

**AN OBSERVATIONAL RETROSPECTIVE DEMOGRAPHIC STUDY OF PATIENTS
WITH ORAL SQUAMOUS CELL CARCINOMA TREATED WITH RADIATION
THERAPY AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
(2014-2019)**



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of Medicine in Radiation Oncology

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DECLARATION

I, Gal Feller, declare that this dissertation is my own work. It is submitted for the Degree of Master of Medicine in Radiation Oncology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signed: gfeller

14th Day of October 2024

DEDICATION

I would like to thank my sisters Shani and Romy, and my parents, Terry and Liviu, for their encouragement and patience.

Their support was one of the major elements driving this research project to completion.

ABSTRACT

Background and objectives

Squamous cell carcinoma (SCC) of the oral cavity comprises defined anatomical subsites and is related to known risk factors such as alcohol consumption and tobacco smoking. It is more prevalent in men than in women and commonly develops in middle-to older age. Unfortunately, it is often diagnosed late during its natural course when the disease is already at an advanced clinical stage, and consequently, patients with the disease have a low 5-year survival rate. Definitive radiation therapy and concurrent chemoradiation therapy are the primary options of treatment for patients with unresectable oral SCC or for those who cannot, or do not want to undergo surgery. Radiation therapy is also an important adjuvant treatment following primary surgery in select cases, and has a role in the salvage and palliative settings.

The aim of this study was to describe the relationship between the demographic characteristics of patients who presented to the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital, and the clinical and pathological features of the disease, and to describe the treatment-induced toxicities that occurred.

Materials and methods

In this cross-sectional, retrospective study, clinic records were reviewed of all patients with oral cavity SCC treated with radiotherapy in the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital, between January 1st 2014 and December 31st 2019.

Only patients with histologically confirmed oral cavity SCC were included; other anatomical subsites (such as oropharyngeal carcinoma, among others), and other oral cavity malignancies (such as adenocarcinoma or lymphoma, among others) were excluded.

Age, sex, race/ethnicity, smoking and alcohol consumption, clinical stage, histopathological grade, oral cavity subsite, treatment intent and radiation-induced toxicities were recorded, tabulated, and statistically analyzed.

Results

Of the 119 cases of oral SCC included in this study, 71% were males (mean age: 59 years) and 29% were females (mean age: 62 years). The mean age of the study population at the time of radiotherapy was 60 years. The percentage of males that smoked (94%) was significantly higher than that of females (66%), and the percentage of males that consumed alcohol (73%) was significantly higher than the percentage of females who consumed alcohol (49%).

The tongue was the most frequent subsite affected followed by the floor of the mouth. The tongue and floor of the mouth accounted for 71% of all cases. Both the tongue and floor of the mouth were associated with advanced clinical stage (stage III and IV) and most of the oral SCC at the different subsites were moderately-differentiated.

In this study, 72/119 patients (61%) experienced oral mucositis, in line with the prevalence reported in the literature, with males affected to a statistically significantly greater degree than females. Salivary gland dysfunction was noted in 13% of patients and most frequently affected patients who received definitive chemoradiotherapy. Radiation-induced dermatitis was present in 62% of patients (74/119) and was also most frequently observed in patients who had received definitive chemoradiotherapy.

Conclusion

The results of this study confirm that oral SCC is predominantly a disease of middle-aged or elderly people, is more frequently observed in males than in females, and may affect any oral subsite, although the tongue and floor of mouth were noted to be the most common in our study. Our results are also in line with previous findings that show that men with oral cavity SCC smoked and consumed alcohol to a greater degree than did women, and that this may be the reason for the observed gender disparity seen in the literature.

All patients in this study were affected by one or more radiation-induced toxicities. Dermatitis, oral mucositis and dysphagia were the most frequently observed adverse side-effects, and some of the patients experienced more than one radiation-induced toxicity. All toxicities were managed as per Departmental protocols.

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TABLE OF CONTENTS

Title.....	i
Declaration.....	ii
Dedication.....	iii
Abstract.....	iv
Acknowledgements.....	vi
Table of contents	vii
List of figures	ix
List of tables.....	x
List of abbreviations	xi
Chapter 1: Introduction.....	1
1.1 Background	1
1.2 Literature review	2
1.2.1 Epidemiology	2
1.2.2 Aetiology	4
1.2.3 Treatment Options	6
1.2.4 Radiation-induced toxicity	12
1.2.4.1 Radiation-induced mucositis.....	12
1.2.4.2 Salivary gland dysfunction (xerostomia)	15
1.2.4.3 Radiation-induced dermatitis.....	16
1.2.4.4 Trismus	18
1.2.4.5 Osteoradionecrosis	19
1.3 Objectives of this study.....	20
1.3.1 Primary objectives.....	21
1.3.2 Secondary objectives	21
Chapter 2: Research methodology.....	22
2.1 Materials and methods	22
2.2 Statistical analysis	23
Chapter 3: Results	25
3.1 Introduction.....	25
3.2 Oral cavity subsite involved	25
3.3 Demographics	30
3.4 Treatment intent	31
3.5 Radiotherapy- induced toxicity.....	34

Chapter 4: Discussion	38
4.1 Introduction.....	38
4.2 Clinico-pathological features of oral cavity SCC.....	38
4.3 Radiation-induced tissue toxicities in relation to our study	40
4.3.1 Radiotherapy-induced oral mucositis.....	40
4.3.2 Salivary gland dysfunction.....	41
4.3.3 Radiation-induced dermatitis	41
4.3.4 Osteoradionecrosis of the jaw	42
4.4 Limitations of the study	42
Chapter 5: Conclusion and recommendations.....	45
5.1 Conclusion.....	45
5.2 Recommendations.....	46
6. References	47
7. Appendix.....	511
7.1 Human research ethics committee certificate	511

LIST OF FIGURES

Figure 1:	Distribution of oral mucosal cavity subsite involved	28
Figure 2:	Breakdown of radiation-induced toxicities in relation to gender	36

LIST OF TABLES

Table 1:	AJCC 8 th edition TNM staging of oral cavity squamous cell carcinoma	10
Table 2:	Grading criteria for oral mucositis as per the RTOG classification system	13
Table 3:	Classification of acute radiation dermatitis according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3	17
Table 4:	The age, and gender of the 119 patients with oral SCC in relation to the oral mucosal subsite involved	27
Table 5	The histopathological grade and clinical stage in relation to the oral mucosal subsite treated	29
Table 6	Distribution of age, gender, histopathological grade, and clinical stage for the entire study population	33
Table 7	Gender in relation to history of alcohol consumption and smoking for the entire study population	34
Table 8	Frequencies and percentages of radiation-induced toxicities/side-effects in relation to age, gender and AJCC prognostic group stage	35
Table 9	Radiation-induced toxicities/side-effects in relation to treatment intent	37

LIST OF ABBREVIATIONS

2D-CRT	Two-dimensional conformal radiotherapy
3D-CRT	Three-dimensional conformal radiotherapy
AJCC:	American Joint Committee on Cancer
CT:	Computed tomograohy
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
DOI:	Depth of invasion
ENE:	Extranodal extension
IMRT:	Intensity modulated radiation therapy
NCCN:	National Comprehensive Cancer Network
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
PORT:	Postoperative radiotherapy
RT:	Radiotherapy
RTOG:	Radiation Therapy Oncology Group
SCC:	Squamous cell carcinoma
TNM:	Tumour-node-metastasis
WCCNR:	Western Consortium for Cancer Nursing Research
WHO:	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Background

South Africa's Gauteng province has only two publicly funded hospitals providing radiation oncology services to a population of approximately 15 million; Steve Biko Academic Hospital in Pretoria serves the northern part of the province and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the heart of Johannesburg serves the southern part.

CMJAH is a quaternary academic hospital that offers both Medical Oncology and Radiation Oncology services, and as such there is one ward in the hospital that accommodates radiation oncology patients and is shared with the Medical Oncology Department.

As such, the Head and Neck Unit at the Department of Radiation Oncology at CMJAH receives many patient referrals from surgical departments in hospitals all over the province, and even further afield.

Many of these patients are presented at a combined multidisciplinary meeting and are deemed inoperable by the surgeons primarily due to their advanced clinical stage. Consequently, they are offered either definitive radiotherapy or concurrent chemoradiotherapy as primary treatment options. Patients who present at an earlier stage may undergo surgical resection and be referred to our department for adjuvant radiotherapy, as appropriate.

Once patients complete treatment, they are followed up closely in our department to assess any potential complications from their treatment, and to ensure rapid diagnosis and management should recurrence be suspected.

Cancers of the head and neck region comprise many different clinical entities and histological subtypes, each of which has a different aetiology, epidemiology, natural course and management options. It was therefore decided to limit the scope of this study to patients who were diagnosed with histologically confirmed squamous cell carcinoma (SCC) of the oral cavity and its various subsites.

The aim of this study is to describe the demographic characteristics and clinic-pathological features of patients who present to our Department with oral cavity SCC, as well as to describe the radiation-induced toxicities that occurred.

1.2 Literature review

1.2.1 Epidemiology

More than 90% of oral cancers are squamous cell carcinoma (SCC), which is a malignancy affecting the mucosal surfaces of the mouth, comprising the anterior tongue, floor of the mouth, buccal mucosa, labial mucosa, gingiva and alveolar mucosa, hard palate and the retromolar trigone (1-4) . Other oral cancers include haematological malignancies, minor salivary gland tumours, mucosal melanoma, osteosarcoma and other rare sarcomas, and metastasis to the mouth/jaws, particularly from the breast, lung, kidney and prostate (5-7).

According to the latest GLOBOCAN statistics (dated 2020), squamous cell carcinomas of the head and neck region are listed as the seventh most frequent cancer worldwide, comprising an estimated 890,000 new cases per year (4.6% of all cancer diagnoses globally). It also accounts for approximately 450,000 deaths per year around the world. These figures include an estimated 380,000 new cases of cancer diagnoses of the lip and oral cavity (8).

In 2023, Statistics South Africa, an official Department within the Government of South Africa, released their “Cancer in South Africa (2008-2019)” report which estimated the incidence of cancer of the lip, oral cavity and pharynx to be 2.6% (9).

According to South Africa’s National Cancer Registry, in 2020 there were 1 007 histologically confirmed cases of oral cavity cancers diagnosed in South Africa; of these 364 were in females (amounting to 0.9% of all newly diagnosed female

cancers) and 643 were diagnosed in males (or 1.75% of all newly diagnosed male cancers) (10).

Sung et al., (8) reported that 1.8% of all cancers diagnosed in South Africa in 2020, were lip and oral cavity, and between 1997-2001 Botha et al., (11), reported that 5% of all cancers in males and 0.6% of all cancer in females were oral cancers.

Oral SCC most frequently affects the anterior tongue, followed by the floor of mouth, the gingiva and the alveolar mucosa, and is predominantly a disease of elderly males who have a long history of heavy tobacco smoking and alcohol consumption (1-3, 12). Other risk factors include betel nut chewing, use of smokeless tobacco, a diet low in vegetables and fresh fruits, as well as genetic predisposition (2, 13, 14). Exposure to environmental and occupational carcinogens, high-risk lifestyle, low levels of education and socioeconomic status, limited access to healthcare services, and in the South African context, consulting traditional healers as opposed to conventional medical practitioners are important factors that have an impact on the clinical course of oral SCC and its prognosis (1, 14).

In Europe and North America oral SCC affects the tongue in 20-40%, and the floor of the mouth in 15-20% of cases and together these oral mucosal sites account for about 50% of all oral SCC cases (14). In a study conducted in Portugal in 2007 by Dias and Almeida, it was found that the tongue was involved in 43% of the cases, followed by the floor of mouth (19%), the palate (7%), and the gingiva and retromolar trigone each about 7% (15). However, a study conducted in Pakistan in 2017 found that the most frequent sites affected by oral SCC were the buccal mucosa (36%), labial mucosa (26%), tongue (20%) and gingiva (18%) (16). This disparity in the results between cases in Asia and in Western countries is most probably related to geographic- and population- specific factors (14).

Although oral SCC is relatively uncommon in people aged 40 years and younger, in recent times there has been an increase in the reported incidence of the disease

affecting the tongue in younger people, particularly in females. It is still unclear whether the prognosis of oral SCC in young people is any different than in older people (1).

The 5-year survival rate of patients with oral SCC is about 50% with no gender differences, but black people have a lower 5-year survival rate than other races (14); and the oral SCC is at a significantly more advanced stage at time of diagnosis for black people than for other races. This racial disparity is probably owing to the fact that for cultural, educational or socioeconomic circumstances, black people delay to a greater extent seeking medical assistance than white people; and the fact that black people have more limited access to healthcare services than whites (14).

1.2.2 Aetiology

While there is a causal association between high-risk human papilloma virus (HPV) genotypes and a subset of cases of oropharyngeal SCC, there is no causal association between HPV and oral SCC. In contrast to HPV-cytopositive oropharyngeal SCC, HPV-cytopositive oral SCC are characterized by low HPV DNA copy numbers, by infrequent integration of HPV DNA within the cellular genome and by lack of expression of transcriptional activity of E6/E7 oncoprotein mRNA. Thus, even if HPV DNA is detected in oral SCC malignant cells, its presence is most probably not biologically significant (17, 18).

It is evident that oral SCC is either a monoclonal or an oligoclonal lesion arising from one or several stem/progenitor cell(s) in the basal layer of the oral epithelium that underwent cytogenetic alterations. Such a cell(s) acquires with time additional genetic changes and evolves into an expanding clone or clones of precancerized oral keratinocytes, thereby creating a field of precancerization in normal-appearing oral epithelium. Such a field of precancerization may manifest clinically as potentially malignant lesions such as leukoplakia or erythroplakia (19-21).

The genetically altered keratinocytes in the oral field of precancerization are at different stages of transformation, and once they acquire a critical number of genetic

lesions comprising a complete set of genetic mutations of a malignant phenotype, these cells will demonstrate enhanced fitness (competitive advantage) and selective growth advantage manifesting as increased survival and uncontrolled proliferation (18-20). Although multiple genetic and epigenetic alterations and dysregulated intracellular signaling pathways that are associated with the initiation and promotion of oral SCC have been defined, no molecular biomarkers that can predict with confidence which of the initially transformed keratinocytes in the oral epithelial field of precancerization will progress to acquire a fully malignant phenotype have been found. Likewise, no molecular biomarkers that can predict with confidence response to radiotherapy, or that can prognosticate survival, have been discovered (2).

Oral squamous cell carcinoma is characterised by considerable genetic heterogeneity, which influences biological behaviour, clinical course, response to treatment and prognosis. On a cellular level, Oral SCC is a complex structure of spatially disparate subclones which differ in cell population size, molecular profiles and phenotypic features. The size of each subclone is determined by the biological fitness of its cell population (survival, replication) and its selective growth advantage (22, 23); and the reciprocal communications between the different subclones influence each other's biological behaviour, and have an effect on tumour evolution, progression and response to chemo/radiotherapy (24).

In addition, oral SCC is characterised by diversity of its cell population comprising tissue specific cancer stem/progenitor epithelial cells, transient amplifying cancer cells, post-mitotic cancer cells at different stages of maturation and de-differentiated cancer cells, all of which contribute to the genetic heterogeneity of oral SCC (14).

The clinical manifestation of oral SCC is variable, and it may appear as leukoplakia, verrucous leukoplakia, erythroleukoplakia, erythroplakia, a necrotic ulcer with raised, irregular, indurated borders, or as a broad based exophytic mass with a surface texture that may be verrucous, pebbled or relatively smooth (12, 14).

1.2.3 Treatment Options

A number of treatment modalities are available for the treatment of oral SCCs, including resection (for early stage cancers), radiotherapy, chemotherapy, targeted therapy and immunotherapy, or a combination of these, either concurrently or in sequence. Surgery is preferred whenever possible, but advanced-stage disease usually necessitates a combined treatment program (2, 14, 25). The selection of a specific treatment modality is determined by disease-related factors such as the tumour-node-metastasis (TNM) staging system and histopathological characteristics; and by patient-related factors including age, general health, financial considerations, life-style and habits, and anticipated functional and cosmetic outcomes (21).

High-risk histological features including a poorly differentiated grade, perineural spread at the invasive front, lymphovascular invasion, tumour thickness, positive resection margins, extracapsular spread, and the presence of two or more positive regional lymphnodes are significant risk factors for locoregional recurrence and portend a poor prognosis (26, 27).

The American Joint Committee on Cancer (AJCC) published their 8th edition staging manual in 2017 (28). In their TNM staging system, T describes the size and location of the primary tumour; N the nature of locoregional lymphnode involvement; and M the status of distant metastasis. The information derived from an assessment of the TNM staging system determines both the clinical and pathological stage of the disease, which is then used for estimating the risk of recurrence, prognosis and survival, and is thus used for clinical decision making regarding different treatment options (3, 29). The AJCC TNM staging is shown in Table 1.

Cancer radiotherapy can be defined as the use of high-energy ionizing radiation with the intent to control tumour growth by killing cancer cells either directly through fatally injuring their DNA, or indirectly by promoting immunogenic cell killing mediated by cytotoxic T cells. Radiotherapy is described in terms of radiation dose,

fractionation and sequencing, and is used as either a definitive, adjuvant, neoadjuvant or palliative agent (30).

Definitive radiotherapy and concurrent chemoradiation therapy is practiced as a primary choice for patients with unresectable oral SCC, or those who cannot, or do not want to undergo surgery (30). Cisplatin may be administered concurrently with radiotherapy at 100 mg/m² for a total of 2-3 cycles depending on the radiation fractionation scheme. Cisplatin is a commonly used radiosensitizer that augments radiation-induced DNA damage and inhibits damaged-DNA repair, resulting in a more effective cancer cell killing (31, 32). Cisplatin exerts its cytotoxic effects by binding to the purine base of nuclear DNA and thus causing DNA damage and interfering with DNA replication and normal transcription. This mechanism induces apoptosis of rapidly replicating cancer cells (33, 34).

Adjuvant radiation therapy may be offered following primary surgery for advanced-stage disease when the histopathological features are indicative of high-risk of loco-regional recurrence. In addition, radiotherapy may be employed as a salvage treatment for persistent or recurrent disease, and is also an option in the palliative setting (3, 21, 35). In any event, the treatment modality chosen is selected by a shared decision-making process involving the oncologist, surgeon, and the patient.

The decision to follow surgical resection with post-operative radiotherapy (PORT) is based on the presence of high-risk features for loco-regional recurrence or for metastasis. Accepted high-risk factors that are indications for PORT include advanced stage disease as determined by the TNM staging system; the presence of involved surgical margins at the primary tumour site; and the presence of extranodal extension (ENE). On the other hand, there is no clinical evidence to support PORT in patients with low- risk of recurrence. (35, 36).

For definitive radiotherapy as a standalone treatment modality, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Version 3, recommends multiple suitable radiotherapy regimens for each involved anatomical site. For high-risk sites that include the primary tumour and involved

lymph nodes, a total dose of between 66 Gy (2.2 Gy per fraction) to 70 Gy (2.0 Gy per fraction) daily Monday to Friday over 6-7 weeks is recommended. A hyperfractionated regimen of 81.6 Gy over 7 weeks at 1.2 Gy per fraction twice daily, as well as a concomitant boost accelerated regimen are also accepted options. For low- to intermediate- risk sites that are suspected of subclinical spread, total doses ranging from 44-50 Gy (2.0 Gy per fraction) with 3D conformal radiotherapy or 54-63 Gy (1.6-1.8 Gy per fraction) with intensity-modulated radiation therapy are recommended (37). In comparison to conventional fractionation, hypofractionated radiotherapy in which the total dose of the radiation that is delivered is divided into fewer, but larger dose fractions (>2Gy), is associated with better clinical outcome, but also with increased potential of late radiation-induced toxicity (38).

For patients who have undergone surgery, the NCCN Clinical Practice Guidelines recommends PORT of 60-66 Gy (2 Gy per fraction) daily Monday to Friday for 6 to 6.5 weeks to high-risk sites with adverse histological features (37) and 44-50 Gy (2 Gy per fraction) to 54-63 Gy (1.6–1.8 Gy per fraction) for low- to intermediate- risk sites suspected of subclinical spread (37). The preferred interval time between resection and postoperative RT is less than or equal to 6 weeks (37).

According to the NCCN Guidelines, palliative radiotherapy should be considered in patients with advanced disease who have a poor performance status or who have widely metastatic disease and where curative intent is not appropriate, primarily for the relief or prevention of locoregional symptoms. There are no standard radiotherapy regimens for palliative treatment and such treatment should be tailored individually to relieve symptoms and avoid severe treatment toxicity. Some recommended NCCN radiotherapy regimens include 50 Gy in 20 fractions, 37.5 Gy in 15 fractions and 30 Gy in 10 fractions. (37).

The actual size of the field irradiated when targeting oral SCC routinely accommodates neighboring normal looking tissue surfaces. The reason for this is two-fold: the first, because these closest surrounding tissues may contain

subclinical disease; and the second to account for potential errors related to patient positioning, target location and instrument inaccuracy, that not infrequently occur in everyday radiation oncology clinical practice. For these reasons, the actual operational irradiation field is larger than the margins of the gross volume of the targeted SCC as calculated from imaging and clinical examination studies. It is reasonable to assume, therefore, that the inclusion of additional uninvolved tissue into the irradiated field may exaggerate the radiation-induced adverse biological reactions, thereby leading to increased tissue toxicity (21).

The NCCN Guidelines recommend radiation treatment be delivered either by intensity modulated radiotherapy (IMRT) or 3D conformal radiotherapy (3D CRT) techniques. These techniques make use of radiological imaging, such as computed tomography (CT) scans, to accurately target lesions with radiotherapy while minimizing radiation exposure to surrounding organs at risk (37). Institutes with older technological facilities and limited specialized staff may not have the relevant equipment or technical expertise to employ these advanced techniques, and may be reliant on older 2D radiotherapy techniques, which make use of fluoroscopic and standard X-ray modalities.

The NCCN guidelines recognize the equivalence of definitive radiotherapy and surgery for oral squamous cell carcinoma in many cases, with both achieving comparable overall survival rates. The choice between these two approaches often depends on factors such as the stage of the cancer, patient preference, cosmetic outcome and the surgeon's expertise. For advanced-stage disease, surgery is generally preferable, if the tumour is resectable (37).

Table 1: AJCC 8th edition TNM staging of oral cavity squamous cell carcinoma

T Category	T Criteria
Tx	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T1	Tumour less than or equal to 2cm and DOI less than or equal to 5mm
T2	Tumour less than or equal to 2cm and DOI greater than 5mm but less than or equal to 10mm, or tumour more than 2cm but less than or equal to 4cm and DOI less than or equal to 10mm
T3	Tumour greater than 4cm or any tumour size with DOI greater than 10mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease (lip) Tumour invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose), (oral cavity) Tumour invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumour as T4
T4b	Very advanced local disease Tumour invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery
DOI, depth of invasion	
N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-); or metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension

	and ENE (-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE (-); or metastasis in any node(s) with clinically overt ENE (+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE (-)

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, ENE (extra-nodal extension) should be recorded as ENE (-) or ENE (+).

M Category	M Criteria		
M0	No distant metastasis		
M1	Distant metastasis		

When T is...	When N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1,2,3	N1	M0	III
T4a	N0,1	M0	IVA
T1,2,3,4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Source: adapted from Amin et al., 2017. [29].

1.2.4 Radiation-induced toxicity

Many patients with oral SCC experience pain during the course of their disease and the pain appears to intensify as the disease progresses. About 70% of cases of cancer pains are caused by cancer-related factors such as invasion of nerves, bone and mucous membranes, by local inflammatory reactions and by superficial ulceration with secondary infection (2, 39).

Effective radiotherapy for oral SCC induces inevitable adverse side-effects that frequently may include oral mucositis, xerostomia, altered taste, dysphagia, dermatitis, fibrosis and osteoradionecrosis as well as a generalized feeling of dysfunction, suffering and distress (2, 39). These side-effects necessitate treatment and if unresolved may jeopardise the effectiveness of radiotherapy outcomes.

There are many factors that affect the development of radiation-induced toxicity, and include patient-related factors such as nutritional status, smoking during treatment and the presence of anaemia, as well as treatment-related factors such as the total dose of radiotherapy administered, the dose per fraction, whether or not concurrent chemotherapy is administered and the dose of the administered chemotherapy.

1.2.4.1 Radiation-induced mucositis

Oral mucositis is a radiation-induced, complex debilitating condition characterized by erythematous, atrophic, erosive or ulcerative painful lesions, that often become secondarily infected. The pain impairs physiological functions including sleep, speech, eating and swallowing, with consequent inadequate nutritional intake and associated weight loss; and with psychosocial dysfunction and reduced quality of life (40). Patients with severe oral mucositis are at risk of septicaemia and may require hospitalization for the management of life-threatening infection, dehydration, nutritional deficiency, and pain. Severe oral mucositis may necessitate de-escalation or interruption of the radiotherapy program with subsequent impaired anti-cancer treatment outcome (40-42).

Several systems have been used to grade the severity of oral mucositis including the Radiation Therapy Oncology Group (RTOG) system, the World Health Organisation (WHO) system, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and the Western Consortium for Cancer Nursing Research (WCCNR) system (41-43). Table 2 describes the RTOG scale, which is routinely used in the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital.

Table 2: Grading criteria for oral mucositis as per the RTOG classification system

Grade	I	II	III	IV
Signs and symptoms	Erythema	Patchy reactions (<1.5cm, non-contiguous)	Confluent mucositis (>1.5cm, confluent)	Ulceration, necrosis, bleeding

Source: adapted from Moon et al., 2017 (44)

Radiation-induced oral mucositis typically starts 5 days after the initiation of the radiotherapy treatment and peaks at 7 to 14 days later (40, 43). Initially the lesions are erythematous, and then progress to painful erosions and ulcers (40). The oral mucositis is a self-limited condition, persists during the duration of treatment and usually resolves between 4 to 6 weeks following the termination of radiotherapy (42, 43, 45).

The evolution of radiation-induced oral mucositis is mediated by inflammatory cytokines, chemokines, growth factors, reactive oxygen species and a variety of other inflammatory mediators released into the microenvironment by injured local endothelial, connective tissue and epithelial cells, and by locally recruited immunoinflammatory cells (42, 43, 45).

The treatment of radiation-induced oral mucositis is symptomatic (palliative) and includes cryotherapy, low-energy laser therapy and the use of anti-inflammatory, antibacterial, saline or sodium bicarbonate mouthwashes, topical analgesic agents, adhesive protective agents, topical or systemic antibiotics and systemic analgesics (41, 42, 46). Although these interventions may sometimes be effective, treatment outcome is unpredictable (40, 45).

Maintaining a good oral hygiene status with minimal load of dentogingival plaque is essential and is achieved by periodic professional scaling and polishing; and by personal effective gentle 'tooth' brushing with an ultra-soft toothbrush and fluoridated toothpaste, and with frequent mouth-rinsing with either saline or sodium bicarbonate solution. When the oral mucositis advances to become high-grade (severe) causing intense pain and interferes with sleep and everyday oral functions, then systemic pain control, nutritional support and prevention/treatment of secondary infection is necessary (indicated) (41-43, 46).

Radiation-induced injury to the oral mucosal membrane barrier, alterations to the salivary composition and flow, and dysregulation of local immuno-inflammatory responses, predispose the oral mucosa to microbial growth and colonization by bacteria and fungi, particularly gram-negative bacteria and *Candida albicans*. If present, such secondary infections promote local inflammatory reactions that further aggravate the signs and symptoms of the established mucositis (42).

Severe oral mucositis may be treated by swish-and-spit route of local anesthetic agents, opioid-based analgesic mouthwashes (i.e. 2% morphine mouthwash); anti-inflammatory agents such as corticosteroids, and anti-microbial agents. In case of oral candidiasis, topical administration of daktarin gel, amphotericin B or nystatin is necessary. Systemic administration of analgesics such as morphine to control the severe pain, and corticosteroids to reduce damaging immunoinflammatory reactions may be indicated (41, 42). Salicylic acid derivatives for the treatment of pain should be avoided owing to increased risk of bleeding. Maintaining a well-balanced nutritional diet, avoiding rough spicy food and abstaining from alcohol

beverages and tobacco smoking are important measures in the management of radiation-induced oral mucositis (41, 42).

When the course of the radiotherapy has been completed, the undifferentiated, slow-cycling, self-renewing epithelial stem cells, which contain the genetic information of the epithelium, and survived the radiation-induced damage, will re-establish the integrity of the injured epithelium. At the margins of the mucositis, the epithelial stem cells divide, giving rise to transient-amplifying daughter cells that enter the process of maturation, driving the operations of epithelial healing. This epithelial healing process occurs concurrently with connective tissue repair, bringing about complete regeneration (40).

1.2.4.2 Salivary gland dysfunction (xerostomia)

Radiation-induced damage to the major salivary glands (parotid, submandibular, sublingual) results in alterations to the volume, composition, consistency and pH of the secreted saliva, which becomes viscous and acidic; and in a reduction in the salivary flow, and in lubrication and anti-microbial capacities of the secreted saliva. All these generate serious ramifications that include dry mouth (xerostomia), burning-mouth sensation, predisposition to oral candidiasis and dental caries, difficulty and discomfort on eating and talking, and taste impairment (47-49).

The reduction in the salivary flow may start already during the first week of the radiation treatment, and may last for months, with some recovery of the salivary gland functioning occurring only 12-18 months post-radiotherapy. Not uncommonly, xerostomia becomes a persistent, irreversible radiation- induced complication (48, 49).

Current treatment options for xerostomia are palliative in nature and include using saliva substitutes that mimic natural saliva and are available in different forms, such as solutions, sprays, gels, lozenges; and homeopathic remedies such as olive oil and aloe vera gel. Maintaining a meticulous oral hygiene regimen by employing

both professional (scaling and polishing) and personal measures (tooth and interdental brushing) are essential in order to reduce the burden of dento-gingival bacterial plaque thereby preventing dental caries and oral mucosal infections (gingivitis, periodontitis); as are frequent professional and personal fluoride applications and twice daily mouth rinsing with chlorhexidine mouthwash, which are measures to combat dental caries, gingivitis and periodontitis (46, 48, 49).

If the radiation- induced salivary gland damage is not complete and the glands show some functional activity, stimulating salivary production by the residual operational salivary glandular tissue may be possible (48, 49). This can be achieved by mechanical manipulation of major salivary glands; by sucking acidic sugarless candies or by chewing gum containing xylitol, which has the capacity to stimulate saliva production (49); and by systemically administered sialagogic agents such as pilocarpine or cevimeline which are muscarinic-cholinergic agents, but these may have significant side-effects (47).

1.2.4.3 Radiation-induced dermatitis

Radiation-induced dermatitis is usually categorized into early (acute) and late (chronic) skin reactions, and the clinical manifestations of both are more severe in sun-exposed areas of the skin than in sun-protected areas. This is probably because the sun's ultraviolet radiation-related skin damage adds to the radiotherapy-induced damage; and although melanin is an effective absorber of ultraviolet radiation and thus confers some protection against sunlight induced skin damage, it appears that the high melanin content of dark-skinned patients does not confer protection against radiotherapy-induced skin reactions (50).

Early radiotherapy dermatitis is brought about by a radiation-induced acute inflammatory response; and is characterized by the following clinical features: pain, erythema, oedema, heat (rise in temperature in the affected area/s), melanin hyperpigmentation and ulcerations (50-53). The severity may range from mild erythema to necrosis. It usually starts with erythema and dry desquamation and

progress to brisk erythema and patchy moist desquamation, and then to blister formation, necrosis, and ulcers (Table 3) (54, 55).

Table 3: Classification of acute radiation dermatitis as per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3

Grade	1	2	3	4
Signs and symptoms	Faint erythema or dry desquamation	Moderate to brisk erythema or patchy dry desquamation, mostly confined to skin folds and creases; moderate erythema	Moist desquamation other than skin folds; pitting oedema, bleeding from minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; may have spontaneous bleeding from affected area

Source: adapted from Bray et al., 2016 (50)

Early radiation dermatitis usually develops within a few weeks after the start of the radiotherapy program, and may be painful, and in general resolves gradually over 2-3 weeks post-treatment (51). It affects up to 90% of patients undergoing radiotherapy, and a high-grade skin reaction may require interruption of the radiotherapy treatment, and this may negatively impact cancer treatment outcomes (50).

Late (chronic) radiation dermatitis appears three or more months post-radiotherapy and is characterized by the clinical features of xerosis, hyperkeratosis, telangiectasia, fibrosis, dyspigmentation and itchiness, some of which may be irreversible (51). The affected skin may become prone to secondary immunoinflammatory conditions such as eczema, contact dermatitis and other cutaneous allergic reactions; and may become sensitive to direct sunlight exposure (51).

Maintaining proper skin hygiene at all times is essential as it may minimize the development of early acute radiation-induced skin reactions; and may moderate the adverse effects of radiation-induced chronic reactions and favour healing (54, 56). The skin to be included in the irradiation field should be washed with lukewarm water and mild soaps that help keep the affected skin hydrated. This together with application of lipid-free hydrophilic moisturizers may have the capacity to avert some of the post-radiotherapy skin reactions (52).

Skin affected by radiation-induced dry desquamation, should similarly be treated with hydrophilic moisturizers; pruritis, irritation and itchiness with low-to-mild potency corticosteroids; and moist desquamation with either hydrogel or hydrocolloid dressings that maintain a wet environment over the damaged, de-epithelialized skin, and which have the capacity to improve patient comfort, to reduce the risk of secondary infection and to promote healing (52, 54, 55). The evolution of non-healing ulcers and full thickness skin necrosis mandates interruption of the radiotherapy program and referral of the patient for treatment to be provided by a multidisciplinary medical team that includes radiation oncologists, dermatologists, wound specialists and dedicated nurses (54, 55).

1.2.4.4 Trismus

Trismus refers to restricted mouth opening of $\leq 35\text{mm}$, and in the context of oral SCC may be brought about by direct tumour-invasion into masticatory muscles, by tumour-related inflammation and radiation-induced fibrosis affecting the temporomandibular joint (TMJ) and/or masticatory muscles, and by post-surgical scarring. Trismus hinders routine functional activities such as eating, speaking, kissing and maintaining proper oral hygiene, and negatively impacts one's mental well-being and quality of life (53, 57, 58).

Trismus is a late radiotherapy induced complication, typically peaking 12-18 months post-treatment (53), with a reported incidence ranging from 25% to 42% (57). The nature of the pre-radiotherapy surgery, whether there was hypomobility prior to radiotherapy, the size of the irradiated field, the oral subsite irradiated and the

nature of the administered chemotherapy, are all factors influencing the incidence and prevalence of radiation-mediated trismus (47, 56), and may account for the great variety in the reported incidence and prevalence rates of this phenomenon.

There is no consensus on treatment guidelines for post-radiotherapy trismus, thereby the management is empirical. It includes mechanical therapies such as simple exercises, guided manipulation of mandibular movements, and massages of the TMJ and of masticatory muscles; chemotherapeutics such as muscle relaxants, analgesics and anti-inflammatory agents; acupuncture for pain management and muscle relaxation; and for refractory cases, surgery (47).

The prevalence of pre-radiotherapy trismus in patients with oral SCC ranges between 35% (57) and 55% (58), and this may affect the accuracy of the reported incidence and prevalence of post-radiotherapy trismus, as it is not always possible to differentiate between pre and post-radiotherapy trismus. Therefore, when designing this research, at the time of writing the research protocol for this study, we have decided not to investigate the parameter of post-radiotherapy trismus.

1.2.4.5 Osteoradionecrosis

Osteoradionecrosis is a late uncommon complication of oral SCC-related radiotherapy that usually occurs 1-3 years post-treatment. The mandible with its more limited blood supply is by far more affected than the maxilla that is richly vascularised (53, 56, 59, 60). Clinical manifestations include pain, swelling, ulceration and necrosis of the local oral mucosa, suppuration, orofacial fistula, exposed necrotic bone, trismus, dysgusia, dysphagia and chewing and speech difficulties (47, 56).

The reported incidence of osteoradionecrosis when using two-dimensional conformal radiotherapy (2D-CRT) and 3D-CRT ranges from 13% to more than 20%, but with the use of the modern intensity modulated radiotherapy (IMRT) technique,

the incidence has dropped and ranges from 0 to about 8% (44, 61, 62). Radiation-induced damage to the bone vasculature and cellular network results in hypovascularity, hypocellularity and hypoxic microenvironment, with consequent impaired bone turnover, functionality, and healing. In turn, this subsequently may cause necrosis and possible secondary infection (44, 47, 63). Mild osteoradionecrosis is treated with frequent oral rinsing with saline and antimicrobial solutions, and with systemic antibiotics, local debridement and removal of superficial necrotic bone. Severe osteoradionecrosis may necessitate radical resection with microvascular reconstruction to provide well vascularized tissue (56, 64), and the use of hyperbaric oxygen (63, 64).

It is evident that there is a positive association between carious and periodontally compromised teeth present pre-radiotherapy and subsequent post-radiotherapy osteoradionecrosis (61, 64). Therefore, it is prescribed to extract all unrestorable carious and unsavable periodontally compromised teeth; and to treat existing periodontal diseases and other soft tissue inflammatory conditions before irradiating the mouth. Importantly, it is essential to establish an effective oral hygiene and dento-gingival plaque control regimen that has the capacity to reduce the development of oral soft tissue inflammatory/infective conditions such as gingivitis, periodontitis, mucositis and candidiasis which favour the development of osteoradionecrosis (64); and to stop tobacco smoking which interferes with tissue healing (65).

1.3 Objectives of this study

With this background in mind, the purpose of my study is to provide information about oral SCC as it relates to the 8th edition AJCC prognostic stage group at the time of radiotherapy, to the mucosal sites affected, to the tumour histopathological and clinical features and to the characteristics of the radiotherapy regimen employed.

1.3.1 Primary objectives

To describe and characterise the demographics and other patient-specific relevant information as well as the clinico-pathological features of the tumour in the patient population.

1.3.2 Secondary objectives

To describe and characterise the radiation-induced toxicity in the patient population.

CHAPTER 2: RESEARCH METHODOLOGY

2.1 Materials and methods

This cross-sectional, retrospective study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital. The study reviewed patient records of all cases of patients diagnosed with oral cavity SCC treated with radiotherapy in the Department of Radiation Oncology over the 6-year period 2014-2019.

Inclusion criteria comprised all new patients presenting to the Department with histopathologically confirmed SCC of the oral cavity and its various subsites, between January 1st 2014 and December 31st 2019.

Exclusion criteria included all other head and neck cancer sites, such as oropharyngeal, nasopharyngeal and salivary gland cancers, among others. In addition, histologically confirmed cancers of the oral cavity other than SCC, such as adenocarcinoma, lymphoma, melanoma and sarcoma, among others, were excluded as well.

Since many of the patients were referred from many hospitals, medical clinics and dental clinics throughout Gauteng Province to the Department at a clinically advanced stage, it is often not possible to assess the presence of a pre-existing potentially malignant oral condition, and such information is not routinely provided by the referring clinicians; therefore the status of premalignant oral conditions was omitted from the study.

The study period was limited to the 6-year period between January 1st 2014 and December 31st 2019 as the worldwide Covid-19 pandemic resulted in multiple nationwide shutdowns in 2020 which disrupted transportation and affected patient accessibility to healthcare facilities, including to our Department. During 2021, CMJAH suffered a fire on its premises which resulted in its closure for several

months, further limiting access for patients to radiation treatment. during this period, As a result, during this period fewer patients presented for assessment and treatment to our Department.

Age, sex, race/ethnicity, stage group, histopathological grade (well-differentiated, moderately-differentiated, poorly-differentiated), radiation-induced side-effects; smoking and alcohol consumption, and treatment-intent were recorded and statistically analysed.

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (Clearance Certificate No. M220869) (Appendix 7.1) and received permission from Ms G Bogoshi, the CEO of Charlotte Maxeke Johannesburg Academic Hospital, Gauteng Department Health and Dr D Ramiah, the Head of the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital and the University of the Witwatersrand, Johannesburg.

2.2 Statistical analysis

Basic and inferential statistics were performed to report on the results and on the associations between the variables. The results were presented in the form of tables and graphs using the total numbers for categorical data and the mean and standard deviation for continuous data.

Categorical variables such as gender, site of cancer, grading, side effects, type of treatment and staging were presented using frequencies and percentages. When associating categorical variables such as gender and race to the demographics like smoking and alcohol, the Fishers exact test was used. When comparing the race and gender to the age of the participant, the Fishers exact test was used.

When comparing the continuous variable such as age with gender and race, the z-test was used to compare the mean age to gender and race. The statistical package SPSS version 24.0 for windows (SPSS, Chicago, IL, USA) was used to perform all the statistical analysis.

CHAPTER 3: RESULTS

3.1 Introduction

This chapter will describe the results of the study as it relates to the objectives set out in the previous chapter.

A total of 119 patients with histologically confirmed oral cavity SCC were seen at the Department during the study period of January 1st 2014 and December 31st 2019.

In terms of the primary objectives of this study, the patients' demographic information was analysed in relation to their smoking and alcohol consumption, as well as to the clinico-pathological features of the malignancy, namely oral subsite affected and clinical stage at presentation.

The clinical TNM stage was determined by the clinician on duty at the time of patient assessment, using physical examination and results of imaging reports, according to the eighth edition of the AJCC staging system. Only 25 patients (21%) underwent post-operative radiotherapy (data not shown). Therefore, for most of the patients in the study, the pathological TNM could not be calculated, analysed and related to other variables of interest, and thus the pathological TNM was excluded from the data analysis.

In terms of the secondary objectives, the radiation-induced toxicities noted in the patient records were described and characterized.

3.2 Oral cavity subsite involved

The study investigated the different subsites in the head and neck population of oral cavity cancers that were treated in the Department. Table 4 and Figure 1 below show the distribution of the cancers among the various subsites.

There were 27 patients (23%) in whom more than one subsite was affected by oral SCC. These subsites were adjacent to each other, for example, floor of the mouth

and ventral anterior tongue or floor of the mouth and lingual alveolar mucosa. It was not possible to determine whether these lesions at multiple, but adjacent oral subsites were individual oral SCC of multifocal origin or were a manifestation of local (lateral) spread of monofocal origin. Thereby, although the study population comprised 119 patients, there were 143 oral subsites involved. However, for practical reasons our data analysis was done in relation to the 119 patients (Tables 4 and 5). Furthermore, as at the time of radiotherapy, in 19 patients both the tongue and the adjacent floor of mouth were concurrently affected. Therefore, it was decided to form a category that combines these two adjacent subsites and to term it 'tongue and floor of mouth'. The same applies to the 'retromolar trigone and buccal mucosa', 'floor of mouth and retromolar trigone', 'floor of mouth and alveolar mucosa', 'buccal mucosa and alveolar mucosa' and 'retromolar trigone and gingiva', and their distribution is represented in Table 4 and Figure 1.

The differences in histopathological grading by oral subsites are shown in Table 5. Most of the oral SCC at the different subsites were moderately-differentiated.

Five of the patients (4.2%) had no documented histopathological grade, 10 (8.4%) had no documented prognostic stage group, and for one patient (0.8%) the anatomical subsite was not recorded. This missing data was omitted from the tables.

Table 4: The age and gender of the 119 patients with oral SCC in relation to the oral mucosal subsite involved

Site	Age (years)		Number of patients		Gender, N=119			
	Mean	Range	N	%	Male (84)		Female (35)	
					n	%	n	%
Tongue	61	43-79	35	29	30	36	5	14
Floor of the mouth	60	40-76	30	25	20	24	10	28
Tongue & floor of the mouth	57	40-73	19	16	16	19	3	9
Retromolar trigone	62	50-72	12	10	7	8	5	14
Palate	63	49-74	6	5	3	4	3	9
Labial mucosa	43.5	26-63	4	3	1	1	3	9
Retromolar trigone & buccal mucosa	58	49-67	3	3	1	1	2	6
Buccal mucosa	43.5	42-45	2	2	2	2	-	-
Alveolar mucosa	58	49-67	2	2	-	-	2	6
Floor of mouth & retromolar trigone	61	58-64	2	2	2	2	-	-
Floor of mouth & alveolar mucosa	60	60	1	1	-	-	1	3
Buccal & alveolar mucosa	81	81	1	1	-	-	1	3
Retromolar trigone & gingiva	73	73	1	1	1	1	-	-

Values as per departmental files. Value totals may not add up to 100% due to rounding errors and missing file data. Missing file data not shown in the table. The dash sign, – , denotes a zero value.

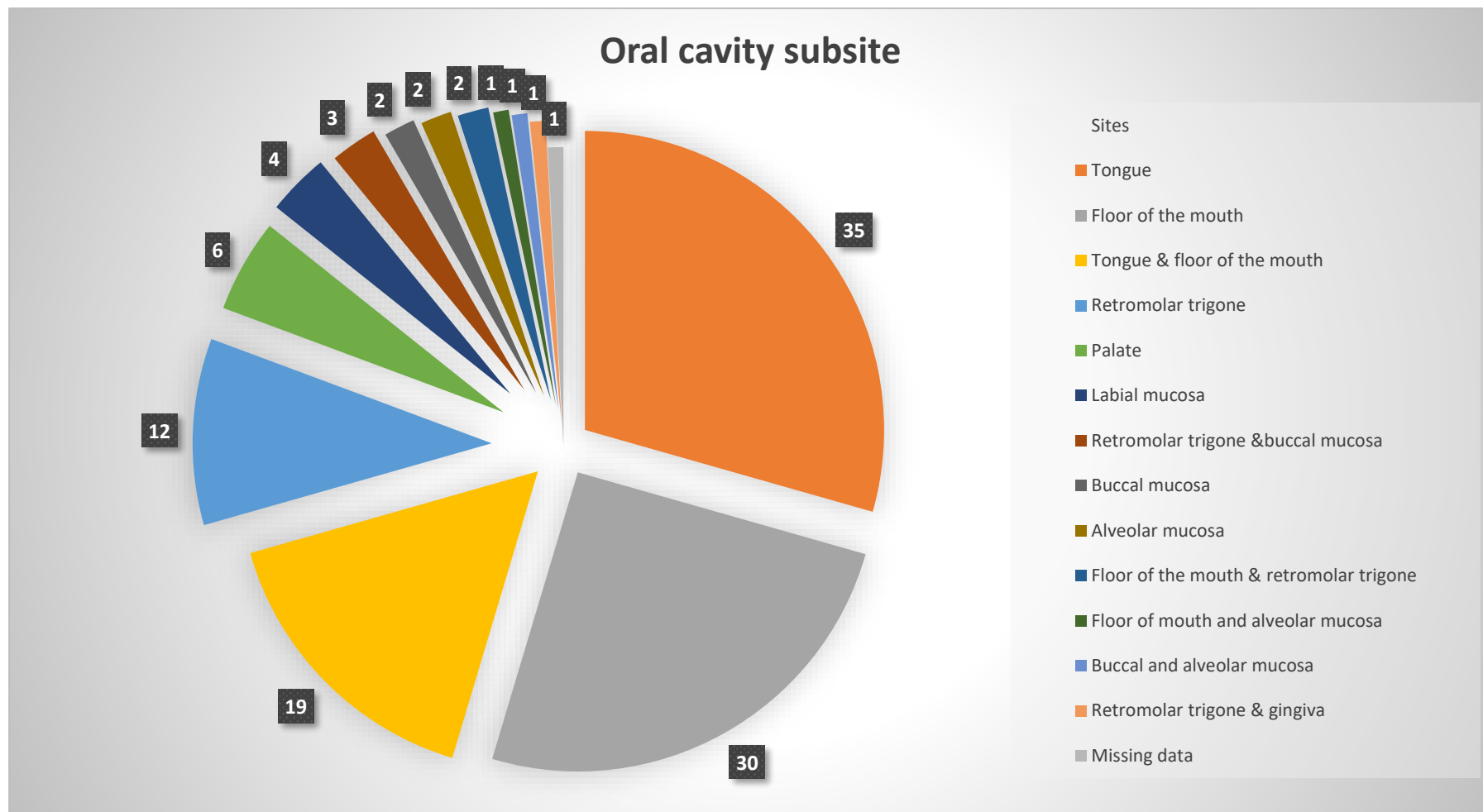


Figure 1: Distribution of oral mucosal cavity subsite affected

Table 5: The histopathological grade and clinical stage in relation to the oral mucosal subsite treated

Sites (N)	Histopathologic grading						AJCC Prognostic Stage Group					
	Well differentiated		Moderately differentiated		Poorly differentiated		II		III		IV	
	N	%	N	%	N	%	N	%	N	%	N	%
Tongue (35)	-	-	31	89	3	9	5	14	1	3	27	77
Floor of the mouth (30)	1	3	27	90	2	7	2	7	4	14	23	77
Tongue & floor of the mouth (19)	-	-	15	79	4	21	-	-	-	-	16	84
Retromolar trigone (12)	-	-	9	75	1	8	-	-	3	25	8	67
Palate (6)	1	17	4	67	-	-	1	17	4	67	-	-
Labial mucosa (4)	1	25	3	75	-	-	-	-	1	25	2	50
Retromolar trigone & buccal mucosa (3)	-	-	2	67	-	-	-	-	-	-	2	67
Buccal mucosa (2)	-	-	2	100	-	-	-	-	-	-	2	100
Alveolar mucosa (2)	-	-	2	100	-	-	-	-	-	-	2	100
Floor of mouth & retromolar trigone (2)	-	-	2	100	-	-	-	-	-	-	2	100
Floor of mouth & alveolar mucosa (1)	-	-	1	100	-	-	-	-	-	-	1	100
Buccal & alveolar mucosa (1)	-	-	1	100	-	-	-	-	-	-	1	100
Retromolar trigone & gingiva (1)	-	-	1	100	-	-	-	-	-	-	1	100

Values as per departmental files. Value totals may not add up to 100% due to rounding errors and missing file data. Missing file data not shown in the table. The dash sign, –, denotes a zero value. None of the patients in the sample had stage I disease.

3.3 Demographics

Of the 119 patients with primary oral SCC included in this study, 84 (71%) were males and 35 (29%) were females. At the time of radiotherapy, the age of the females ranged from 26 to 81 years (61.76 mean), while male age ranged from 36 to 79 years (58.7 years mean) (Table 6). The tongue was the most frequent subsite affected by SCC (N=35, 30%) followed by floor of mouth (N=30, 25%), and the tongue and floor of mouth combined (N=19, 16%). Tables 4 and 5 show the relation between the different subsites on the one hand and the patient's gender, age, histopathological grading and AJCC prognostic stage groups on the other hand.

The percentage of males who smoked (79/84=94%) and consumed alcohol (61/84=73%) was significantly higher than the percentage of females who smoked (23/35=66%) ($p<0.01$) and consumed alcohol (49%) ($p=0.012$) (Table 7). The percentage of black patients who consumed alcohol (55/80=69%) and those who smoked (68/80=85%) was similar to the percentage of white patients who consumed alcohol (16/26=62%) ($p=0.51$) and those who smoked (25/26=96%) ($p=0.07$) respectively.

Among the black patients, the most frequently affected oral subsite was the floor of mouth (29%; 23/80), followed by the tongue (25%; 20/80) and the combined tongue and floor of mouth category (18%; 14/80). In contrast, among the white patients the most frequently affected oral subsite was the tongue (50%; 13/26) followed by the floor of the mouth (20%; 5/26) and the combined tongue and floor of mouth category (8%; 2/26). Altogether, these subsites accounted for 78% (20/26) of the presentations of the white patient population.

In terms of the gender distribution, the most commonly affected subsite for males was the oral tongue, 36% (30/84), followed by the floor of mouth (24%; 20/84), the tongue and floor of mouth category (19%; 16/84) and retromolar trigone, 8%. For females, the most common site affected was the floor of mouth (28%; 10/35), followed by the anterior tongue and retromolar trigone, both accounting for 14%

(5/35). The tongue and floor of the mouth together only affected three patients or 9% of the female population (Table 4).

There were significantly more males than females with oral SCC, male (M): female (F) = 2.4:1. The M:F ratio in black patients was 2.5:1 and in white patients 1.6:1 and this difference was not statistically significant ($p=0.32$). Black patients at the time of radiotherapy were at a younger mean age (58.85 years) than white patients (63.96 years). This mean age difference was statistically significant ($p=0.021$), and the proportion of black patients with advanced disease (clinical stage group III and IV) was higher (70/80=88%) than the proportion of white patients with advanced disease (19/26=73%) ($p=0.037$).

3.4 Treatment intent

All 119 patients included in this study were treated with two-dimensional conformal radiotherapy (2D-CRT). Post-operative chemoradiotherapy was administered to 21 of the 119 patients (18%); four of 119 patients (3%) received post-operative radiotherapy without concurrent chemotherapy; 67 of 119 patients (56%) received definitive chemoradiotherapy with curative intent; and 18 of 119 patients (15%) received definitive radiotherapy without concurrent chemotherapy. Eight of 119 patients (7%) received palliative radiotherapy without concurrent chemotherapy. Treatment-related data for one patient (0.8%) was not recorded.

For both post-operative, and definitive radiotherapy regimens administered with curative intent, doses to the high-risk targets volumes comprised either 66 Gy in 33 fractions or 70 Gy in 35 fractions. For post-operative curative regimens, the dose and fractionation depended on high-risk histopathological features, such as residual disease, positive margins and extra-nodal extension, among others.

Typically, the palliative radiotherapy regimens comprise either 30 Gy in 10 fractions or 20 Gy in 5 fractions, with the particular palliative regimen depending on the extent

of the disease and the patient's performance status. One patient in the series received 30 Gy in 15 fractions, but this was due to the patient's deteriorating general condition and a decision to stop his initially curative regimen early.

In all cases, cisplatin at a dose of 70mg/m² administered three-weekly was the cytotoxic chemotherapeutic/radiosensitiser agent used. This dose is lower than that recommended by NCCN, but due to high patient volumes and hospital bed shortages limiting ability to admit patients for medical management should supportive care be required, it is considered acceptable in our setting. Contra-indications to concurrent chemotherapy in patients treated with curative intent included age greater or equal to 70 years, patients experiencing renal dysfunction with a creatinine clearance of less than 60 ml/min, and patients with a poor performance status.

Table 6: Distribution of age, gender, histopathological grade, and clinical stage for the entire study population

Characteristic	Sample population (119)	
	n	%
Gender		
Males	84	71
Females	35	29
Histopathological grading		
Well-differentiated	3	3
Moderately-differentiated	101	85
Poorly-differentiated	10	8
AJCC Prognostic Stage Group		
I	-	-
II	8	7
III	9	8
IV	92	77
Age (years)	Sample population (119)	
	Mean	59.59
	Median	60
	Range	26-81
	Standard deviation	9.949
Males (years)		
	Mean	58.70
	Median	59
	Standard deviation	9.349
Females (years)		
	Mean	61.76
	Median	62.5
	Standard deviation	11.409

Values as per departmental files. Value totals may not add up to 100% due to rounding errors and missing file data. Missing file data not shown in the table. The dash sign, –, denotes a zero value.

Table 7: Gender in relation to history of alcohol consumption and smoking for the entire study population

Characteristic	Alcohol consumption		Smoking	
	N	%	N	%
Males All males (84)	61	73	79	94
Females All females (35)	17	49	23	66

Values as per departmental files.

3.5 Radiotherapy- induced toxicity

The most common radiation-induced toxicity was dermatitis (N= 74, 62%) followed by oral mucositis (N= 72, 61%) and dysphagia (N= 25, 21%). The relation between the various side-effects on the one hand and the patient's gender, age, and prognostic stage group on the other hand, is shown in Table 8, and Figures 2 and 3. There were no documented cases of osteoradionecrosis, and every patient reported at least one radiation-induced toxicity. Some of the 119 patients experienced more than one radiation-induced toxicity; and the radiation-induced toxicity in relation to treatment intent is shown in Table 9.

Table 8: Frequencies and percentages of radiation-induced toxicities/side-effects in relation to age, gender, and AJCC prognostic group stage

Radiation-induced toxicity/side effect	Age (years)		Total Number of patients (119)		Gender				AJCC Prognostic Stage Group					
	Mean	Range	N	%	Male (84)		Female (35)		II (8)		III (9)		IV (91)	
					N	%	N	%	N	%	N	%	N	%
Dermatitis	57.84	26-79	74	62	59	70	15	43	8	100	8	89	50	55
Mucositis	58.25	26-76	72	61	57	68	15	43	8	100	9	100	48	53
Xerostomia	58.73	47-69	16	13	13	15	3	9	3	38	4	44	8	9
Altered taste	61.43	52-75	15	12	12	14	2	6	2	25	1	11	9	10
Dysphagia	56.4	26-79	25	21	22	26	3	9	2	25	3	33	17	21
Fibrosis	56.2	42-72	22	18	18	21	4	11	2	25	4	44	12	13
Haematologic	54.58	40-72	11	9	9	11	2	6	2	25	2	22	6	7

Values as per departmental files. Value totals may not add up to 100% due to rounding errors and missing file data. Missing file data not shown in the table. The dash sign, – , denotes a zero value. There were no patients with stage I disease. There were no recorded instances of osteoradionecrosis. None of the patients reported experiencing no radiation-induced toxicities.

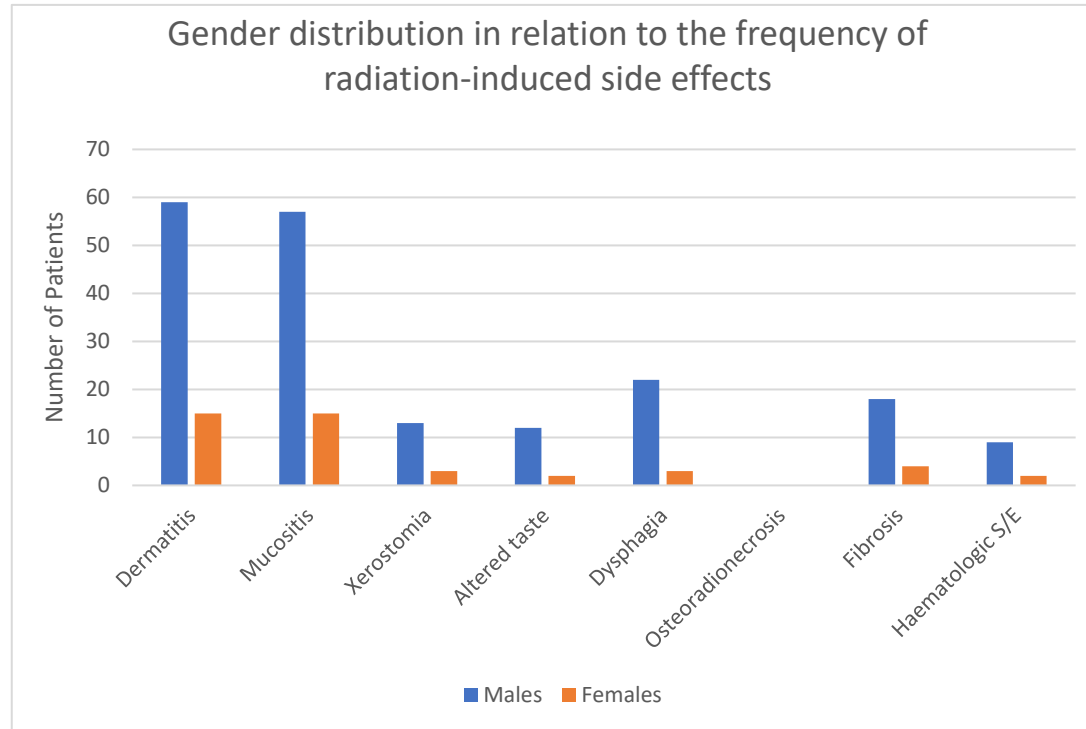


Figure 2: Breakdown of radiation-induced toxicities in relation to gender

Table 9: Radiation- induced toxicities/side-effects in relation to treatment intent

Radiation-induced toxicity/side effect	Post-operative radiotherapy		Definitive radiotherapy		Definitive chemoradiotherapy		Palliative radiotherapy	
	N	%	N	%	N	%	N	%
Dermatitis	21	28	7	9	41	55	2	3
Mucositis	19	26	7	10	41	57	2	3
Xerostomia	5	31	2	13	7	44	1	6
Altered taste	4	27	2	13	7	47	1	7
Dysphagia	3	12	3	12	19	76	-	-
Fibrosis	9	41	1	5	10	45	1	5

Values as per departmental files. Value totals may not add up to 100% due to rounding errors and missing file data. Missing file data not shown in the table. The dash sign, – , denotes a zero value. There were no recorded instances of osteoradionecrosis. None of the patients reported experiencing no radiation-induced toxicities.

CHAPTER 4: DISCUSSION

4.1 Introduction

The study described the relationship between the patients' demographic characteristics, the tumour histopathological and clinical features, the oral cavity subsite affected and the treatment-induced toxicities. The results of our study confirm previous findings that oral SCC is generally a disease of middle-aged or elderly people, and more frequently observed in males than in females and may affect any oral subsite (12, 66, 67). In this study, the mean age of the study population at the time of radiotherapy was 60 years, similar to the mean age of 62 years reported in the USA (1, 67); and the M:F ratio was 2.4:1, similar to M:F ratio of 2:1 reported in the United Kingdom (67). It is probable that oral SCC affects males more frequently than females because the former indulge in high-risk habits more than the latter (14). In this study, the percentage of males (94%) that smoked was significantly higher than that of females (66%) ($p<0.01$), and the percentage of males that consumed alcohol (73%) was significantly higher than the percentage of females who consumed alcohol (49%) ($p=0.012$) (Table 7).

4.2 Clinico-pathological features of oral cavity SCC

In our study population, the tongue was the most affected oral subsite (35/119=30%) followed by the floor of the mouth (30/119=25%), and by floor of the mouth together with the tongue occurring concurrently as a distinct site category (19/119=16%). Taken together the floor of the mouth and the tongue accounted for 71% (84/119) of the oral subsites affected by SCC. This is consistent with the findings in the literature, that taken together oral SCC of the tongue and the floor of the mouth are the most frequently affected oral sites, constituting more than 60% of all oral SCC (14, 66). The distribution of oral SCC among the various oral subsites are shown in Table 4.

In general, disease-specific survival rates differ between patients with oral SCC who have been diagnosed at an early stage of the disease and those at advanced stage of the disease; and between patients with different oral mucosal subsites affected by SCC, with the various subsites showing different group stages at the time of diagnosis (68, 69). However, it is accepted that the overall five-year survival rate of people with oral SCC ranges from 55% to 70% (25, 70, 71).

With regard to the prognostic group stage at the time of radiotherapy, the relationship between the stage and tumour subsite show that both the tongue and the floor of the mouth are associated with advanced stage disease (stages III and IV) (Table 5), which is indicative of poor prognosis. How this has influenced the prognosis of our patients is unknown because the design of the study did not allow for any investigation about disease-specific and overall survival rates.

A study by Jehn et al.,(69) in Germany, found that SCC of the buccal mucosa and alveolar mucosa are associated with the highest survival rate (68%) followed by anterior tongue (63%) (69), with a mean overall 5-year survival rate of about 55%. However, since the authors included in their investigation the anatomical sites of the base of the tongue and oropharynx, their reported overall mean survival rates need to be interpreted with caution. In Taiwan, on the other hand, where the habit of chewing betelnut is common, the buccal mucosa (35%) followed by the tongue (30%) and the alveolar mucosa (16%) are the most frequent oral subsites affected by SCC; and the highest mortality rate is associated with the hard palate followed by the alveolar mucosa and the retromolar trigone (26).

The variance in the incidence and prevalence of oral SCC at different subsites, and in the mortality/survival rates associated with the different subsites that have been reported from different countries may be attributed to different country-specific population groups, which are dissimilar with regard to genetic predisposition, culture, life-style and dietary habits (26).

In the United States of America (USA), the overall 5-year survival rate for patients with oral SCC is 67%, but if the disease is diagnosed at an early stage it can reach 85% (72). In general, oral SCC is diagnosed at a significantly more advanced clinical stage in black people than in white people (14, 66), and in the USA the overall 5-year survival rate for black people is 51% while for white people is 69% (72).

The fact that in our Department oral SCC is diagnosed late in its clinical course is worrying and frustrating as it can easily be identified at an early stage by self-examination, and by routine professional examination conducted by dentists, oral hygienists and medical doctors (73).

4.3 Radiation-induced tissue toxicities in relation to our study

Regardless of the body site irradiated, fatigue, manifested as physical tiredness, emotional exhaustion, mental weariness and/or lack of mental energy, and nausea/vomiting are common side-effects of radiotherapy (50). In this study, 13% of patients experienced fatigue and 8% nausea (data not shown). All were treated symptomatically with good outcomes.

It has been reported that for patients receiving radiotherapy for their head and neck cancer, up to 60% may experience dysphagia and up to 75% may experience taste impairment (48). Likewise, in this study, 21% (25/119) of patients complained of dysphagia and 12% (15/119) of taste alterations (Table 8).

4.3.1 Radiotherapy-induced oral mucositis

Oral mucositis occurs in up to 90% of patients who receive radiotherapy with concurrent chemotherapy for oral SCC (41-43), and it affects more frequently the non-keratinised than the keratinized oral mucosa (40). The incidence and severity of radiation-induced mucositis is directly related to the characteristics of the radiotherapy course received (accumulative dose, fractionation, duration), and to

the characteristics of the adjunct anti-cancer chemotherapeutic agents. Patient-related risk factors include old age, female gender, genetic predisposition, xerostomia, tobacco smoking, alcohol consumption, poor oral hygiene, increased dento-gingival bacterial load and low neutrophil counts (40-43, 46).

In this study, 72/119 patients (61%) experienced oral mucositis, in line with the prevalence reported in the literature as described above. The proportion of males affected by oral mucositis (68%) was statistically significantly greater than the proportion of females affected (43%) ($p=0.035$) (Table 8). The proportion of white patients (69%) compared to black patients (55%) was not statistically significant ($p=0.418$) (Table 8). Radiation-induced oral mucositis most frequently affected patients that received definitive chemoradiotherapy (Table 9). All patients were treated according to the guidelines described below and no patients needed to be hospitalized.

4.3.2 Salivary gland dysfunction

Salivary gland dysfunction is reported to affect up to 80% of patients, who receive radiotherapy for their head and neck cancer (49, 74). In this study, 13% ($N=16/119$) of the patients complained of xerostomia, in accordance with the reported incidence range cited in the literature. For unknown reasons, the proportion of males affected by xerostomia (15%) was greater than the proportion of females affected (9%); but the proportion of black patients (11%) and white patients (15%) affected by xerostomia was very similar (Table 8). Radiation-induced salivary gland dysfunction most frequently affected patients who received definitive chemoradiotherapy (Table 9).

4.3.3 Radiation-induced dermatitis

In this study, 62% (74/119) of patients experienced radiation-induced dermatitis, but there was no need to modify the radiotherapy regimen (Table 8). Radiation-induced dermatitis was most frequently observed in patients who had received definitive

chemoradiotherapy (Table 9). According to the Departmental records, none of the patients included in this study developed radiation-induced skin cancer.

In our study, a similar percentage of black patients ($49/80=61\%$) and of white patients ($16/26=62\%$) developed radiation-induced dermatitis, suggesting that as previously reported in the literature (50), the increased cutaneous melanin in black people does not provide additional protection against radiation-induced dermatitis (50). The proportion of black patients ($16/80$, 20%) that developed fibrosis was not significantly greater than the proportion of white patients ($4/26$, 15%) that developed fibrosis ($p=0.65$).

4.3.4 Osteoradionecrosis

Not a single patient included in our study experienced osteoradionecrosis. This is not surprising as osteoradionecrosis is uncommon and our study sample was small; and as osteoradionecrosis is a late radiation-induced side-effect occurring many months post-radiotherapy, even if some of our study patients did eventually experience osteoradionecrosis, they may likely have sought medical assistance at local facilities and thereby not even presented at our department.

4.4 Limitations of the study

The filing system in the Department is paper-based. Each patient opens a patient file on presentation, and these physical files are stored centrally and managed by clerks. Only authorized staff are permitted to remove them from their storage unit, usually for clinical care. When removed, these files must be physically 'signed out', and likewise 'signed back in' when returned. Although this system is in place to mitigate patient files going missing, files are nonetheless susceptible to potential misplacement. Although unlikely, the misplacement of files from their storage area may potentially result in underreporting of the actual number of patients that were presented to the Department over the study period.

Due to the nature of a paper-based filing system, important individual medical reports, including staging investigations and histological reports, are usually attached to the patient file. Nonetheless, these individual reports are liable to be misplaced and get lost and may account for the occasional 'missing data' documented in this study.

The record keeping in the patient files is reliant on accurate and clear documentation by the relevant registrar in the clinic attending to the patient. Difficult-to-read handwritten reports and errors in documentation may occasionally be in clinical and radiological reports. In addition, important positive and negative findings in both the history and physical examination sections, such as the consumption of alcohol or history of smoking, and the presence or absence of radiation-induced toxicities, may not be rigorously documented at every patient interaction. Such occasional errors are natural and may occur due to fatigue on the part of the healthcare provider, poor compliance and co-operation by the patient, as well as due to language barriers.

This study highlights the critical importance of accurate and comprehensive documentation of patients' personal details, health status, disease features, clinical course, and treatment outcomes. Proper documentation is essential for producing meaningful research. The introduction of electronic medical records and digital clinical support systems is expected to address many of these research-related challenges in the future.

The results of this study regarding late radiation-induced toxicities (osteoradionecrosis, salivary gland dysfunction, late skin reactions) may be compromised. Firstly, because it is a cross-sectional and retrospective study and therefore does not reflect incidence of toxicities but rather only prevalence. Secondly, since the study period comprised only a limited number of years (2014-2019) and radiation-induced late toxicities may occur many years post-radiotherapy, these findings may not be accurate, as some late toxicities may not yet have manifested. Thirdly, an unknown number of patients may have had their late radiation-induced complications managed at other Departments (Maxillofacial and Oral Surgery, Oral Medicine, ENT or Dermatology) either in our Academic

Hospital or at their local facilities, such that some patients may not have presented at our Department. Therefore, the complications may not have been recorded in our Departmental files. Lastly, some of our patients may have been lost to follow-up owing to problems of transportation, accessibility, or costs. Thus, the results of this study regarding radiation-induced late complications should be regarded with caution.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The primary objective of this study was to investigate the demographic, clinical and pathological characteristics of patients with oral cavity SCC who presented to the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital between January 1st 2014 and December 31st 2019. Demographic and social information, clinical staging and pathological features were analysed and radiation-induced toxicities were recorded and described.

The results of this study confirm that oral SCC is predominantly a disease of middle-aged or elderly people, is more frequently observed in males than in females, and may affect any oral subsite (1, 12, 67). Our results are also in line with previous findings that show that men with oral cavity SCC smoked and consumed alcohol to a greater degree than did women, and that this may be the reason for the observed gender disparity seen in the literature (14, 67).

In our study population, the tongue was the most affected oral subsite followed by the floor of the mouth, and taken together the floor of the mouth and the tongue accounted for 71% (84/119) of the oral subsites affected by SCC. This is consistent with the literature and findings elsewhere in the world (14, 66). In our study, both the tongue and the floor of the mouth were associated with advanced stage disease (stages III and IV), and most of the oral SCC at the different subsites were moderately-differentiated.

The secondary objective of this study was to characterise the radiation-induced toxicities experienced by this patient population as a result of their treatment. All patients in this study were affected by one or more radiation-induced toxicities. Dermatitis, oral mucositis and dysphagia were the most frequently observed adverse side-effects, and some of the patients experienced more than one radiation-induced toxicity. All toxicities were managed as per Departmental protocols.

5.2 Recommendations

This study is important as it shows similarities in our patient population when compared to international reports in terms of the demographic patient profile and the clinic-pathological features of the patients' oral cavity squamous carcinomas.

It is worrying and frustrating that oral cavity SCC is diagnosed late in its clinical course as it can be easily detected at an early stage by self-examination, and by routine examination conducted by trained medical professionals (73).

In order to address the incidence of this disease in South Africa, public health interventions at a population-based level could be considered. Public campaigns could be employed to increase the awareness of this disease entity among at risk target populations. The aim would be to decrease the prevalence of high-risk habits such as smoking and alcohol consumption, to decrease the stigma associated with cancer and to increase presentation of high-risk groups at healthcare facilities for routine assessment and check-up in order to promote improved oral hygiene.

This study further opens channels to investigate the relationship and impact between patient demographics and overall survival in patients with oral SCC.

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7. Appendix

7.1 Human research ethics committee certificate



UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr Gal Feller

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220869

NAME: Dr Gal Feller
(Principal Investigator)
DEPARTMENT: Radiation Oncology
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: *An observational retrospective demographic study of patients with oral squamous cell carcinoma treated with radiation therapy at Charlotte Maxeke Johannesburg Academic Hospital (2014-2019)*

DATE CONSIDERED: 26/08/2022

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr F. Mahomed and Prof R. Khammissa

APPROVED BY: 
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 20/10/2022

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 **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

20/10/2022
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES