, 2003). The system is confined to limited options and the majority of the diagnosed cases are categorized under the grade "moderately differentiated squamous cell carcinoma" (Woolgar, 2006).

2.5.3 Management

Many advances have been introduced into the management field of OSCC, but surgery remains the treatment of choice with or without other modalities (Scully and Bagan, 2009).

The goal of the surgical intervention is to excise the affected tissue and evaluate it histologically to determine the prognostic outcome and the need for further treatment such as radiotherapy (Scully and Porter, 2000).

Many surgical approaches are used and the intervention is usually guided by factors that are largely related to the tumor itself (Shah and Gil, 2009).

For example, for tumors present at stage I and II, the peri-oral approach is the most popular including a resection of the whole tumor along with safety margins (Kalavrezos and Bhandari, 2010).

The prognosis for these earlier stages has been described as good and surgery alone is almost satisfactory (Kalavrezos and Bhandari, 2010).

The late stage tumors (stage III and IV), in which more than one area are involved, are often more challenging and pose more postoperative complications (Kalavrezos and Bhandari, 2010; Shah and Gil, 2009).

The intervention is often more aggressive and is followed by a reconstruction of the ensuing defect. Factors that determine the type of the approach include the closeness of the tumor to the bone and to the external skin along with its location and size (Kalavrezos and Bhandari, 2010).

The neck dissection is performed in many ways depending on the condition and can be radical, modified radical or selective (Kalavrezos and Bhandari, 2010).

The radical neck dissection is a complete removal of the cervical nodes with a scarification of vital structures such as sternomastoid muscle, accessory and jugular nerves (Scully and Porter, 2000).

The methods other than radical dissection are trying to confine to the affected nodes while preserving the vitality of the uninvolved structures (Scully and Bagan, 2009).

The biopsy of the sentinel lymph node (the node that is probable to be firstly involved when the original tumor metastasized), has also been increasingly used, especially for early stages tumors (Kalavrezos and Bhandari, 2010; Scully, 2013).

The procedure of reconstruction aims to partially retrieve the function and anatomy of resected tissues in order to minimize the morbidity associated with their loss (Kalavrezos and Bhandari, 2010; Scully and Porter, 2000).

This is achieved via restoration of hard and soft tissue defects, closure of wound from external side along with using dental appliances (Kalavrezos and Bhandari, 2010).

The free tissue transfer flap is the most popular method for a reconstruction followed by the regional pedicle flaps (Kalavrezos and Bhandari, 2010).

The soft tissue defects are usually repaired by radial forearm free flap while the bony restorations are carried out by fibula free flap (Vaughan, 2009).

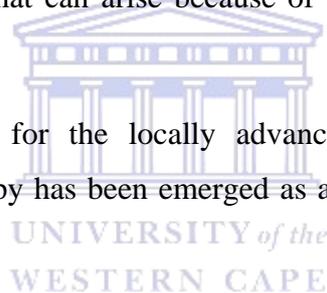
The distant metastasis is not frequently reported in OSCC patients (Scully and Porter, 2000), but when it is encountered, the prognosis is virtually poor and an intervention may become ineffective (Shiono *et al.*, 2009).

Radiotherapy can be used alone or beside the surgical intervention with or without chemotherapy depending on the stage of the tumor (Mazeron *et al.*, 2009).

Radiotherapy has an acceptable cosmetic outcome and less anatomical and functional distortion. However, it can result in side effects on many organs and renders the surgical intervention -if needed in the future- more complicated (Scully and Porter, 2000).

Recent advances in radiotherapy are aiming to achieve an adequate dose while minimizing the side effects that can arise because of the treatment (Mazeron *et al.*, 2009).

Such advances are favored for the locally advanced disease, where combined chemotherapy and radiotherapy has been emerged as a promising regimen (Mazeron *et al.*, 2009).



In addition to that, the classical methods of delivering radiotherapy are still active and in use (Scully and Porter, 2000).

Plesiotherapy (implantation of a radioisotope into and around the neoplasm), is effective mainly against tumors less than 2 cm and is characterized with less side effects (Scully and Porter, 2000).

Teletherapy, which uses an external beam, is more appropriate for larger tumors, but with much more damaging effect and complications (Scully and Porter, 2000).

The complications that can ensue because of radiotherapy include mucositis, pain, dry mouth, infections, dental defects in children, disturbance of taste and osteoradionecrosis (Scully and Porter, 2000).

Chemotherapy can be used as a palliative treatment in desperate cases or concurrently with radiotherapy. Cisplatin is the preferred agent for the locoregional advanced cases (Specenier and Vermorken, 2009).

Though combination chemotherapy has no advantage over the single agents, the regimen is recommended for younger patients with non-advanced disease (Specenier and Vermorken, 2009).

Chemotherapy in combination with epidermal growth factor receptor antagonist is considered as a breakthrough in cancer field management and has shown to improve the survival in cancer patients (Specenier and Vermorken, 2009).

The desperate cases with incurable disease or inability to undergo treatment are delivered with palliative care which is mainly directed towards relieving pain and discomfort and is carried out by a palliative care team (Shah and Gil, 2009).

2.5.4 Prognosis

Prognosis is worse with tumors which are locally or distantly metastasized, poorly differentiated, deeply infiltrated, thick in size, affecting older males, and presenting at late stages at the time of diagnosis (Scully and Bagan, 2009; Scully, 2013).

In conclusion, this literature review may be summarized in the following points:

-The incidence of OSCC is rising worldwide and most of patients present at a late stage at the time of diagnosis. Though risk factors are mostly life style related and can be controlled, the disease remains fatal and a significant burden on the health systems.

-The disease can involve any part of the mouth and is mostly seen at the lower lip or tongue margins. Each site affected presents with distinct features and different prognoses. The diagnosis requires histopathological confirmation and surgery is the most commonly used intervention with or without other modalities.

-OSCC in young people may show some features that are not reported in the classical disease of older patients. However, the literature did not distinguish the disease as a stand-alone entity. The scarcity of this entity (less than 7%) may contribute to this confusion.



CHAPTER THREE: STUDY DESIGN & METHOD

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3.1 Aim and Objectives

3.1.1 Aim

The aim of this study is to describe the epidemiological pattern of oral squamous cell carcinoma (OSCC) seen at the Tygerberg academic complex.

3.1.2 Objectives

- A) To describe the pattern of OSCC in patients' age, sex, risk factors and primary site of disease.
- B) To describe the difference in OSCC regarding patients' age, sex, risk factors and primary site of disease in young patients as compared to older ones.

3.2 Methodology

3.2.1 Study design

The study was a retrospective descriptive cross-sectional hospital based study.

3.2.2 Study Site

Tygerberg hospital, Cape Town, South Africa.

3.2.3 Sample size

All records which met the inclusion criteria of the study were electronically retrieved and included. The sample size comprised 2220 registers, representing the total number of OSCC patients who have been diagnosed by the oral pathology department of Tygerberg hospital from 1996 to 2013.

3.2.4 Data collection

Data was collected from the histology reports of confirmed diagnosis of OSCC patients who were referred to the oral pathology department at Tygerberg hospital from 1996 to 2013. The data was extracted from the information technology office (IT office) at the laboratory services, which belong to the Hematology department of Tygerberg hospital.

All diagnoses of squamous cell carcinoma were filed under the code M-80XXX. This code was then matched with the different peri-oral and intra-oral sites, which are tabulated below.

Site	Code
Lip	T-52XXX
Tongue	T-52XXX
Gingiva	T-54XXX
Palate	T-511XX
Floor of the mouth	T-512XX
Retromolar area	T-51600
Oropharynx	T-55XXX

All data meeting the requirements of the objectives of the study including age, sex, risk factors and primary site of disease were gathered, categorized, coded, and then entered into an Excel® spreadsheet (appendix 1).

3.2.5 Inclusion Criteria

OSCC patients who have been diagnosed by the oral pathology department of Tygerberg hospital from 1996 to 2013.

OSCC Patients with a lab number or electronic file.

Primary site located in the lip, oral cavity and oropharynx.

3.2.6 Exclusion criteria

Non OSCC patients, including metastatic carcinomas to the oral cavity.

OSCC patients who are out of the period 1996-2013.

3.2.7 Data Analysis

Data was checked for consistency and completeness and then transported to IBM SPSS® version 20 for analysis. Descriptive analysis was performed for age, sex, risk factors and primary site of tumor. The frequency of OSCC patients was calculated manually from the total number of oral biopsies. A comparison between the occurrences of OSCC through three periods was performed. Results were presented as appropriate in tables and figures. Tables were constructed using Microsoft word® 2010 and figures were constructed using Microsoft Excel® 2010. Chi-square or

Fisher's exact tests were used as appropriate. Probabilities of less than 0.05 were regarded as significant.

3.2.8 Ethical Considerations

The names of diagnosed patients were not recorded.

The privacy and confidentiality of collected data and any relevant information were preserved.

The protocol was submitted to the Senate Research Ethics Committee of the University of the Western Cape for approval and permission to carry out the study.

The study was independently reviewed and approved by Senate Research Ethics Committee of the University of the Western Cape.

The study was performed in accordance with the ethical principles of the University of the Western Cape.





CHAPTER FOUR: RESULTS

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4.1 Introduction

The aim of this study was to describe the epidemiological pattern of oral squamous cell carcinoma in patients diagnosed at Tygerberg Hospital between 1996 and 2013.

The data recorded included the age, sex, smoking and alcohol habits of patients and the oral site affected.

Patients were grouped by age into two groups, one that included patients of 40 years and younger, the other included patients who were older than 40 years (See table 4.1).

The selection of 40 years of age was proposed by similar studies in this field (Muller *et al.*, 2008; O'Regan *et al.*, 2006; Udeabor *et al.*, 2012).

Patients were also categorized into three groups according to the oral site of the tumor. These groups included lip squamous cell carcinoma (LSCC), oral cavity proper squamous cell carcinoma (OCSCC) and oropharyngeal squamous cell carcinoma (OPSCC).

4.2 Age and sex

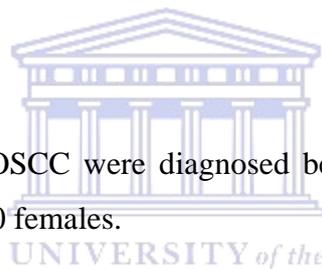
A total of 2220 patients of OSCC were diagnosed between 1996 and 2013. These composed 1650 males and 570 females.

2131 (96%) of patients were above 40 years of age, whereas 89 patients (4%) were below 40 years of age (See table 4.1).

Of those who were above 40 years of age, 1589 were males (74.6%) and 542 (25.4%) were females. For the age category below 40 years, 61 (68.5%) were males, and 28 (31.5%) were females (See table 4.1).

The mean age was 57.6 ± 11.1 with a minimum age of 16 years and maximum age of 98 years (See table 4.1).

The disease was most frequently diagnosed during the sixth decade of life with 822 patients, representing 37% of all the patients, followed by 515 patients (23.2%) who were diagnosed during the seventh decade (See figure 4.1). As figure 4.1 shows the critical span of age where the disease of OSCC abounds (in both sexes) in 40-60 years. Thereafter, it declines.



Sex	≤40 years		>40 years	
	(n)	(%)	(n)	(%)
Male	61	68.5	1589	74.6
Female	28	31.5	542	25.4
Total	89	4	2131	96

Mean age (SD) = 57.6 ±11.1. Minimum and maximum age=16 and 98.

(Chi-squared=1.3255, df = 1, p-value = 0.2496)

(n): Frequency

=: Proportion

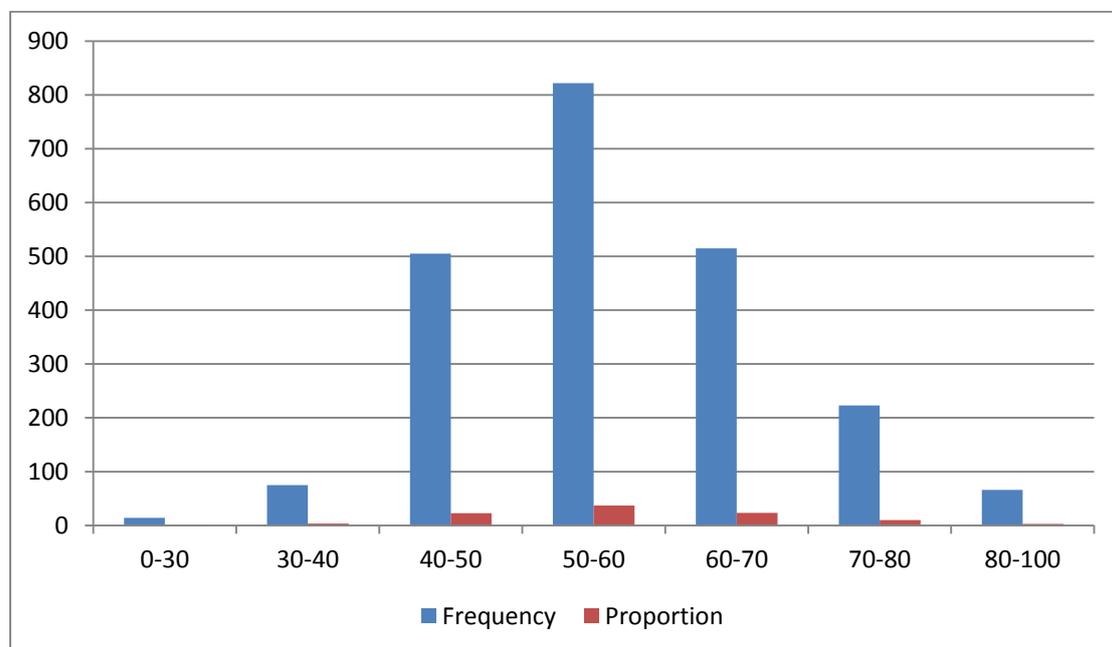


Figure 4.1 Frequency of OSCC patients by decades of life (n=2220) (p-value<2.2e 16)

4.3 Risk factors

An electronic search of histopathological reports was performed to elicit information regarding oral habits of patients such as smoking and alcohol drinking. There were 838 patients with information on these habits. This represented 37.7% of the total number of patients.

Of the 838 patient records accessed for oral habits, 638 (76.1%) were males and 200 (23.9%) were females. 801 patients (95.6%) were above 40 years of age (with 576

males and 225 females), while 37 (4.4%) were below this age (with 27 males and 10 females) (See table 4.2 and table 4.4).

765 patients were reported with oral habits. 385 Patients were current smokers, 66 were previous smokers, 308 were current smokers and alcohol drinkers, 6 were alcohol drinkers. 73 patients were not reported to practice any kind of habits (See table 4.3).

Table 4.4 shows that the male to female ratio was about 3.2:1, and that smoking and alcohol consumption were together more conducive to affliction with OSCC than either of them alone. Smoking alone seems to be much more attended with the possibility of developing the malady than alcohol drinking alone.

Table 4.2 Distribution of OSCC patients with reported habits by age and sex stratified by age (n=765)				
	≤ 40 years		> 40 years	
Sex	(n)	%	(n)	%
Males	19	61.3	533	72.6
Females	12	38.7	201	27.4
Total	31	100	734	100

Table 4.3 Distribution of OSCC patients with no reported habits by age and sex stratified by age (n=73)				
	≤ 40 years		> 40 years	
Sex	(n)	%	(n)	%
Males	4	66.7	28	41.8
Females	2	33.3	39	58.2
Total	6	100	67	100

(Chi-squared = 0.045, df = 1, p-value = 0.833)

Table 4.4 Distribution of OSCC patients' habits by age group and type of oral habit (n=838)				
	≤ 40 years		> 40 years	
Type of oral habit	(n)	%	(n)	%

Smoking	18	48.6	367	45.8
Smoking & Alcohol	11	29.7	297	37.1
Alcohol	1	2.7	5	0.6
Ex-smoking	1	2.7	65	8.1
No smoking or Alcohol	6	16.2	67	8.4
Total	37	100	801	100

4.4 Site

In this study, Patients were categorized into three groups according to the oral site of tumor. These groups included lip squamous cell carcinoma (LSCC), oral cavity proper squamous cell carcinoma (OCSCC) and oropharyngeal squamous cell carcinoma (OPSCC) (See table 4.5).

Lip squamous cell carcinoma (LSCC) patients included 10 patients (6.8%) below 40 years of age and 138 patients (93.2%) above this age (See table 4.5).

Oral cavity proper squamous cell carcinoma (OCSCC) patients comprised 52 patients (3.5%) below 40 years of age and 1415 patients (96.5%) above this age (See table 4.5).

Oropharyngeal squamous cell carcinoma (OPSCC) patients consisted of 27 patients (4.5%) below 40 years old and 578 patients (95.5%) above 40 years old (See table 4.5).

Table 4.5 demonstrates almost similar high proportions of the occurrence of lip squamous cell carcinoma, oral cavity proper squamous cell carcinoma, and oropharyngeal squamous cell carcinoma among patients older than 40 years. People younger than 40 years of age were much less afflicted. However, they are not immune, especially when exposed to the relevant precipitating risk factors. Furthermore, many of them would probably contract the disease when they get older and become sufficiently exposed.

Table 4.5 Distribution of OSCC subtypes by age group (n=2220)				
	≤ 40 years		> 40 years	
	(n)	%	(n)	%
oral squamous cell carcinoma				

subtype				
Lip squamous cell carcinoma	10	6.8	138	93.2
Oral cavity proper squamous cell carcinoma	52	3.5	1415	96.5
Oropharyngeal squamous cell carcinoma	27	4.5	578	95.5

Table 4.6 Distribution of OCSCC subtypes by age group (n=1467)

OCSCC subtype	≤40 years		>40 years	
	(n)	%	(n)	%
Tongue squamous cell carcinoma	26	3.8	657	96.2
Palatal squamous cell carcinoma	13	4.4	285	95.6
Floor of the mouth squamous cell carcinoma	6	2.1	277	97.9
Not otherwise specified squamous cell carcinoma	5	4.9	98	95.1
Gingival squamous cell carcinoma	1	1.7	57	98.3
Retromolar area squamous cell carcinoma	1	2.4	41	97.6

(Chi-squared = 3.6451, df = 5, p-value = 0.6016)

4.5 Biopsies

OSCC patients were 2220, representing 27.7% of total oral biopsies which were 8020. LSCC patients were 148, representing 6.7% of OSCC patients and 1.8% of total oral biopsies (See table 4.7).

OCSCC patients were 1467, representing 66.1% of OSCC patients and 18.3% of total oral biopsies.

OPSCC patients were 605, representing 27.3 % of OSCC patients and 7.5 % of total oral biopsies.

Table 4.7 Proportion of OSCC patients and its subcategories in relation to total oral biopsies		
	Proportion in relation to OSCC patients	Proportion in relation to oral biopsies
Oral squamous cell carcinoma	100	27.7
Lip squamous cell carcinoma	6.7	1.8
Oral cavity proper squamous cell carcinoma	66.1	18.3
Oropharyngeal squamous cell carcinoma	27.3	7.5

4.6 Time period comparison

In order to check for possible changes in the trend of OSCC, the whole period of the study has been divided into three equal periods. These periods are 1996-2001, 2002-2007 and 2008-2013.

The disease showed a constant increase in frequency through the three periods from 669 patients (31.1 %) during 1996-2001, to 718 patients (32.3%) during 2002-2007 and to 833 patients (37.5%) during 2008-2013 (See figure 4.2).

Among patients ≤ 40 years, 22 patients (24.7%) were diagnosed during 1996 to 2001, 35 patients (39.3%) during 2002 to 2007 and 32 patients (35.95%) during 2008 to 2013(See Figure 4.3).

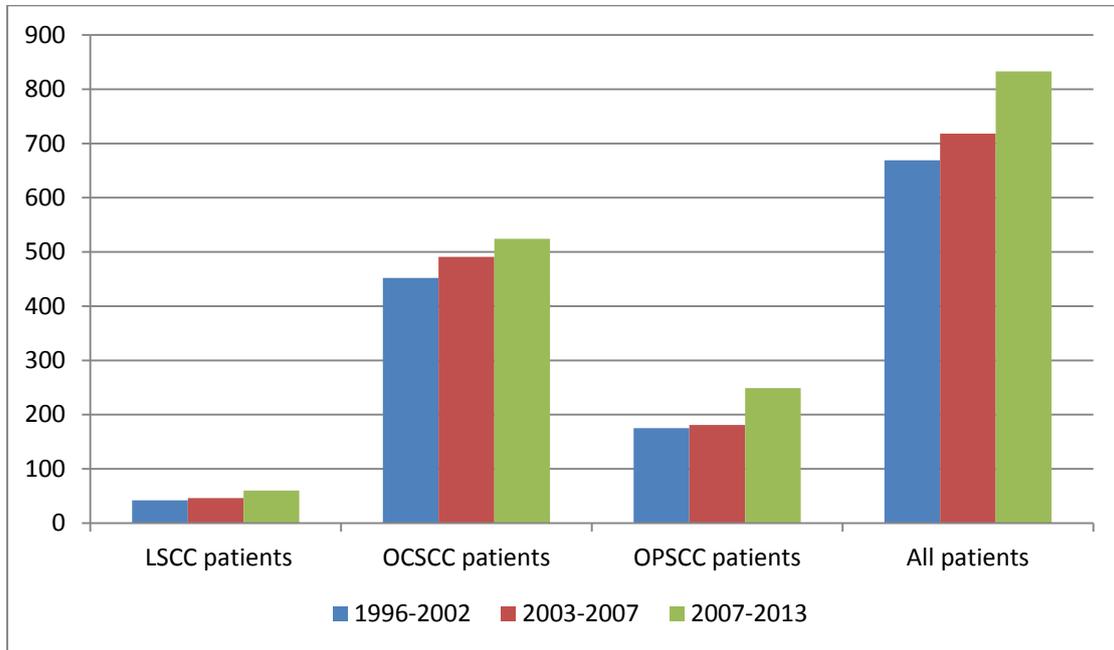


Figure 4.2 Frequency of OSCC patients through three periods from 1996 to 2013 (P-value<0.001)

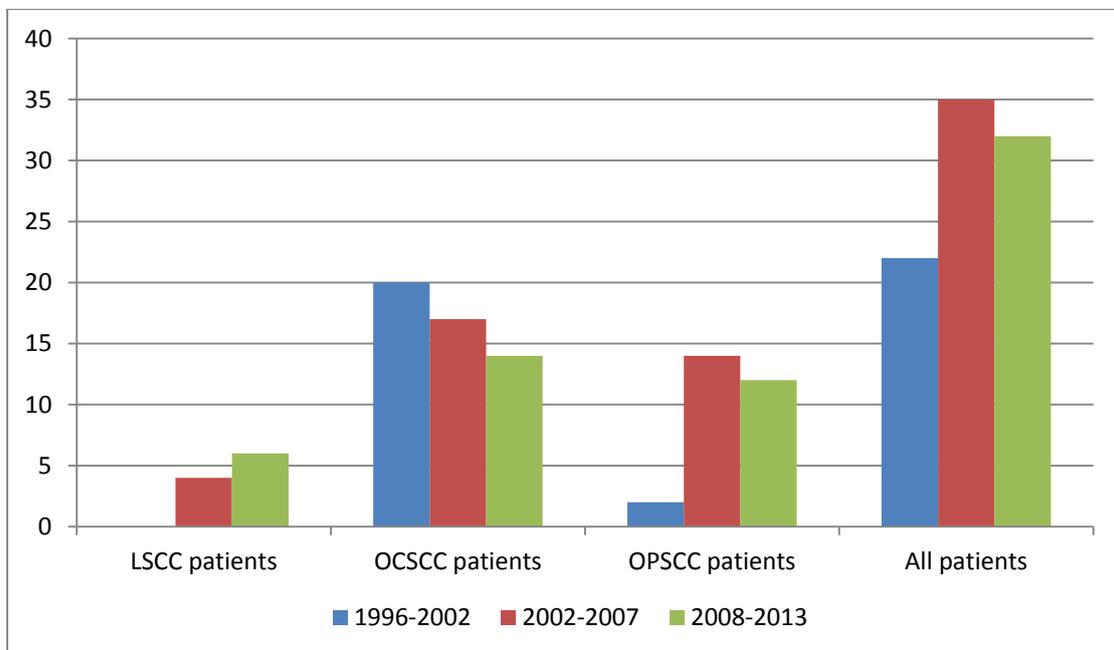


Figure 4.3 Frequency of OSCC among patients ≤ 40 years through three periods from 1996 to 2013 (P-value=0.210)



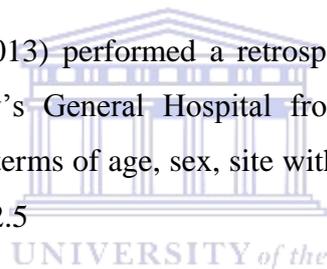
Oral squamous cell carcinoma (OSCC) is a major health hazard that represents a global burden. Analysis of available data revealed an increased incidence and mortality of the disease. In this report, the trend of OSCC has been analyzed by patients' age, sex, risk factors (i.e. smoking and alcohol) and primary site of tumor. The discussion is followed by recommendations of future research required in this field and strategies for disease prevention.

5.1 Age and sex

The mean age of patients diagnosed with OSCC at Tygerberg hospital over this said period of time was 57.6 years. This was exactly the same as reported by Udeabor et al (2012) who conducted a similar study in Hannover, Germany between 1980 and 1999 with a sample size of 977 patients.

Other studies such as Hernández-Guerrero et al (2013) and Muller et al (2008) reported a higher mean age and showed 62.5 and 63.7 respectively.

Hernández-Guerrero et al (2013) performed a retrospective review on 531 patients with OSCC at Mexico City's General Hospital from 1990 to 2008. The study analyzed the disease trend in terms of age, sex, site within oral cavity and histological grading. The mean age was 62.5



Muller et al (2008) recruited 1,919 patients who have been diagnosed with OSCC by the Oral Pathology department of Emory University, Atlanta, USA from 1971 to 2006.

Muller and his group aimed to investigate the demographic information, frequency, location and histological grading of OSCC in young patients as compared to older ones. The study showed a mean age of 63.7.

These reports revealed that OSCC has a peak incidence during the sixth and seventh decade of life. In this study, OSCC was most commonly diagnosed during the sixth decade of life with 822 patients (37%), followed by 515 patients (23.2%) who were diagnosed during the seventh decade.

This can be due to an exposure to carcinogens early in life or as a result of genetic influences that accelerated the malignant transformation in this segment.

Concerning the young patients (arbitrarily aged as 40 years old or less), the majority (84.3%) were in their fourth decade of life, in line with many other studies which detected the same decade as the commonest in term of frequency (Marocchio *et al.*, 2010; O'Regan *et al.*, 2006).

The male to female ratio was 2.9:1 for all age groups and 2.2:1 for young patients. This was in accordance with the literature which indicated that males are more affected with OSCC than females (O'Regan *et al.*, 2006; Parkin *et al.*, 2005).

5.2 Risk factors

Of a total of 2220 patients recruited to the study, 838 patients were found to have information on oral habits such as smoking and alcohol drinking. This represented 37.7% of total number of patients.

Of these 838 patients, 638 (76.1%) were males and 200 (23.9%) were females. 801 patients (95.6%) were above 40 years of age (with 576 males and 225 females), and 37 (4.4%) were below this age (with 27 males and 10 females).

385 Patients were current smokers, 66 were previous smokers, 308 were current smokers and alcohol drinkers, 6 were alcohol drinkers and 73 were not reported to practice any kind of habits.

Only those who had never smoked or drank alcohol were regarded as non-smokers, while ex-smoker patients were grouped with the category of patients who have been practicing oral habits.

Oral habits (e.g. smoking and alcohol) were practiced by 765 patients, representing 91.3% of the study's sample. This result was higher than that reported by O'Regan *et al.* (2006) and Hirota *et al.* (2008) who reported 82% and 72.7% for sample sizes of 130 and 116 respectively. Though, the latter studies were limited by the small number of patients included.

However, the result of our study may indicate the heavy indulgence of our patients in these habits and emphasize the need to raise the awareness about the risks of such life style.

Regarding the practice of these habits, Durazzo *et al.* (2005) indicated that the ratio of males to females is decreasing since these habits are considered now as socially more

acceptable among females than in the past. However, in this study, the ratio was 2.6:1. This was in line with other studies (Hirota *et al.*, 2008; O'Regan *et al.*, 2006) which confirmed the tendency of males to practice these habits more than females.

Patients with no reported oral habits were 73, representing 8.7 % of the whole sample included. This percentage is lower than what was reported globally which indicated that factors other than smoking and alcohol (e.g. viruses and micronutrient deficiencies) are responsible for about one fourth of all OSCCs (Dahlstrand & Dalianis, 2005; Siebers *et al.*, 2008).

The male to female ratio in patients with no history of smoking and alcohol was 1:1.3. This result was consistent with other studies which also revealed a female preponderance in this category, especially among patients older than 40 years (Koo *et al.*, 2013; Kruse *et al.*, 2010).

Koo et al (2013) found that of a total of 169 patients who were diagnosed with OSCC between 2007 and 2010 in Royal Melbourne Hospital, Australia, there were 41 patients (24.3%) with no history of smoking and alcohol exposure. The distribution of these patients included 31 females (75.6) and 10 males (24.4) with a mean age of 71 years.

Kruse et al (2010) studied the risk factors of 278 patients who were diagnosed with OSCC by the department of Craniomaxillofacial and Oral Surgery at University Hospital Zurich, Switzerland. The study reported 67 patients (24.1%) with no history of tobacco or alcohol use. Of the 67 patients, 45 (67.2%) were females and 22 were males with a mean age of 70 years.

In this study, the gender distribution of patients with no reported oral habits showed that there were 41 females (56.2%) and 32 males (43.8) with 39 females (58.2%) and 28 males (41.8%) being diagnosed above 40 years of age. This may identify OSCC in nonsmoking and non-alcohol drinking older females as a potentially distinct subgroup (See table 4.3).

Among young patients, the current study demonstrated that 31 patients (83.8 %) of this group were practicing at least one oral habit during their life. This is compared to 83% and 75% reported by O'Regan et al (2006) and Llewellyn et al (2003) respectively.

Though some studies indicated that smoking and alcohol are not strongly associated with OSCC of young patients (Kuriakose *et al.*, 1992; Toner and O'Regan, 2009), the finding in this study was different, emphasizing the role of these factors among this age category (see table 4.4).

The distribution of young patients who had no history of smoking and alcohol exposure revealed that there were 4 males (66.7%) and two females (33.3%) among this group. This result was different from several reports which indicated that the diagnosis of OSCC among young patients is more established in nonsmoking females (Llewellyn *et al.*, 2004; O'Regan *et al.*, 2006; Toner and O'Regan, 2009).

However, this result was not statistically significant as our young patients sample was not large enough to provide conclusive inferences about the exact influence of these factors.

Therefore, in order to examine these risk factors among young patients, a more comprehensive study can be performed including a bigger sample size along with investigating factors such as viral, dietary, genetic and socioeconomic implications.

5.3 Site

The sites affected with OSCC in this study included the tongue with 683 patients (30.8%), oropharynx with 605 patients (27.3%), palate with 298 patients (13.4%), floor of the mouth with 283 patients (12.7%), lip with 148 patients (6.7%), mouth not otherwise specified with 103 patients (4.6%), gingiva with 58 patients (2.6%), and finally retromolar area with 42 patients (1.9%).

The most affected sites with OSCC in the literature include in a descending manner the tongue, oropharynx, lip, floor of the mouth, palate, gingiva, and buccal mucosa (Barnes *et al.*, 2005; Petti and Scully, 2005).

In our study, the number of LSCC was unusually low and included only 148 patients, representing 6.7% of the total number of patients. This is attributed to the anatomical overlapping of the lip, which is considered by the National Cancer Registry of South Africa as a part of skin rather than the oral cavity (Abram *et al.*, 2012). As a consequence of this, a large number of lip cancers are thought to be included under the umbrella of skin malignancies.

Furthermore, there is a tendency in patients with lip illnesses to consult physicians rather than dentists, which may also potentiate misclassification of disease (Marocchio *et al.*, 2010). Accordingly, some authors considered lip cancer as a distinct entity, rather than being a part of another cancer category such as skin cancer (Chen *et al.*, 1992; Moore *et al.*, 1999).

Another uncommon finding was associated with PSCC which was the third most common subtype of OSCC, following TSCC and OPSCC in frequency and order of locations involved. This may highlight the need to investigate reverse smoking which is a well-known risk factor for this location (i.e. the palate).

The sites involved for the young patients included the oropharynx with 27 patients (30.3%), tongue with 26 patients (29.2%), palate with 13 patients (14.6%), lip with 10 patients (11.2%), floor of the mouth with 6 patients (6.7%), mouth not otherwise specified with 5 patients (5.6%), retromolar area with one patient (1.1%) and gingiva with one patient (1.1%).

Though many studies indicated that OSCC that affects young people is most frequently diagnosed in the tongue (Mackenzie *et al.*, 2000; O'Regan *et al.*, 2006; Patel *et al.*, 2011), the current study revealed no significant difference between OSCC of the tongue and oropharynx among this age group.

Other reports indicated a rise in frequency in OSCC of the pharynx (Llewellyna *et al.*, 2003; Schantz and Yu, 2002), and attributed that to HPV.

In this respect, future studies in South Africa, including viral screening may help confirm the exact influence of HPV in OSCC of young patients.

5.4 Biopsies

The current study recruited 2220 patients' records, representing 27.7% of total oral biopsies taken within same time period.

In Ireland, between 1993 and 2003, 653 patients were diagnosed with head and neck squamous cell carcinoma in St. James's and Dublin dental school hospitals, representing 30% of this neoplasm over that time (O'Regan *et al.*, 2006).

Muller *et al.* (2008) found that of 159,407 oral biopsies, OSCC patients were 1,919, representing 1.2% of all patients.

Hernández-Guerrero et al (2013) found 282 patients registered with OSCC in the General Hospital of Mexico between 2000 and 2008. These patients represented 5.7% of all diagnosed cancers.

Kiran et al (2012) reported 1005 oral biopsies through five years period (from 2007 to 2011). Of these, 293 (29.2%) were malignancies.

In South Africa, OCSCC and OPSCC were estimated as (1.913% for males and 0.614% for females), and (0.554% for males and 0.132% for females) in relation to all cancers respectively. These percentages exclude skin carcinomas which were considered as a separate identity (Abram *et al.*, 2012).

Hirota et al (2008) performed a retrospective study among young patients to examine risk factors and clinical aspects associated with OSCC compared to older patients. The study showed 13 patients out of 121 who were younger than 40 years of age. This represented 10.7% of all patients.

O'Regan et al (2006) analyzed 130 patients with OSCC diagnosed between 1993 and 2003 at St. James's Hospital, Dublin. The study detected 30 patients (23.1) as younger than 40 years of age.

Though these results look different, the global range of OSCC among young patients is 4-6 % (Llewellyn *et al.*, 2004). Factors that may affect the distribution of young patients include sample size, time period, population and geographical location.

In this study which looked at data from 1996 to 2013 and recruited 2220 patients, young patients represented 4% of total patients included. This can confirm the rarity of this disease among this category.

This assumption may be supported by the large sample of patients included in this study unlike other studies such as Hirota et al (2008) and O'Regan et al (2006) who included 121 and 130 patients respectively.

5.5 Time period comparison

In order to check for possible changes in the trend of OSCC, the whole period of the study was divided into three equal periods. These periods are 1996-2001, 2002-2007 and 2008-2013 (See figure 4.2).

The frequency of OSCC was constantly increasing through the three periods from 669 patients (31.1 %) during 1996-2001, to 718 patients (32.3%) during 2002-2007 and to 833 patients (37.5%) during 2008-2013 (See figure 4.2).

Among young patients, OSCC exhibited an increased frequency in the second period (2003-2007) following the first period (1996-2002). After that, the frequency stopped rising but remained high (See figure 4.3).

22 patients (24.7%) were diagnosed during 1996 to 2001, 35 (39.3%) during 2002 to 2007 and 32 (35.95%) during 2008 to 2013 (See figure 4.3).

In contrast to other OSCC sub sites, LSCC patients showed a consistent increase in frequency among young patients over the 18-years of the study period.

LSCC patients increased from no patients (0%) during 1996 to 2001, to 4 patients (40%) during 2002 to 2007 and lastly to 6 patients (60%) during 2008-2013.

This would draw attention to this entity, which has not been included in the literature when discussing this phenomenon.

However, the sample of LSCC patients who were below 40 years of age was very small (10), and hence, more studies with large sample size are required to confirmed this trend.

Among other studies, Marocchio et al (2010) reported that during the periods 1961-1980, 1981-1990, 1991-2000 and 2001-2008, there were 1564 cases of OSCC distributed as 263, 159, 463 and 679 respectively. As can be seen, the frequency of these cases which covered all age groups was dropped during the second period of the study but started to rise persistently after that.

Hernández-Guerrero et al (2013) analyzed 531 patients with OSCC diagnosed from 1990 to 2008. The whole period was divided into 4 equal periods (1990-1994, 1995-1999, 2000-2004 and 2005-2008). The frequency reported showed 135, 114, 163 and 119 patients respectively.

Muller et al (2008) found that during a 35-year study period, 95 patients with OSCC were below 40 years of age. Through this sample, 8 cases were diagnosed during

1971 to 1980, compared to 36 during 1981–1990, 31 during 1991–2000 and 21 during 2001-2006.

Although the literature presents many variations, our results were in harmony with some of them “e.g. Muller et al (2008)”. However, on the basis of our study, there was a constant increase in OSCC patients diagnosed at Tygerberg hospital (See figure 4.2, where p value = <0.001).

It is unclear whether this is because of increased number of Cape Town population or whether it is a result of increased number of oral biopsies due to increase oral cancer awareness.

In this respect, a future population based study can help detect the prevalence and possible trend changes of OSCC among these years.

5.6 Limitations

The study was hospital-based and did not give an exact prevalence rate in comparison to the total population (per 100.000) individuals.

The study was confined to interpret the samples of OSCC patients who were reported at one center.

The study was restricted by the retrospective design, which may be limited by variation in the completeness of records available.

The possibility for misclassification of primary tumor origin could not be excluded, especially for LSCC patients.

The extraction of information regarding oral habits was confronted with insufficiencies, as some clinicians were not committing to record the history of oral habits.

In addition to that, the recorded oral habits were not reported scrupulously such as type of smoking and alcohol and their frequency. Therefore, oral habits in this study were included as whether current smokers and alcohol drinkers or non-smokers and alcohol drinkers in addition to ex-smokers.



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**CHAPTER SIX: CONCLUSION &
RECOMMENDATIONS**
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6.1 Conclusion

The study confirmed that OSCC is still an affliction of people older than 40 years and males are predominantly affected.

Smoking and alcohol are strong risk factors for OSCC irrespective of patient's age.

Tongue and oropharynx are the commonest sites associated with OSCC for all age groups.

The current data show no difference in the sex distribution, oral habits (i.e. smoking and alcohol) and site of the disease among different age groups of persons afflicted by OSCC.

6.2 Recommendations

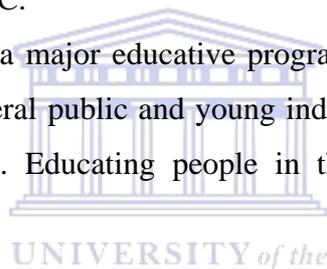
Future studies may expand this work by being multi-centred in the design to establish a National prevalence of OSCC.

There is a need to introduce a major educative program about the risks of smoking and alcohol amongst the general public and young individuals. The laws may not be very effective in themselves. Educating people in this respect is probably more important.

A consensus about the definition of young patients is needed along with further accurate registration of data.

Health professionals who are involved in screening of oral cancer are strongly recommended to record the history of oral habits scrupulously, as this will help improve future epidemiological studies.

Given the large sample of patients involved in this study during 18 years, our center can be considered as an epidemiological reference center for future studies.



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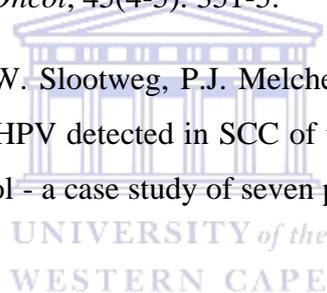
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Appendix 2. Ethical clearance letter



**Office of the Deputy Dean
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Faculty of Dentistry & WHO Collaborating Centre for Oral Health



UNIVERSITY OF THE WESTERN CAPE
Private Bag XI, Tygerberg 7505
Cape Town
SOUTH AFRICA

Date: 20th September 2013

For Attention: Dr AA Hamid
Diagnostic Cluster

Dear Dr Hamid

STUDY PROJECT: Pattern of oral squamous cell carcinoma diagnosed at referral oral and maxillofacial centers in Cape Town from 1982 to 2013

PROJECT REGISTRATION NUMBER: 13/8/20

ETHICS: Approved

At a meeting of the Senate Research Committee held on Friday 20th September 2013 the above project was approved. This project is therefore now registered and you can proceed with the study. Please quote the above-mentioned project title and registration number in all further correspondence. Please carefully read the Standards and Guidance for Researchers below before carrying out your study.

Patients participating in a research project at the Tygerberg and Mitchells Plain Oral Health Centres will not be treated free of charge as the Provincial Administration of the Western Cape does not support research financially.

Due to the heavy workload auxiliary staff of the Oral Health Centres cannot offer assistance with research projects.

Yours sincerely

A handwritten signature in black ink, appearing to read 'S. Naidoo', written over a horizontal line.

Professor Sudeshni Naidoo

Appendix 3. Letter for title change



FACULTY OF DENTISTRY

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Prof. M Parker
Dentistry Higher Degrees Committee
30 May 2014

Dear Prof. Parker

Re: Change in title for Dr Hamid's research: Project registration number 13/08/20

This letter serves as a request to change the title of the abovementioned research from;

"Pattern of oral squamous cell carcinoma diagnosed at referral oral and maxillofacial centres in Cape Town from 1982 to 2013"

To

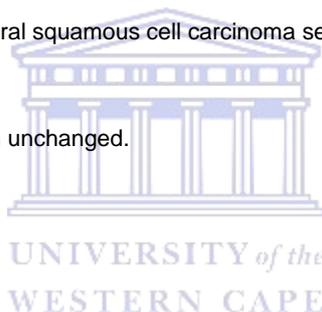
"Epidemiological pattern of oral squamous cell carcinoma seen at the Tygerberg academic complex"
(New topic)

The methodology will remain unchanged.

Sincerely

Dr AA Hamid

PROF L X G STEPHEN
Head: Diagnostics Cluster



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