A RETROSPECTIVE STUDY OF HISTOLOGICALLY DIAGNOSED INTRA-ORAL LESIONS WITHIN UGU DISTRICT, KZN, SOUTH AFRICA.

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A research report submitted to the School of Oral Health Sciences, Faculty of Health Science, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Dentistry, in the branch of Maxillofacial and Oral Surgery.

Johannesburg, Gauteng, South Africa.

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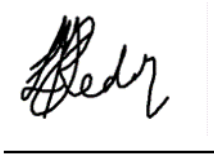
Declaration

I, Larisha Yashoda Reddy, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Science in Dentistry at the University of Witwatersrand, Johannesburg. It has not been submitted before any degree or examination at any other University.



Dr. Larisha Yashoda Reddy

On this 02 day of November 2023.

I certify that the study contained in this research report has the approval of the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg. The Ethics clearance certificate number is M 220620.

Dedication

This research report is dedicated to my unwavering support system, my parents, Mr. G.C. Reddy and Mrs. D.M. Reddy. Their valuable guidance and encouragement have been my place of solace.

Abstract

Introduction:

The oral cavity is exposed to a magnitude of physical and chemical trauma, carcinogenic agents and microbial pathogens that may cause a wide spectrum of oral lesions. These oral lesions may appear as benign, potentially malignant, or malignant thereby requiring biopsies to determine histopathological features to confirm a diagnosis. Oral lesions have the potential to hinder the quality of life for the afflicted patient. The patients' speech, mastication, swallowing may be affected with the occurrence of oral dysesthesia. With the confirmation of a positive malignant biopsy, the afflicted individual will have to endure the possible side effects of chemotherapy and radiation.

In global studies, the prevalence of oral lesions may vary amongst different countries, geographical areas, ethnicities, cultural practices, and social habits.

Aim:

To identify the different types of intra-oral lesions and the prevalence of malignant oral lesions within UGU district, Kwa- Zulu Natal (KZN).

Objectives:

1. To identify the different types of intra oral lesions and characterise by demographics.
2. To determine the prevalence of malignant oral lesions within UGU district, KZN.
3. To determine the association between patients' social habits and the development of the most common intra oral lesions, with the differentiation of malignant vs non-malignant oral lesions.
4. To assess the concordance of a clinical differential diagnosis and histopathological diagnosis.

Study design and Methodology:

A quantitative, retrospective case review of dental patient files and histopathological reports of the four selected hospitals in UGU were analysed from January 2016 to August 2022. One hundred and thirty-four patient records were reviewed. Data collected included patients' age, gender, comorbidities, social habits, differential diagnosis, and histological diagnosis. The data was analysed using a free open-source statistical software program called "R".

Study results:

One hundred and thirty-four patients met the criteria of this study. The age of patients ranged between seven and eighty-seven (M= 46.37; SD= 20.77). There were 81 females (60.4%) and 53 males (39.6%).

Benign lesions had represented 67.2% (N: 90) of the intra oral biopsies, with the remaining 32.8 %, (N:44), representing malignant lesions.

The most common lesions presenting in UGU district were fibrous epulis (N: 15, 11.2%), pyogenic granuloma (N:36, 26.9%) and squamous cell carcinoma (N:37, 27.6%). No statistical relation was proven between ethnicity, sex, and social habits with the benign lesions of fibrous epulis and pyogenic granuloma. Statistical relation was proven between squamous cell carcinoma and ethnicity, gender, and social habits.

A substantial level of concordance (agreement) was proven with the Kappa Statistic of 0.7437, thereby indicating a good general knowledge of intra-oral lesions amongst the dentist performing the intra oral biopsies within UGU district.

Conclusion:

Fibrous epulis, pyogenic granuloma and oral squamous cell carcinoma had been identified as the three most common lesions in UGU, KZN, representing 65.7% of the confirmed biopsy results. Fibrous epulis and pyogenic granuloma had shown no statistical association to ethnicity, gender, alcohol consumption and smoking. In this study, oral squamous cell carcinoma had shown statistical association to white males and consumption of alcohol and smoking. This study has demonstrated the diversity and prevalence of intra-oral lesions within the rural district of UGU, KZN, South Africa as compared to global studies.

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Nomenclature

Clinical differential diagnosis	CDD
Degree of freedom	DF
GJ Crooks Hospital	GJCH
Human immunodeficiency virus	HIV
Histopathology report	HR
Human research ethics committee	HREC
Kwa-Zulu Natal	KZN
Lichen planus	LP
Murchison hospital	MH
National health research database	NHRD
Oral lesion	OL
Oral mucosal lesion	OML
Oral squamous cell carcinoma	OSCC
Pyogenic Granuloma	PG
Port Shepstone Regional Hospital	PSRH
St. Andrews Hospital	SAH
Squamous cell carcinoma	SCC
Tuberculosis	TB
United States of America	USA
World Health Organisation	WHO

Chapter 1

Introduction/Background

The oral cavity can give a unique understanding of an individual's general health (Mohan et al., 2016). The orofacial area is exposed to a magnitude of physical and chemical trauma, carcinogenic agents and microbial pathogens that cause a broad variation of lesions (Kamble et al., 2017; Saleh et al., 2017). Thus, the oral mucosa acts as a defensive barrier against these injurious agents. The undergraduate training of a dentist prepares the clinician to perform meticulous clinical examinations of the orofacial structures, thereby allowing the identification of the most common to the rarest of lesions (Da Silva et al., 2018). Oral mucosal changes such as an altered appearance in colour, texture, size, and location from the general appearance of healthy oral mucosa will raise the index of suspicion for further investigation (Williams et al., 2008).

Not all changes of the oral mucosa are considered an abnormality. Exceptions such as tori, exostosis, carious teeth lacking soft tissue attached tissue could be considered an abnormality but does not require a biopsy. A dental clinician should explore and evaluate if a lesion requires a biopsy before treatment. Identification of possible irritant factors should be removed, and the lesion should be observed for approximately 14 days before proceeding with a biopsy if required (Kumaraswamy at al.,2012).

A differential diagnosis is formulated, based on oral mucosal changes and a detailed medical history, but it is with a biopsy that a definitive diagnosis will be provided (Williams et al., 2008). The frequency of oral mucosal lesions (OMLs) varies between 10.8% to 81.3% amongst international studies (Kansky et al., 2018).

In recent years, the World Health Organization (W.H.O), has published global reviews that have shown oral health has greatly improved in the general population of many countries, but there is still a significant problem amongst the underprivileged in developing and developed

countries (Petersen, 2003). As a developing country, South Africa has strived to provide sustainable health services to the greater parts of the country but there have been shortfalls in providing dental treatment for the underprivileged. Thereby resulting in a system limited to pain relief or emergency care (Petersen et al., 2005).

W.H.O had performed numerous epidemiological surveys and socio-epidemiological studies relating to the burden of dental disease. Through these studies and surveys, diminished oral health had a significant influence on the overall health of an individual. Poor oral health results in the increase of oral bacteria that are involved in the development and progression of dental diseases, resulting in an individual displaying premature loss of teeth, oral mucosal lesions such as oral ulcers, gingival hyperplasia and even carcinomas when combined with the use carcinogenic agents, i.e., alcohol consumption, tobacco use and betel nut chewing. (Petersen et al., 2005). These lesions may be associated with a systemic or chronic disorder in the individual, as seen in the presentation of necrotising gingivitis, pseudomembranous candidiasis and herpes labialis in immune compromised patients and the presentation of intra oral Kaposi sarcoma lesions amongst patients with a CD4 count < 200 cells/mm3 (Sousa et al., 2020; Malele et al., 2019; Petersen et al., 2005).

Chapter 2

Literature Review

Oral lesions (OLs) are described as an “abnormal alteration in the surface appearance, colour, expansion or loss of the integrity of the oral mucosal surface” (Feng et al., 2015). Oral lesions, can present as benign growths, thickening of the buccal mucosa, that may require no active treatment, such as linear alba, but there may be other lesions that present with significant pathology that will require immediate dental management. Over years of dental research, there has been particular importance placed on “potentially malignant oral disorders which may progress into malignancy” (Feng et al., 2015; Funk et al., 2002).

2.1. Malignant and potentially malignant disorders:

Developing countries around the world have identified oral cancer as a paramount health problem. Oral cancer, if left untreated, is a fatal disease. Oral cancer has been ranked sixth globally due to its increasing prevalence amongst the developing countries (Arotiba et al.,2010). Squamous cell carcinoma (SCC) has been identified as the most diagnosed malignant neoplasm of the oral cavity and represents 90% of all orofacial malignancies (Saini et al.,2019). The prognosis of oral cancers differs significantly between each anatomical site, such as the carcinoma of the lip having a better prognosis than that of base of the tongue or gingiva (Mehrotra et al., 2008).

Rautava et al. (2007) hypothesized that the development and prognosis of oral malignancies can be explained by the epithelia from which the lesion originated from. Each type of epithelium namely keratinized masticatory mucosa, non-keratinized lining mucosa and specialised mucosa of the oral cavity, has a significant different cellular protein content, molecular characteristics, and cellular turnover rates. Rautava et al. (2007) depicted lesions originating from non-keratinized epithelia were more prevalent and supported the theory that

non-keratinized lining epithelium was less defensive and susceptible to external trauma, carcinogenic agents, and microbial pathogens.

Oral squamous cell carcinoma (OSCC) is a historic factor of morbidity and mortality. The incidence rate of OSCC varies widely by geographic location. For example, oral cancer in India is a serious health concern, which accounts up to 40% of all malignancies (Saini et al., 2019). Approximately, 90% to 95% of studies pertaining to oral cancer have identified tobacco and alcohol consumption as a main risk factor for oral cancer, but a study based on the Indian population by Saini et al. (2019) has recorded habits such as the use of smokeless tobacco, chewing of pan and gutkha (a form of chewing tobacco mixed with crushed betel nut, spices, paraffin wax and slaked lime) as a potential risk factors. These habits have induced mucosal changes following prolonged contact of the carcinogens with the mucosa.

2.1.1. Common potentially malignant lesion disorders:

The predominant potentially malignant oral disorders associated with the oral cavity are leukoplakia, erythroplakia, erythroleukoplakia, lichen planus and oral submucous fibrosis (Maymone et al., 2019). A potentially malignant disorder, such as leukoplakia and erythroplakia, is described as "morphically altered tissue in which oral cancer is more likely to occur than it's apparently normal tissue". A potentially malignant disorder, i.e., Lichen planus and oral submucous fibrosis, "is a nonspecific state associated with a significant increased risk of cancer" (Pawar and de Souza, 2010).

Leukoplakia is characterized as a "white plaque of questionable risk". With non-specific histology such as "atrophy, hyperplasia and epithelial dysplasia", thus demonstrating a variable behavioural pattern, but the proclivity for malignant mutation (Warnakulasuriya et al., 2007).

The greatest potential of malignant transformation has been seen in erythroplakia (Kameswari et al., 2020; Maymone et al., 2019). The clinical presentation of erythroplakia is described as a "red fiery patch that cannot be characterized clinically or pathologically as another definable disease" (Warnakulasuriya, 2018).

A relatively common potentially malignant mucosal disorder is erythroleukoplakia or previously known as speckled leukoplakia. The main characterization of erythroleukoplakia is the association of white areas scattered with red mucosal alterations such as atrophy.

Compared to leukoplakia and erythroplakia, erythroleukoplakia presents with an irregular margin and in many cases with pain due a colonisation by candidal hyphae (Warnakulasuriya, 2018; Mehrotra et al., 2008; Warnakulasuriya et al., 2007).

Lichen planus (LP) is described as the presence of "white lace-like reticular lesions with or without erosive atrophic lesions" (Radochova′ et al., 2021). Numerous studies have reported that LP may present with a low malignant transformation rate (0.74%), while social habits such as smoking have shown a greater rate of malignant transformation (Offen & Allison., 2022; Radochova′ et al., 2021).

Oral submucous fibrosis (OSF) is defined as a "chronic disorder characterised by fibrosis of the lining mucosa of the upper oral cavity, oropharynx and upper third of the oesophagus" (Warnakulasuriya et al.,2007). A study conducted by Srivastava et al. (2019), reported 25.77% of OSF lesions transformed into OSCC. This indicates the high risk of malignant transformation amongst OSF lesions.

2.2. Common non-neoplastic oral lesions

Pyogenic granuloma:

Pyogenic granuloma (PG) is described as "inflammatory hyperplasia of a large range of nodular growths of the oral mucosa" (Sharma et al., 2021). Research has shown that 75% of pyogenic granulomas have a predilection for the gingiva with the most common site being the interdental papilla. There are many stimuli for the formation of PG's, such as injury, local irritation, hormonal factors, and certain drugs (Sharma et al., 2021).

Mucocele:

Mucoceles are "benign salivary gland lesions" that can emerge in any area of the "mucosal surface of the oral cavity", although the lower lip has been the most frequently documented site of involvement (Jose et al., 2018).

Fibrous epulis:

Ohta and Yoshimura (2021) described fibrous epulis (FE) as a type of "inflammatory fibrous hyperplasia of the gingiva". It is clinically described as an "asymptomatic, exophytic, smooth-surfaced or focally ulcerated mucosal coloured mass". FE displays fluctuating growth rates. There is no definitive origin to the development of FE, but similar to PGs, local irritants

such as ill-fitting dentures, dental restorations and poor oral hygiene have been identified as causative determinant (Ohta and Yoshimura, 2021).

2.3. The significance of histopathological diagnosis of oral lesions.

Oral lesions may show similar clinical features, such as the appearance and positioning of another oral lesion. For example, the differential diagnoses of an oral polypoid lesion include pyogenic granuloma, peripheral ossifying fibroma; hemangioma and Kaposi sarcoma. Due to these similar clinical features, the dentist or specialist may establish a clinical differential diagnosis (Mota-Ramírez et al., 2007).

Histopathological analysis is the "gold standard" for diagnosis of OLs (Soyele et al., 2019; Kumaraswamy et al., 2012). The American Academy of Oral and Maxillofacial Pathology has stated that "any abnormal tissue that has been removed from the oral and maxillofacial area should be submitted to an Oral Pathologist for a histopathological analysis, however confident the clinician may be with the diagnosis" (Kumaraswamy et al., 2012).

Through a biopsy, a diagnosis can be formulated (Mota-Ramírez et al., 2007). Histopathological analysis of biopsied specimens has become a key diagnostic instrument that is strongly guided by a good clinical diagnostic examination, a thorough description of the oral lesion, diagnostic tests such as radiographic and haematology reports that are submitted by the dentist (Alhindi et al., 2019; Poudel et al., 2019; Kumaraswamy et al., 2012).

Data collection bases and studies can provide valuable information for dentists in South Africa to acknowledge the prevalence of certain oral lesion and tumours within the population, thereby assisting in raising awareness and lead to possible early detection of potentially malignant to malignant lesions by clinicians. When a differential diagnoses is deduced, it becomes a valuable asset in determining the nature of biopsies, leading to an accurate and swift diagnosis, resulting in a favourable and quick treatment plan for the patient. With the collaboration of clinical data, demographic characteristics and histopathological analysis, a definitive diagnosis can be formulated (Poudel et al., 2019).

South Africa is recognized as a developing country and as such, the health sector is overwhelmed by the lack of infrastructure, shortage of health care personnel, supplies and the inundation of patients requiring treatment. South Africans are faced with a term "double

burden of disease", as seen with low-income nations such as the rest of Africa and Asian countries such as India (Mohan et al., 2016). The rise of infectious disease such as Human Immunodeficiency Virus (HIV), Tuberculosis (TB), lifestyle diseases such as diabetes, cancer, lupus, epilepsy have been associated with an increased occurrence of oral lesions amongst affected patients. The presenting oral lesions may be the result of an adverse reaction to the pharmaceutical or medical regimen or as an immune reaction (Malele et al., 2019; Moodley & Wood, 2015; Amanat & Zahedani, 2013).

The social habits of individuals, such as smoking and chewing of tobacco, consumption of alcohol, chewing of betel nut have proven to show a synergistic effect in a heightened risk for the development of potentially malignant oral disorders (Chher et al., 2018; Kamble et al., 2017).

The orofacial area has exhibited many diverse types of lesions. It has been conveyed in previous research (Al- Wesabi et al., 2021), that most oral and maxillofacial lesions are benign and necessitate no particular treatment, but some lesions may present with significant pathology. It is this specific pathology that may be malignant or potentially malignant that may exhibit oral epithelial dysplasia with amplified stages of "severity, tissue atrophy and/ or hyperplasia" (Feng et al., 2015). Benign odontogenic tumours i.e., ameloblastoma, odontoma, etc., have been diagnosed at late expansive stages. The possible reasons for late diagnosis could be due to patients presenting with no initial symptoms such as pain, inaccessibility of health facilities, cultural beliefs and miseducation of dental related lesions. Aggressive odontogenic neoplasms, such as ameloblastomas, require wide resections with devastating ramifications in adolescents with respect to orofacial development. (Bilodeau and Seethala, 2019; Mamabolo et al., 2011; Vohra et al., 2009).

Oral lesions have the potential to hinder the quality of life of the afflicted individual thereby resulting a decreased standard of health, comfort, and happiness. Oral lesions can severely affect mastication, swallowing, speech, oral dysesthesia (Feng et al., 2015). It is to be noted that there has been a significant rate of malignant transformation of potentially malignant disorders (Al-Wesabi et al., 2021). Amagasa et al., (2011) has reported a "0.13% to 17,5 % rate of transformation of potentially malignant oral leukoplakia" lesions to a malignant lesion over an observed period of 1 year to 30 years. Nonhomogeneous erosive leukoplakia lesions have shown the highest rate of malignant transformation of 21.4 % (Amagasa et al., 2011, Amagasa et al., 2006). What has consistently been reported is, the data suggests that

occurrence or rate of transformation of a malignant lesion depends on the country of where the study is performed, cultural habits of the population under investigation and the frequency and method of tobacco use and alcohol consumption (Amagasa et al., 2011). Early identification and histopathological diagnosis will play a crucial role in implementation of treatment management and a prognostic outcome.

2.4. South African epidemiological studies on the prevalence of histologically confirmed diagnoses of intra-oral lesions.

Epidemiological studies on the prevalence of histology confirmed oral lesions are few, and those performed are based in the USA, India, parts of Asia and Europe (Alhindi et al., 2019). There are two known epidemiological studies based on intra-oral lesions in South Africa, which are currently based on the Western Cape Province population and the greater area of Johannesburg, Gauteng (Pontes et al., 2020; Khammisa et al., 2014). Research conducted by Pontes et al (2020), has shown the pervasiveness of oral lesions in relation to higher serum cotinine levels. Cotinine constitutes the main metabolite of nicotine, which is also known to be the addictive chemical that tobacco products are composed of. Cotinine has a "longer half-life when compared to nicotine", thereby making cotinine a reliable biomarker for tobacco exposure (Pontes et al., 2020). The study conducted by Pontes et al (2020), confirmed an association between higher cotinine serum levels (above 15ng/ml) had a higher occurrence of OMLs as compared to lower cotinine serum levels.

The second study conducted by Khammissa, R.A. et al., (2014), displayed the significant difference between African and Caucasian persons diagnosed with OSCC with regards to clinical, epidemiology and histopathological features of the disease, based within the larger part of Johannesburg. Through limited international epidemiological research, studies have shown that the prevalence of oral lesions diversify amongst different countries and areas of the world, but also clinical parameters may vary according to geographic areas, ethnicities, specific high-risk habits and cultural practices (Izgi et al., 2021; Khammissa et al., 2014; Patel et al., 2011). Surveying the distribution of oral lesions within specific geographical populations of a country will aid in the understanding of the prevalence and characteristics of OLs. This ultimately, will promote early diagnosis and essentially create health care programs for the communities affected (Al-Wesabi et al., 2021).

It will be crucial to survey the South African population in different provinces of the country to provide base line data about the prevalence and clinical presentation of oral lesions amongst the vast ethnicities of the South African population.

This proposed research study shall expand the knowledge of the prevalence of OLs in specific geographical regions of KZN. Thereby providing enlightenment in the organisation process of pertinent treatment and preventative programs by identifying potential etiological components within the population group (Saleh et al., 2017).

Chapter 3

Aims and Objectives

3.1. Aim

To identify the different types of intra-oral lesions and the prevalence of malignant oral lesions within UGU district, KZN.

3.2. Objectives

1. To identify the different types of intra oral lesions and characterise by demographics.
2. To determine the prevalence of malignant oral lesions within UGU district, KZN.
3. To determine the association between patients' social habits and the development of the most common intra oral lesions, with the differentiation of malignant vs non-malignant oral lesions.
4. To assess the concordance of a clinical differential diagnosis and the histopathological diagnosis.

Chapter 4

Materials and Method

4.1. Ethical clearance

This study involved the assessment of human patient records and required ethics approval. Application for ethics approval were submitted to two ethical bodies due to the study being conducted in KZN., i.e. The University of Witwatersrand Human Research Ethics Committee (HREC) and the National Health Research Database (NHRD). The University of Witwatersrand HREC granted ethics clearance: Certificate No.: M220620 (Appendix A). NHRD granted ethical approval, Certificate No.: KZN 202207_032 (Appendix B) on submission of "Gatekeepers letter" from the UGU district manager (Appendix C).

Permission to carry out the study was obtained from all heads of involved institutions (Appendix D, E, F, G). All information gathered from the study was treated with confidentiality. The patients' details were assigned a cryptic number by the primary researcher.

4.2. Inclusion Criteria:

The study population was based on patients who presented with intra-oral lesions, that had attended the dental departments of Port Shepstone Regional Hospital (PSRH), Murchison Hospital (MH), St. Andrews Hospital (SA) and G.J. Crooks Hospital (GJCH).

Odontogenic, non-odontogenic, oral mucosal lesions and bony intra-oral lesions were included.

Patients from the age of one were included within the study, provided that medical consent was obtained from the parent or guardian prior to procedure commencing. No children under the age of one had presented for treatment for intra-oral lesions within the facilities.

4.3. Exclusion criteria:

Exclusion of patient records that have incomplete medical history, no record of social habits and inconclusive diagnosis.

4.4 Study design:

This study is a quantitative, retrospective case review of patient dental records and histological reports of dental patients that have attended the dental clinics of PSRH, MH, SAH and GJCH during the period of 1 Jan 2016 till 31 August 2022.

4.5. Data collection:

Patient files were reviewed for data collection, and in addition, the histopathology reports from SA Path Care were assessed. Data was collected onto an excel spreadsheet representing the sex, age, ethnicity, comorbidities (clinical factors), lifestyle habits such as, smoking, drinking, chewing of carcinogenic agents, differential diagnosis of clinicians performing the biopsy, histopathology diagnosis and differentiation of malignant or non-malignant lesion (Appendix H). All patient records were given a cryptic number to protect the patient's identity.

4.6. Study population and sample size:

The study was based on patients that have attended dental facilities at PSRH, GJCH, MH and SAH. Patient records with histological reports from 1 Jan 2016 till 31 August 2022 were analysed to identify patients that have undergone biopsy procedures. A sample size of a minimum of 132 biopsies was required for this study, with the margin error of 5%, confidence level of 95%, population size of 200 and population proportion of 50%.

4.7. Data analysis:

Data was captured on an excel spreadsheet, (Appendix H), which was then later imported into "R" for further analysis.

Descriptive statistics of categorical data such types of lesions, sex, ethnicity, comorbidities, smoking, drinking, chewing of carcinogenic agents were measured using frequencies and percentages. Continuous variables such as age were described using measures of central tendency, such as median when non normal and mean when normally distributed.

The Chi- square test was used to assess association between categorical variables, such as to determine if there is an association between the development oral mucosal lesion and patients' social habits and if so the association to cancerous (malignant) oral lesions.

Kappa Statistic was used for the measurements that are continuous. Bland-Altman plots to assess agreement.

4.8. Limitations of the study:

Due to SARS- Covid 19 pandemic, there was a limitation on the number of elective procedures, such as biopsies, which were performed.

Incomplete medical records.

Lost or misplaced files.

Chapter 5

Results

Out of one hundred and eighty-nine patients that had been identified as registered dental patients, that had undergone an intraoral biopsy within their respective dental facilities, only one hundred and thirty-four patient records met the inclusion criteria.

Eighty-one patients were female (60.4%) and fifty-three were male (39.6%).

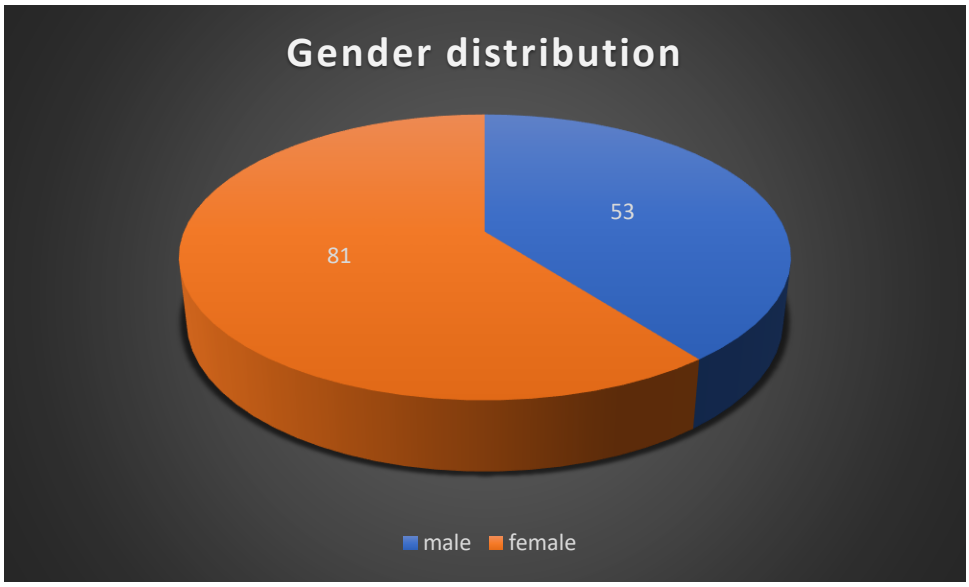

Figure 5.1: Gender distribution of intra-oral biopsies performed in the UGU district of KZN.

Table 5.1: Description of intra oral lesion study population.

VARIABLES	FREQUENCY	PERCENTAGE %
Gender		
Female	81	60.4
Male	53	39.6
Age (mean, std)	46.37 (20.77)	
Social Habits		
Smoking	30	22.4
Alcohol consumption	28	20.9
Chewing of carcinogenic agents	1	0.7
Comorbidities		
Hypertension	48	35.8
HIV positive	22	16.4
Diabetes	18	13.4
Dyslipidemia	10	7.5
Arthritis	3	2.2
Epilepsy	2	1.5
Congenital disorder: Marfan Syndrome	1	0.7
Ethnicity		
African	111	82.8
Indian	11	8.2
Caucasian	10	7.5
Coloured	2	1.5
Malignant /Benign lesion		
Benign lesions	90	67.2
Malignant lesions	44	32.8

Table 5.1 describes the study population by frequency account. As per the first objective of this research, the oral lesions of patients that met the inclusion criteria was characterised by demographics and comorbidities. The median age was 46.37 years. The comorbidities of study population were analysed at identification and biopsy of intraoral lesions. Subsequent diagnosis of comorbidities was not included in study. The highest noted comorbidity was hypertension (35.8%).

Thirty patients (22.4%) of the study population were smokers, twenty-eight patients (20.9%) consumed alcohol and only one patient (0.7%) chewed betel nut (areca catechu, a type of palm tree net).

Of the one hundred and thirty-four patients, patients of African ethnicity depicted the highest number of intra-oral lesions within UGU, that being a total number of one hundred and eleven (82.8%); followed by people of Indian heritage (n= 11 ,8.2%); Caucasians (n=10, 7.5%) and Coloured (n=2, 1.5%).

The lesions were divided into malignant and benign (non-malignant) lesions. Benign lesions were the most histopathologically reported lesions (n= 90, 67.2%). Histopathologically reported malignant lesions represented forty-four (32.8%) of the total study population.

Table 5.2: Chi-squared test of association between malignant and benign intra-oral lesions with gender.

Variables	Malignancy frequency		Hypothesis
	Benign	Malignant	H0: no association between sex and malignancy. H1: there is an association between sex and malignancy. $\chi^2 = 15.894\,; df = 1; p < 0.001$ Reject the null hypothesis and conclude that there is a relationship between the male sex and malignancy.
Female	65	16	
Male	25	28	
	Residuals		
Female	1.44	-2.05	
Male	-1.78	2.54	

Table 5.3. Chi-squared test association between malignant and benign intra-oral lesions with ethnicity.

Variables	Malignancy frequency		Hypothesis
	Benign	Malignant	H0: no association between race and malignancy. H1: there is an association between race and malignancy. $\chi^2 = 16.451\,; df = 3; p = 0.0009$ Reject the null hypothesis and conclude that there is a relationship between Caucasian (white) patients and malignancy. (Caution: small frequencies in some categories).
African	80	31	
Coloured	1	1	
Indian	8	3	
White	1	9	
	Residuals		
African	0.63	-0.90	
Coloured	-0.30	-0.42	
Indian	-0.2	-0.3	
White	-2.2	3.2	

Table 5.4. Chi-squared test of association between malignant and benign intra-oral lesions and alcohol consumption.

Variables	Malignancy frequency		Hypothesis
	Benign	Malignant	H0: no association between alcohol consumption and malignancy. H1: there is an association between alcohol consumption and malignancy. $\chi^2 = 28.534\,; df = 1; p < 0.001$ Reject the null hypothesis and conclude that there is a relationship between alcohol consumption and malignancy.
Nil alcohol consumption	83	23	
Consumed alcohol	7	21	
	Residuals		
Nil alcohol consumption	1.40	-2.00	
Consumed alcohol	-2.72	3.89	

Table 5.5. Chi-squared test of association between malignant intra-oral lesions and smoking.

Variables	Malignancy frequency		Hypothesis
	Benign	Malignant	H0: no association between smoking and malignancy. H1: there is an association between smoking and malignancy. $\chi^2 = 50.789\,; df = 1; p < 0.001$ Reject the null hypothesis and conclude that there is a relationship between smoking and malignancy.
Non-smoker	86	18	
Smoker	4	26	
	Residuals		
Non-smoker	1.93	-2.76	
Smoker	-3.60	5.15	

Table 5.6. Chi-squared test of association between malignant intra-oral lesions and chewing of carcinogenic agents.

Variables	Malignancy frequency		Hypothesis
	Benign	Malignant	H0: no association between chewing of carcinogenic agents and malignancy. H1: there is an association between chewing of carcinogenic agents and malignancy. $\chi^2 = 2.061\,; df = 1; p = 0.1511$ Fail to reject the null hypothesis and conclude that there is no evidence of a relationship between chewing of carcinogenic agents and malignancy. (Caution small frequencies in category).
Chewing of carcinogenic agents	0	1	
Nil Chewing	90	43	

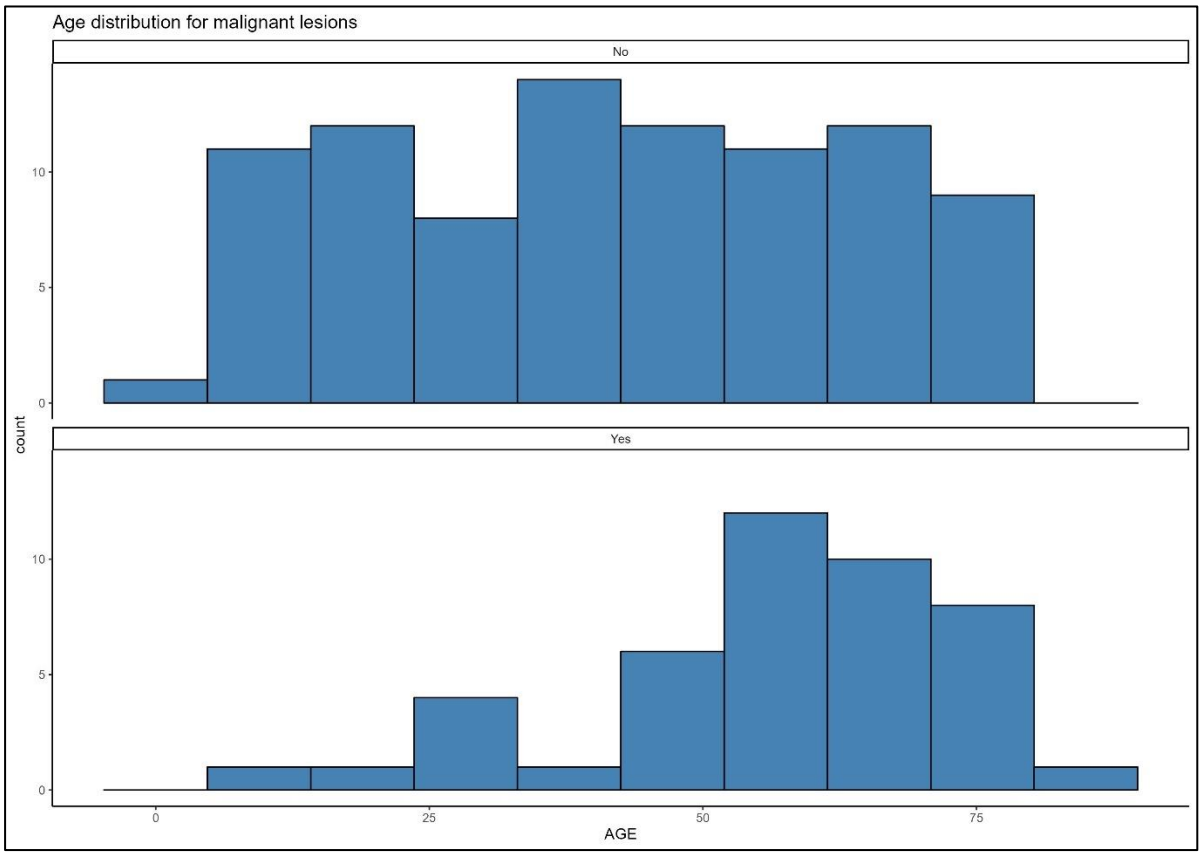

Figure 5.2: Histogram depicting the age distribution of benign (NO) and malignant (YES) intra-oral lesions within UGU district.

Table 5.7: Identification of the varying types of intra-oral lesions by histopathological diagnosis and clinical differential diagnosis by dental practitioners.

HISTOPATHOLOGY REPORT	FREQUENCY	PERCENTAGE	DIFFERENTIAL DIAGNOSIS	FREQUENCY	PERCENTAGE
Squamous cell carcinoma	37	27.6%	Pyogenic Granuloma	46	34.3%
Pyogenic Granuloma	36	26.9%	Squamous cell carcinoma	38	28.4%
Fibrous Epulis	15	11.2%	Fibrous epulis	10	7.5%
Squamous papilloma	5	3.7%	Lipoma	5	3.7%
Lipoma	5	3.7%	Mucocele	5	3.7%
Mucocele	4	3.0%	Osteomyelitis	4	3.0%
Osteomyelitis	4	3.0%	Kaposi sarcoma	3	2.2%
Traumatic neuroma	4	3.0%	Leukoplakia	2	1.5%
Hemangioma	3	2.2%	Residual cyst	2	1.5%
Kaposi sarcoma	3	2.2%	Squamous papilloma	2	1.5%
Non-Hodgkin's lymphoma	2	1.5%	Traumatic neuroma	2	1.5%
Residual cyst	2	1.5%	Adenoid cystic carcinoma	1	0.7%
Keratocyst (dermoid type)	2	1.5%	Adenoma	1	0.7%
Nasopalatine cyst	1	0.7%	Cystic hygroma	1	0.7%
Nodular malignant melanoma	1	0.7%	Fibroma	1	0.7%
Acanthotic squamous mucosa	1	0.7%	Focal epithelial hyperplasia	1	0.7%
Odontogenic myxoma	1	0.7%	Hemangioma	1	0.7%
Oral hairy leukoplakia	1	0.7%	Lichen planus	1	0.7%
Ameloblastoma	1	0.7%	Nasopalatine cyst	1	0.7%
Pleomorphic adenoma	1	0.7%	Non- Hodgkin's lymphoma	1	0.7%
Fibroma	1	0.7%	Odontogenic keratocyst	1	0.7%
Leukoplakia	1	0.7%	Oral hairy leukoplakia	1	0.7%
Buccal furcation cyst	1	0.7%	Peripheral cell granuloma	1	0.7%
Lichen planus	1	0.7%	Pleomorphic adenoma	1	0.7%
Mucoepidermoid carcinoma	1	0.7%	Radicular cyst	1	0.7%

Table 5.7 displays the frequency of each histopathological reported oral lesion and clinical differential diagnosis. Due to the low frequency of certain oral lesions, no statistical relationship could be identified for all presenting lesions within UGU district. Statistical analysis was possible on the three most common lesions with the district, namely: Fibrous Epulis (FE); Pyogenic Granuloma (PG) and Squamous cell carcinoma (SCC).

Table 5.2 – Table 5.12 and Figure 5.2 – Figure 5.7, explicates objectives one, two and three of the research study.

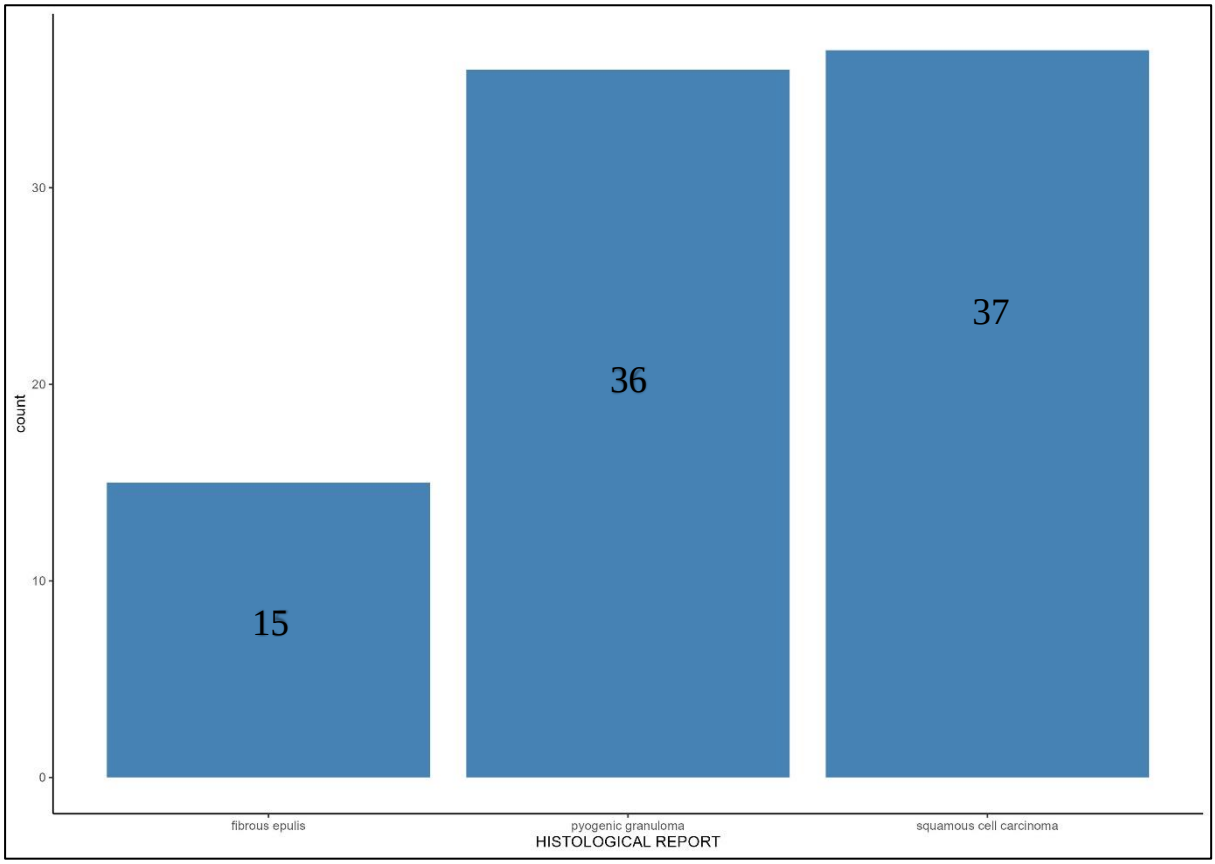

Figure 5.3: Histogram illustrating the prevalence of the 3 most common intra-oral lesions within UGU district.

Table 5.8: Descriptive age analysis of the 3 most common intra-oral lesions within UGU.

AGE	Fibrous epulis (FE)	Pyogenic Granuloma (PG)	Oral Squamous Cell Carcinoma (OSCC)
Mean	48,47	40,14	60,19
Standard Deviation	16,17	19,60	14,41
Median	50	42	62

Table 5.9 Frequency of the 3 most common lesions within UGU.

Variables	Frequencies			Hypothesis
	FE	PG	OSCC	H0: no association between race and common lesion H1: there is an association between race and common lesions. $\chi^2 = 15.838\,; df = 2; p = 0.01465$ Reject the null hypothesis and conclude that there is a relationship between race and OSCC. No relationship between FE and PG with ethnicity has been evident. (Caution small frequencies in some categories).
African	14	32	24	
Coloured	0	0	1	
Indian	1	4	3	
White	0	0	9	
Residuals				
African	0.60	0.63	-1.00	
Coloured	-0.41	-0.64	0.89	
Indian	-0.31	0.40	-0.20	
White	-1.24	-1.92	2.68	

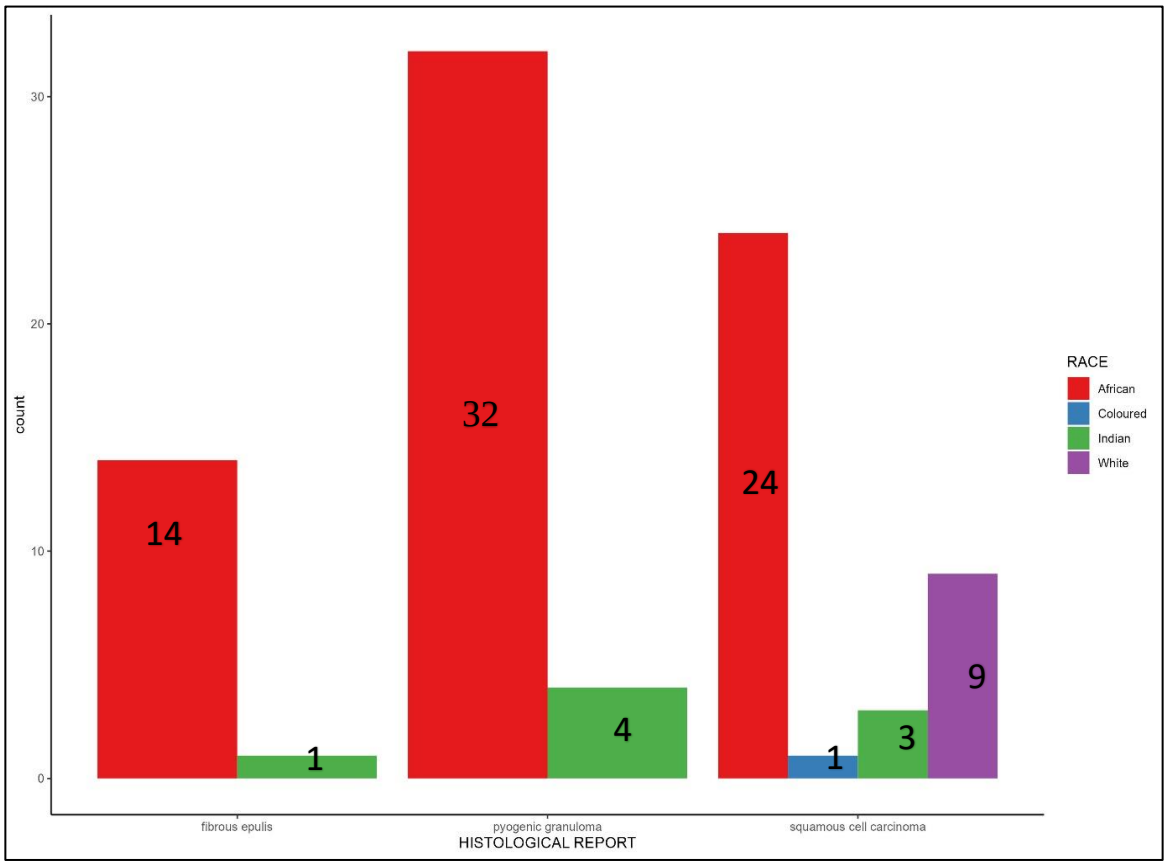

Figure 5.4: Histogram depicting the 3 most common lesions amongst ethnicity.

Table 5.10: Chi -square test of gender association amongst the 3 most common lesions.

Variables	Frequencies			Hyopothesis
	FE	PG	OSCC	H0: no association between sex and common lesions. H1: there is an association between sex and common lesions. $\chi^2 = 18.791\,; df = 2; p < 0.0001$ Reject the null hypothesis and conclude that there is a relationship between male sex and OSCC. There is no relationship between gender and F.E and P.G respectively.
Female	12	28	12	
Male	3	8	25	
Residuals				
Female	1.05	1.46	-2.11	
Male	-1.27	1.75	2.54	

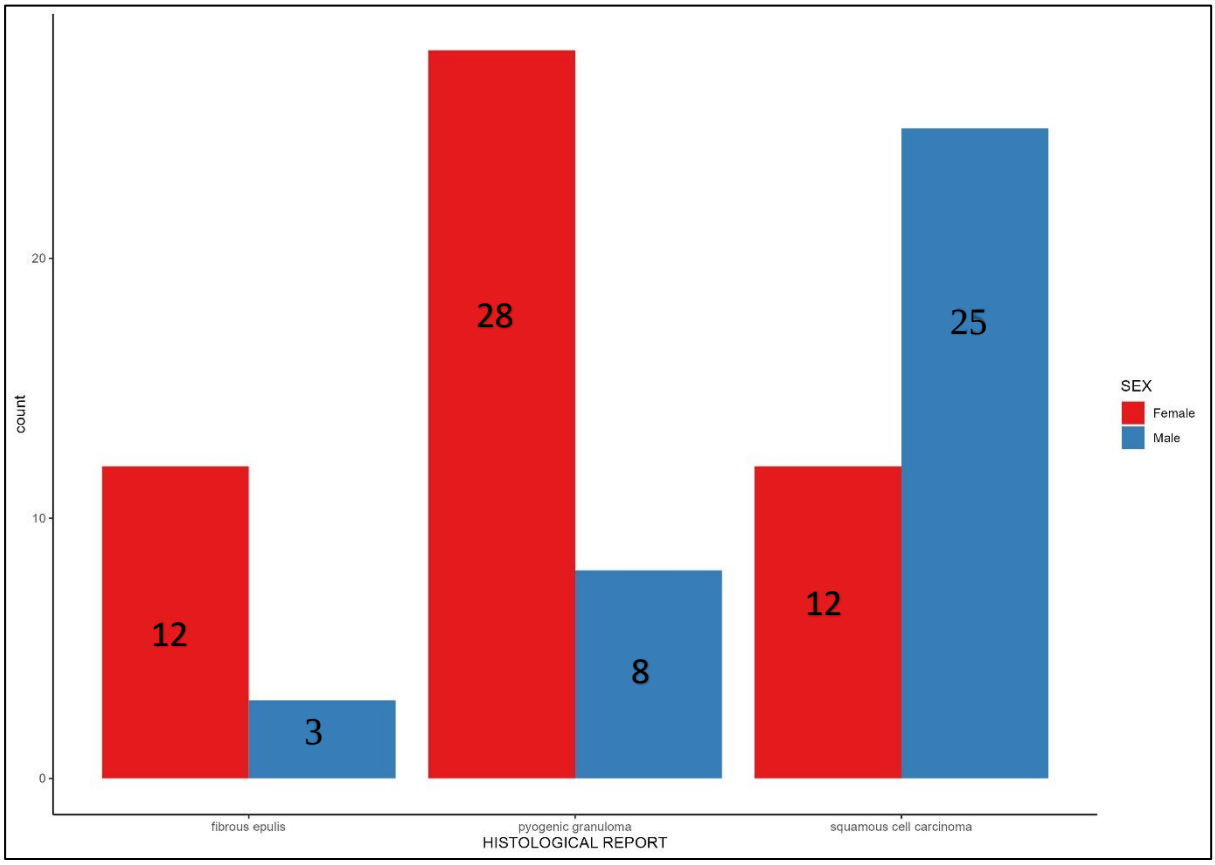

Figure 5.5: Histogram depicting the gender prevalence amongst the 3 most common lesions in UGU.

Table 5.11: Chi-square test of association between alcohol consumption and the 3 most common lesions in UGU.

Variable	Frequency			Hypothesis
	FE	PG	OSCC	NO = No alcohol consumption YES = Drinks alcohol H0:no association between alcohol consumption and common lesions. H1: there is an association between alcohol consumption and common lesions. $\chi^2 = 23.409\,; df = 2; p < 0.0001$ Reject null hypothesis and conclude that there is a relationship between alcohol and OSCC. (Caution small frequencies in some categories).
No	13	34	17	
Yes	2	2	20	
Residuals				
No	0.63	1.53	-1.91	
Yes	-1.01	-2.50	3.12	

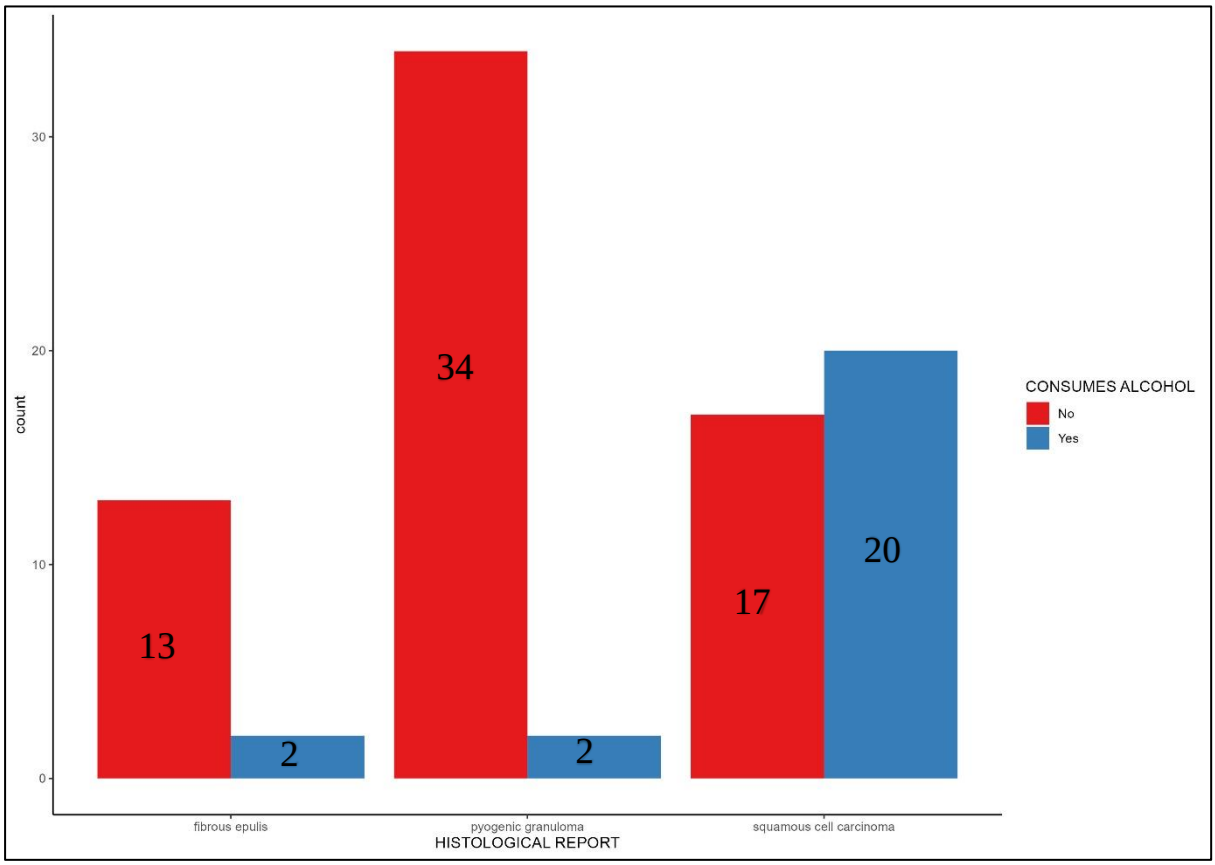

Figure 5.6: A graphical depiction of gender prevalence amongst the 3 most common lesions in UGU.

Table 5.12: Chi-square test of association between smoking and common lesions within UGU.

	Frequencies			Hypothesis
	FE	PG	OSCC	NO = Non-smoker YES = Smoker H0: no association between smoking and common lesions. H1: there is an association between smoking and common lesions. $\chi^2 = 37.616\,; df = 2; p < 0.0001$ Reject the null hypothesis and conclude there is a relationship between smoking and OSCC. (Caution small frequencies in some categories).
No	14	34	12	
Yes	1	2	25	
Residuals				
No	1.18	1.91	-2.63	
Yes	-1.73	-2.79	3.86	

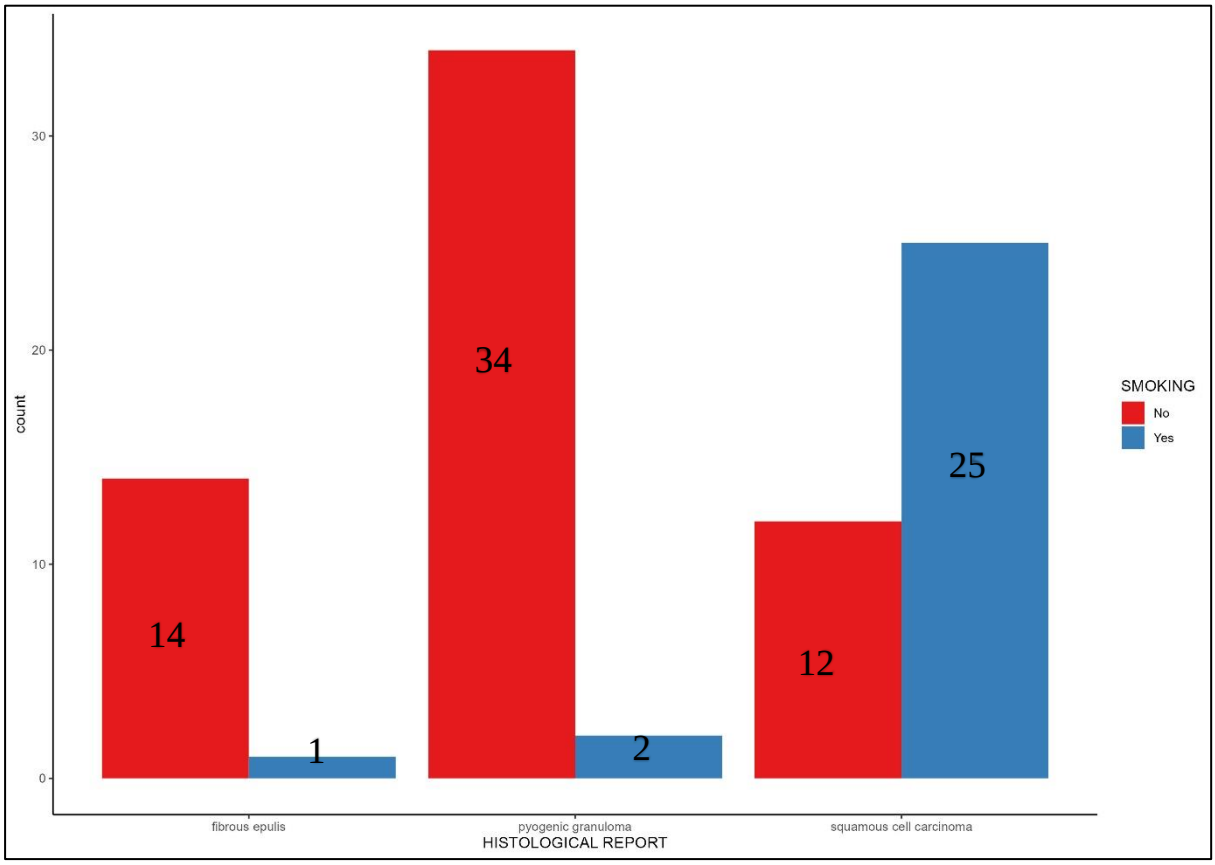

Figure 5.7: Illustration of smoking prevalence amongst the 3 most common lesions in UGU.

Table 5:13: Agreement between clinical differential diagnosis (CDD) and histopathology diagnosis (HD)

Agreement between C.D.D and HD	Frequency	Percentage
Yes	106	79.1%
No	28	20.9%
Total	134	100%

Table 5.14: Kappa statistic measurement of level of agreement between histopathology diagnosis (HD) and clinical differential diagnosis (CDD).

Kappa Statistic	Asymptotic standard error (ASE)	Z	P-Value
0.7437	0.04139	17.97	<0.0001

Table 5.14, depicts the Kappa statistic of 0.7437. Based on these two raters, a "substantial" level of agreement has been established between histopathology diagnosis and differential diagnosis. Objective four of this study, i.e., the assessment of concordance between HR and CDD has been explicated by Kappa statistic.

Chapter 6

Discussion

This retrospective study of histopathological diagnosed lesions assessed the distribution of intra oral lesions within UGU district, KZN, South Africa. All biopsy results are of governmental based hospital patients and have no reflection of the possible intra-oral biopsies performed in the private sector of health care within UGU district.

Agrawal et al., (2015) has discussed the frequency of oral lesions amongst the greater population of the world and how it can be divided by geographical locations and oral habits of those cultural areas. Statistical data recorded by Agrawal et al., (2015),Puasaini and Baral (2011), Poudel et al., (2019) and Kansky et al., (2018) showed a variance in prevalence of oral lesions. The most common lesions presented within each study were lymphoid hyperplasia; pseudoepitheliomatous hyperplasia; haemangioma, mucoceles, odontogenic cysts; fordyce spots and fibromas, respectively. The mentioned studies have statistical recorded the higher prevalence of benign lesions to malignant lesions, as documented in this study (table 5.1). In this study, OSCC was statically reported as one the most common OLs within UGU. These finding correlates with Agrawal et al., (2018) and Poudel et al. (2019).

The statistical analysis of oral lesions (OLs) within UGU:

Twenty-five different types of oral lesions were diagnosed by histopathological examination in this study as depicted in table 5.7. Within UGU district, the female gender represented the highest frequency of intra-oral biopsies with a total number of eighty-one, representing 60.4%, and fifty-three male patients representing the remaining 39.6% of the study population (table 5.1). A male: female ratio of 1: 1.5.A theory as to why females are more commonly diagnosed with oral lesions, is that females are more distressed about their appearance and general health, consequently having an increased need on health care facilities (da Silva et al., 2018). This study contrasted with studies by Agrawal et al., (2015) and Pudasaini and Baral, (2011), where male patients had a higher frequency of oral lesions with male-to-female ratios of 3.3:1 and 2:1, respectively. This disparity could be attributed to

unhygienic oral habits or social habits performed by men (Puasaini and Baral., 2011). Kansky et al., (2018) reported an equal representation of oral lesions with male- to-female ratio of 1:1.

The mean age of presentation of all biopsied cases was 46.37 with standard deviation of 20.77 with a median age of 50. The age range was from the age of 7 to 87 years. This correlates with many studies done in different parts of the world as reported by Agrawal et al., (2015) with a mean age of 40.16 years and an age range of 8 to 80 years. The study performed by Puasaini and Baral (2011) reported a mean age of 46 years and an age range of 12 to 68 years.

South Africa, the "Rainbow Nation" is a country of many ethnicities, and as such the frequency or oral lesions will vary in comparison to European and Asian based studies. Studies reported by as Feng et al., (2015), Kansky et al., (2018) and Poudel et al., (2019), represent the indigenous people of their respective countries (Chinese, Slovakian and Indian) with no distinguishment of ethnicity. With the assistance of epidemiological studies, the prevalence, propagation of OLs and "risk factors" within a population are acknowledged and documented (Feng et al., 2015).

Of the one hundred and thirty-four patient records, one hundred and eleven were African (Black) patients. This represented 82% of the study population size, the highest number of intra-oral lesions performed within the UGU district. Patients of Indian descent was the second highest (n= 11,8.2%), followed by white (caucasian) patient records, (n= 10, 7.5%) and lastly coloured (mixed raced) patients (n=2, 1.5%).

The documented medical history of the study population was taken on the day of the patients' first dental visit. No subsequent diagnosis of medical illness was taken into data collection post biopsy procedure. The 4 highest comorbidities that was documented from this study was Hypertension (n=48, 35.8%), Diabetes (n=18, 13.4%), H.I.V (n=22, 16.4%) and dyslipidaemia (n=10, 7.5%).

Benign (non-malignant) lesions represented the highest amount of the oral lesions, with a total of ninety oral biopsies (67.2%). Of the one hundred and thirty-four oral biopsies done, forty-four were malignant (32.8%). Malignant oral lesions were diagnosed amongst the middle-aged to the elderly, with majority of the malignant lesions being diagnosed within 5th,6th, and 7th decades of life (Figure 5.2) with a mean age of 60.19 years for OSCC.

Khamissa et al., (2014) reported a mean age of 58. Mehrotra et al., (2014) representing a mean age of 55 and Rautava et al., (2007) reporting a mean age of 67. The current study supports the numerous studies that have reported that oral malignancy is a disease of the middle-aged to the elderly, but this does not void the increasing number of younger individuals that are being diagnosed with malignant OLs (Khammissa et al.,2014; Mehrotra et al.,2008; Rautava et al., 2007).

As reported by tables 5.2 through to 5.12 and figures 5.2 to 5.7 of statistical results, objectives two and three of this study are intertwined. The prevalence and association of social habits of malignant lesions are discussed alongside the analysis of benign oral lesions.

What had been proven with the tests of association, malignant lesions and OSCC have an association to ethnicity. As shown in table 5.3. and table 5.9, with p- values = 0.0009 and 0.01465 respectively, an association of oral malignancy with white patients were proven. The caution alluded to small frequencies of certain ethnicities were represented by one coloured patient. This association has displayed a contrast to a South African study performed by Khammissa et al., (2014), where a statistically significant amount of African people was diagnosed with OSCC amongst the greater Johannesburg area as compared to white people. The variation of results can be possibly linked to ethnic-specific high-risk habits, genetic susceptibility, cultural practices, environmental factors, access to health care facilities and metabolic deficiencies (Preety et al.,2020; Maymone et al., 2019; Khammissa et al.2014).

Social habits have been known to be a risk factor for the development of oral cancers and potentially malignant lesions (McCullough et al.,2010). In this study, the documented social habits of the patient were essential in proving a statistically significant association between malignancy and tobacco smoking and alcohol consumption (tables 5.4 and 5.5).

Alcohol consumption and smoking are proven a statically significant risk factors in numerous studies (Chher at al.,2018; Feng et al., 2015; Khammissa et al.,2014). Chi-squared tests of association were done between malignant and benign lesions and risk factors i.e., alcohol consumption and smoking (Table 5.4 and Table 5.5). A statistically significant association between smoking and malignancy were proven. As discussed by Saini et al. (2019), 90-95% of studies have supported the hypothesis of a relationship between alcohol consumption and smoking with the occurrence of oral malignancy.

Chain smokers have a seven times higher chance of being diagnosed with a potentially malignant or malignant lesion compared to non-smokers. Studies have shown with the

removal of tobacco exposure, potentially malignant lesions, such as leukoplakia, can regress approximately by 56% at three months and 78%, twelve months post termination of smoking and or tobacco exposure (McCullough et al., 2010). This has demonstrated how oral health education and the development of preventative programmes could play a major role in bridging the gap of awareness and actively changing risky social habits of the general population.

An association of malignant lesions including OSCC with the male gender have both been statically reported, $p< 0.001$and $p< 0.0001$ (tables 5.2 and 5.10). Oral cancer has been ranked 8th and 13th as the most common malignancy amongst males and females respectively. Through statistical analysis, the current study is in agreement of the higher prevalence of OSCC amongst males. (Preety et al.,2020; Khammissa et al., 2018; McCullough et al., 2010).

Oral Squamous cell carcinoma of the oral cavity is known to be the most common malignant epithelial neoplasm of all oral cancers (Preety et al., 2020). This retrospective study had a total number of forty-four malignant cases. Thirty-seven of the biopsied malignant cases were histopathologically diagnosed as OSCC. OSCC represented 84 % of the total number malignant cases. What has been statistically proven through this study, was the significant relationship with alcohol consumption and smoking as a synergistic risk factor for OSCC (table5.11 and table 5.12), as described by numerous studies such as Rautava et al. (2007) and Saini et al. (2019). A study performed by Preety et al. (2020), had revealed that social habits such as smoking, alcohol consumption and chewing of carcinogenic agents had a proclivity of specific areas of the oral cavity where malignant lesions would develop.

There was no proven association between benign lesions and gender in this given study. Da Silva et al. (2018) had reported a higher incidence of benign lesions amongst females. The study had attributed this higher incidence amongst females due to seeking specialised medical assistance as compared to males.

Due to the small frequencies of OLs, the statical analyses could not be performed on all named oral lesions in table 5.7. In this study, the top 3 lesions were analysed, i.e., Pyogenic granuloma (PG), Fibrous epulis (FE) and Oral Squamous cell carcinoma (OSCC). Though PG's and FE's are frequently applied together in differential diagnoses of exophytic lesions within in the oral cavity, they histopathologically present a specific identity for each diagnosis. PG's exhibit an elevated vascular proliferation that mimics granulation tissue

whereas, FE's are "fibrous hyperplasia of gingiva" that consist of diversified quantity of "irregularly arranged bundles of collagen fibres and fibroblasts" (Xu et al., 2022).

In total, the 3 most common lesions presented in the study had constituted 65. 7% of all biopsied lesions. The chi square test of association was applied to the three most common lesions in UGU. The test statistic was X^2=15.838, df = 2 and p-value= 0.01465. There has been no ethnicity association with FE and PG. To date there is no study that associates FE or PG to any specific ethnicity.

No association of gender to FE and PG were statistically proved through this study (Table 5.10). An eighteen-year retrospective study of pyogenic granulomas performed by Ribeiro et al. (2021), had displayed a modestly higher prevalence amongst females with a representation of 1:1.25 (M: F). A retrospective study performed over a ten-year period by Kilinc et al. (2018) recorded similar results as Riberio et al. (2021), where both PG and FE had also shown to have a higher prevalence amongst the female gender. The current study done within KZN's UGU district, refuted the association, thereby illustrating the dissimilarity between gender prevalence of geographical locations (Xu et al., 2022).

There was no statistical relation proven between alcohol consumption and smoking to FE and PG in this study with a p-value < 0.0001(Table 5.11. and table 5.12). PG's have been described as an oral lesion that had proliferated blood vessels and the most citied etiological factors is "low intensity trauma, poor oral hygiene and hormonal imbalances" (Ribeiro et al.,2021). Observational studies have displayed that the pathogenesis of FE is not completely understood, but there are several factors that may have a role in the "reactive inflammatory component". These notable factors are poor oral hygiene, mechanical irritation and oral ulcers (Xu et al., 2022; Anisuzzaman et al.,2019).

The concordance between histopathological diagnosis (HD) and clinical differential diagnosis (CCD):

The oral cavity is a multiplex region of the head and neck area, which gives host to a variety of cysts, benign and malignant neoplasms of odontogenic and non-odontogenic origin, which may make the clinical diagnosis arduous. Histopathological examinations assist in confirming the clinical differential diagnosis (Tatli et al.,2013).

The histopathological diagnosis in one hundred and six histopathological reports were in accordance with the clinical differential diagnosis as reported in table 5.13. The accordance percentage is similar to findings in a study performed by Farzinnia et al. (2022), Emamverdizadeh et al. (2019) and Saravani et al. (2016), with concordance rates of 72.2%, 72.3% and 70.1%, and higher than findings in studies Talti et al., (2013) and Soyele et al., (2019) with concordance rate of 93.3% and 62.5% amongst oral medicine specialists respectively. This was further statistically measured by Kappa statistic with the level of agreement measuring at 0.7437 (Table 5.14). This suggests a “substantial” level of agreement between clinical differential diagnosis and histopathology reports.

This study illustrated the generalised presentation of oral lesions within UGU district of KZN, South Africa. Due to the generalised profile of the diagnosed lesions, it was difficult to compare results with other studies due to the specificity of the type of lesions being reviewed for accordance and the small frequencies of lesions diagnosed within this study. However, comparisons were made in relation to the three most common lesions associated with ethnicity, gender, risk factors and benign lesions versus malignant lesions. The range of disparity between the studies could be a result of the variation of methodologies, the dental clinician and oral pathologists experience, the validity of the biopsy, sample size and the state of the specimen during transportation. (Farzinnia et al.,2022; Soyele et al., 2019).

Chapter 7

Conclusion

This study has demonstrated the diversity and prevalence of intra-oral lesions within the rural district of UGU, KZN, South Africa. What has been displayed by this study's results, is the multiplicity of the prevalence of oral lesions within global studies. Though this study was done on a significantly smaller study population group, as compared to global studies, the need for widespread exploration and research within different geographical areas had been proven due to the varied international results.

The most recent South African studies on the prevalence of intra-oral lesions presented by Pontes el., 2020 and Khammissa et al., 2014, based on the Western Cape and Gauteng provinces respectively, has exhibited a slight difference in the ethnicity susceptibility to malignant intra- oral lesions. A suggestion could be made that this study could be extended to the greater province of KZN, as a greater number of statistics could illustrate a clearer image on the prevalence, demographics and risk-factors of intra-oral lesions within the province.

Social habits such as alcohol consumption and smoking have been proven to be a significant risk factor in the diagnosis of malignant lesions within this study. The demographics of this study were based on patients with access to only the public health sector and therefore falling within the "lower socially economical" category of the population. UGU is based in a rural setting of South Africa. Access to health care could be an arduous journey for an individual who does not have the means of travel, nor has the knowledge of possible medical avenues that could be utilized before being diagnosed with an incurable disease.

As South Africa is a developing country and is affiliated with the term "double burden of disease", we have an opportunity to research the risk factors and social attributes that could assist in understanding and developing oral health care programs that can assist in relieving an already troubling, burdened health care system.

The clinical picture and history of any biopsy specimen plays a pivotal role in the clinician's differential diagnosis. In limited resourced facilities within the rural South Africa, a broad

clinical acuity may be the difference in early detection of a possibly terminal disease. These diagnostic tools submitted by the clinician assists the oral pathologist in formulating a histopathological diagnosis.

The current study has a substantial level of agreement between clinical differential diagnosis and the histopathological diagnosis, with approximately 79.1% concordance. It will be difficult, if not near impossible to obtain a 100% clinicopathology concordance. Oral lesions have the ability to mimic the clinical image of a histopathologically different lesion. The histopathological diagnosis has remained the “gold standard” of diagnostic tools for the definitive diagnosis of biopsy specimens and avoiding misdiagnosis and improper treatment of a patient.

This study has proven that the distribution of oral lesions within specific geographical populations of a country are diverse. With the assistance of scientific research, development of oral health programmes, seminars and personnel training can successfully assist and educate dental clinicians and allied health workers.

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Appendix

Appendix A: HREC clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr LY Reddy

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220620

NAME: (Principal Investigator)	Dr LY Reddy
DEPARTMENT:	School of Oral Health Sciences Depatrtment of Maxillo Facial and Oral Surgery Dental School Unversity
PROJECT TITLE:	*A retrospective study of histologically diagnosed intra-oral lesions within UGU district, KZN, South Africa*
DATE CONSIDERED:	2022/06/24
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr V Premvijasa
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/09/07

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

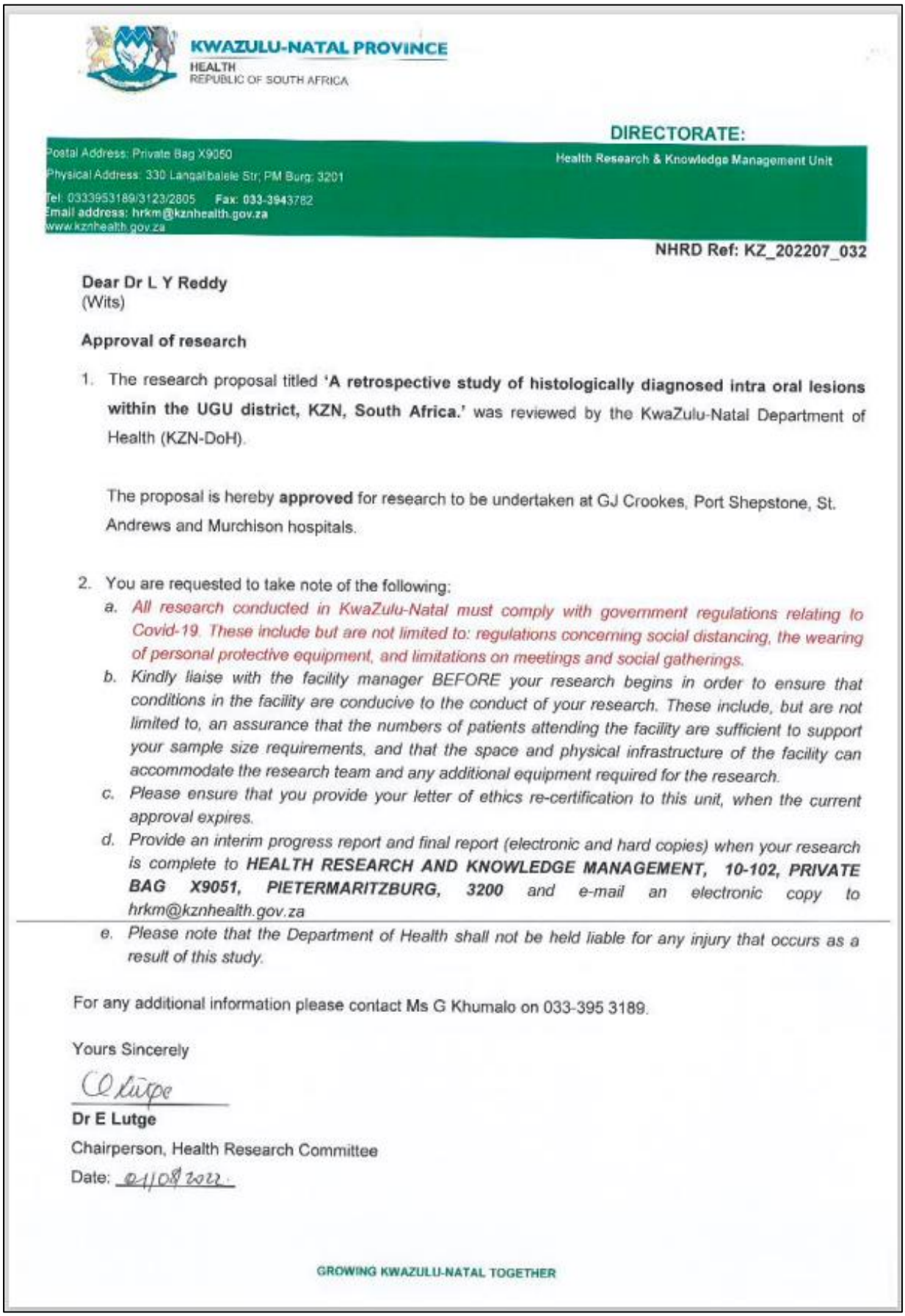
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in June and therefore reports and re-certification will be due in the month of June each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 2022/10/07

Appendix B: NHRD research approval letter



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
Health Research & Knowledge Management Unit

Postal Address: Private Bag X9050
Physical Address: 330 Langalibalele Str; PM Burg; 3201
Tel: 0333953189/3123/2805 Fax: 033-3943782
Email address: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

NHRD Ref: KZ_202207_032

Dear Dr L Y Reddy
(Wits)

Approval of research

1. The research proposal titled **'A retrospective study of histologically diagnosed intra oral lesions within the UGU district, KZN, South Africa.'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at GJ Crookes, Port Shepstone, St. Andrews and Murchison hospitals.

2. You are requested to take note of the following:
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 04/08/2022

GROWING KWAZULU-NATAL TOGETHER

Appendix C: UGU District Approval letter

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
UGU DISTRICT DIRECTOR

Physical Address: 41 Bisset Street, Port Shepstone, 42400
Postal Address: P/Bag X 735,Port Shepstone,4240
Tel: 093 6883000 Fax: 0396826286 Email Address: Linda.Dlamini@kznhealth.gov.za
Www.kznhealth.gov.za

Enquiries: Mrs L. Dlamini
Date: 20 July 2022

To:
Dr L.Y Reddy

PERMISSION TO CONDUCT A RETROSPECTIVE STUDY OF HISTOLOGICALLY DIAGNOSED INTRA-ORAL LESIONS WITHIN UGU DISTRICT

Dear Dr L.Y Reddy

I have the pleasure in informing you that permission has been granted to you by Ugu District Office to conduct a Retrospective study of Histological Diagnosed Intra-Oral Lessons within Ugu District at the following facilities:

1. Port Shepstone Regional Hospital
2. Murchison District Hospital
3. GJ Crookes Hospital
4. St Andrews Hospital

Please note the following:

a) Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health.

b) All research conducted in Ugu District must comply with government regulations relating to COVID-19.These include but are not limited to: regulations concerning the social distancing, the wearing of personal protective equipment and limitations on meetings and social gatherings.

c) Please ensure that this office is informed before you commence with your research.

d) The District Office /Facility will not provide any resources for this research.

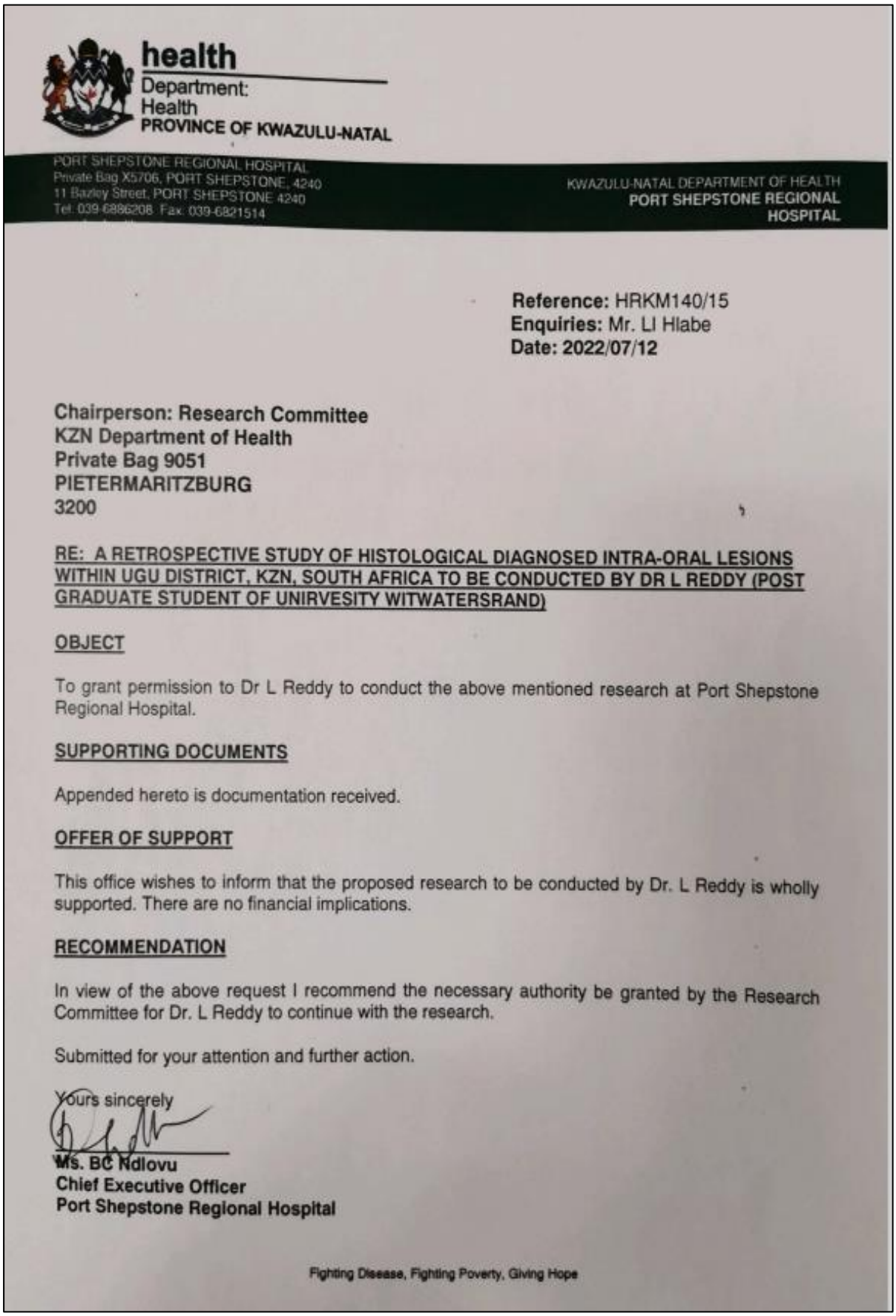
e) You will be expected to provide feedback on your findings to the District Office.

Thank you

Mrs L. Dlamini
District Director
Ugu District Office

GROWING KWAZULU-NATAL TOGETHER

Appendix D: Port Shepstone Regional Hospital research approval letter



health
Department:
Health
PROVINCE OF KWAZULU-NATAL

PORT SHEPSTONE REGIONAL HOSPITAL
Private Bag X5706, PORT SHEPSTONE, 4240
11 Bazley Street, PORT SHEPSTONE 4240
Tel. 039-6886208 Fax. 039-6821514

KWAZULU-NATAL DEPARTMENT OF HEALTH
PORT SHEPSTONE REGIONAL
HOSPITAL

Reference: HRKM140/15
Enquiries: Mr. LI Hlabe
Date: 2022/07/12

Chairperson: Research Committee
KZN Department of Health
Private Bag 9051
PIETERMARITZBURG
3200

RE: A RETROSPECTIVE STUDY OF HISTOLOGICAL DIAGNOSED INTRA-ORAL LESIONS WITHIN UGU DISTRICT, KZN, SOUTH AFRICA TO BE CONDUCTED BY DR L REDDY (POST GRADUATE STUDENT OF UNIRVESITY WITWATERSRAND)

OBJECT

To grant permission to Dr L Reddy to conduct the above mentioned research at Port Shepstone Regional Hospital.

SUPPORTING DOCUMENTS

Appended hereto is documentation received.

OFFER OF SUPPORT

This office wishes to inform that the proposed research to be conducted by Dr. L Reddy is wholly supported. There are no financial implications.

RECOMMENDATION

In view of the above request I recommend the necessary authority be granted by the Research Committee for Dr. L Reddy to continue with the research.

Submitted for your attention and further action.

Yours sincerely

Ms. BC Ndlovu
Chief Executive Officer
Port Shepstone Regional Hospital

Fighting Disease, Fighting Poverty, Giving Hope

Appendix E: Murchison Hospital research approval letter

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
MEDICAL DEPARTMENT

Murchison Hospital
N2 Main Harding Road
Private Bag X701
Port Shepstone
4240
Tel: 039-6877314/5/6 Fax: 039-6877497 Email: Similatha.Lachman@kznhealth.gov.za

Practice Number: 5604664

17 August 2022

ATT: Dr Larisha Reddy
Maxillo-facial and Oral Surgery
University of Witwatersrand

Re: Permission to conduct medical research at Murchison Hospital

Dear Colleague

Your request for permission to carry out the research "**A Retrospective Study of Histologically Diagnosed Intra-Oral Lesions within the Ugu District, KZN, South Africa"** at our facility is hereby granted.

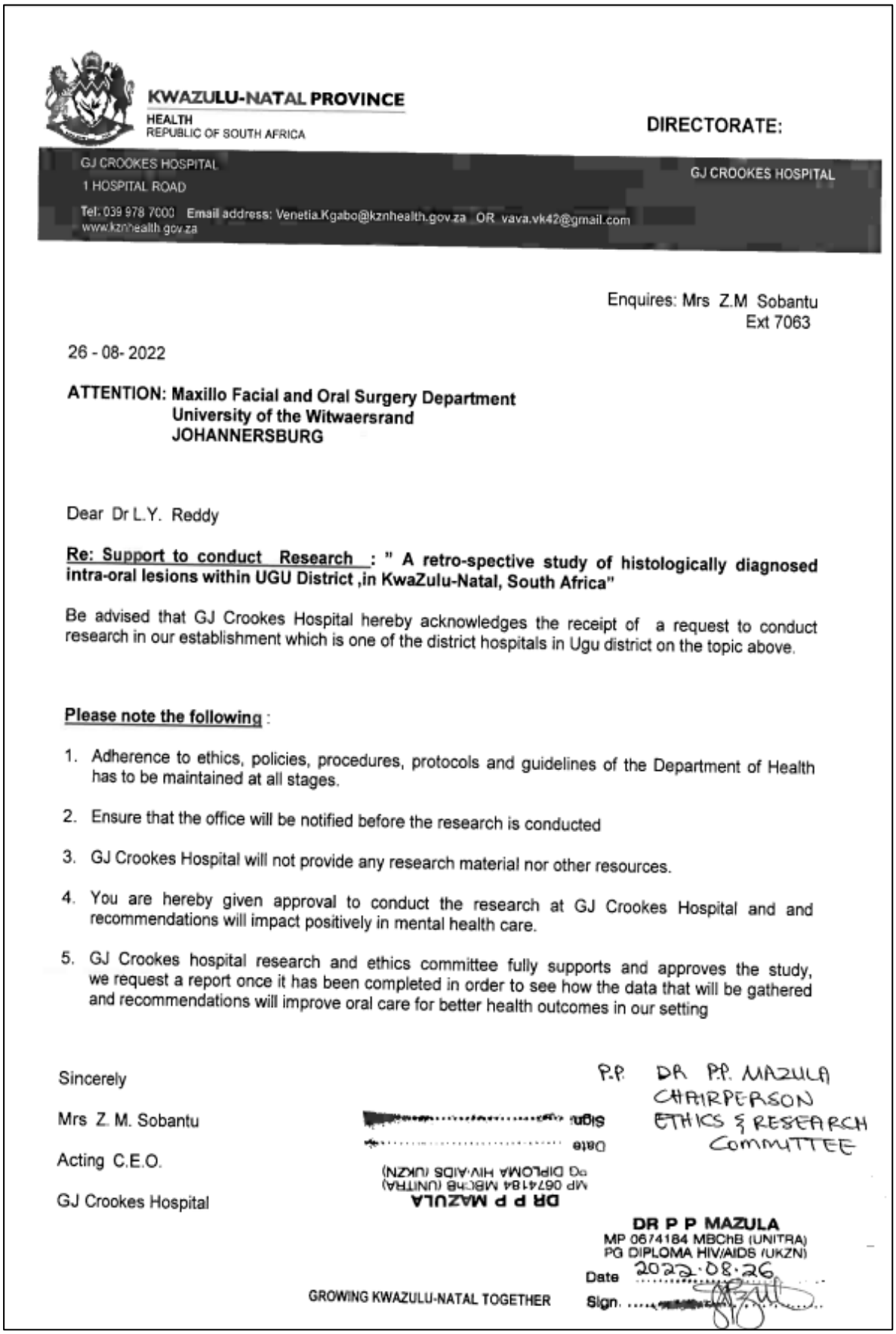
This is subsequent to acknowledgement of the ethical approval by the DOH-KZN Health Research Committee (reference: KZ_202207_032) and pending BREC Committee approvals.

Yours sincerely

Dr S Lachman
Clinical Manager

GROWING KWAZULU-NATAL TOGETHER

Appendix F: GJ Crooks Hospital approval letter



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

GJ CROOKES HOSPITAL
1 HOSPITAL ROAD
Tel: 039 978 7000 Email address: Venetia.Kgabo@kznhealth.gov.za OR vava.vk42@gmail.com
www.kznhealth.gov.za

GJ CROOKES HOSPITAL

Enquires: Mrs Z.M Sobantu
Ext 7063

26 - 08- 2022

ATTENTION: Maxillo Facial and Oral Surgery Department
University of the Witwaersrand
JOHANNERSBURG

Dear Dr L.Y. Reddy

Re: Support to conduct Research : " A retro-spective study of histologically diagnosed intra-oral lesions within UGU District ,in KwaZulu-Natal, South Africa"

Be advised that GJ Crookes Hospital hereby acknowledges the receipt of a request to conduct research in our establishment which is one of the district hospitals in Ugu district on the topic above.

Please note the following :

1. Adherence to ethics, policies, procedures, protocols and guidelines of the Department of Health has to be maintained at all stages.
2. Ensure that the office will be notified before the research is conducted
3. GJ Crookes Hospital will not provide any research material nor other resources.
4. You are hereby given approval to conduct the research at GJ Crookes Hospital and and recommendations will impact positively in mental health care.
5. GJ Crookes hospital research and ethics committee fully supports and approves the study, we request a report once it has been completed in order to see how the data that will be gathered and recommendations will improve oral care for better health outcomes in our setting

Sincerely

Mrs Z. M. Sobantu

Acting C.E.O.

GJ Crookes Hospital

P.P. DR P.P. MAZULA
CHAIRPERSON
ETHICS & RESEARCH
COMMITTEE

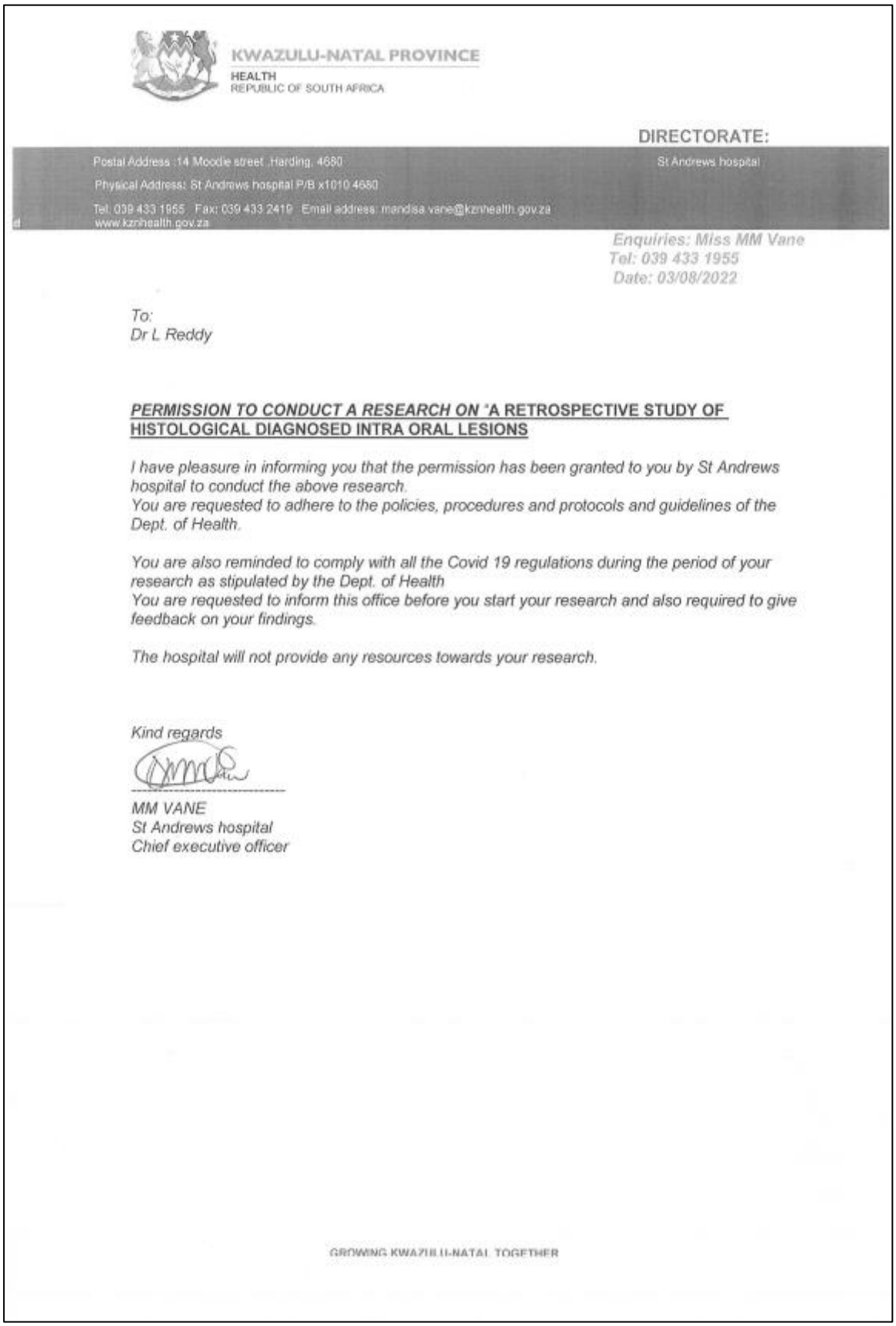
Sign
Date

DR P P MAZULA
MP 0674184 MBChB (UNITRA)
PG DIPLOMA HIV/AIDS (UKZN)

DR P P MAZULA
MP 0674184 MBChB (UNITRA)
PG DIPLOMA HIV/AIDS (UKZN)
Date 2022.08.26
Sign

GROWING KWAZULU-NATAL TOGETHER

Appendix G: St. Andrews Hospital approval letter



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

Postal Address :14 Moodie street ,Harding, 4680 St Andrews hospital
Physical Address: St Andrews hospital P/B x1010 4680
Tel: 039 433 1955 Fax: 039 433 2419 Email address: mandisa.vane@kznhealth.gov.za
www.kznhealth.gov.za

Enquiries: Miss MM Vane
Tel: 039 433 1955
Date: 03/08/2022

To:
Dr L Reddy

***PERMISSION TO CONDUCT A RESEARCH ON* "A RETROSPECTIVE STUDY OF HISTOLOGICAL DIAGNOSED INTRA ORAL LESIONS**

I have pleasure in informing you that the permission has been granted to you by St Andrews hospital to conduct the above research.
You are requested to adhere to the policies, procedures and protocols and guidelines of the Dept. of Health.

You are also reminded to comply with all the Covid 19 regulations during the period of your research as stipulated by the Dept. of Health
You are requested to inform this office before you start your research and also required to give feedback on your findings.

The hospital will not provide any resources towards your research.

Kind regards

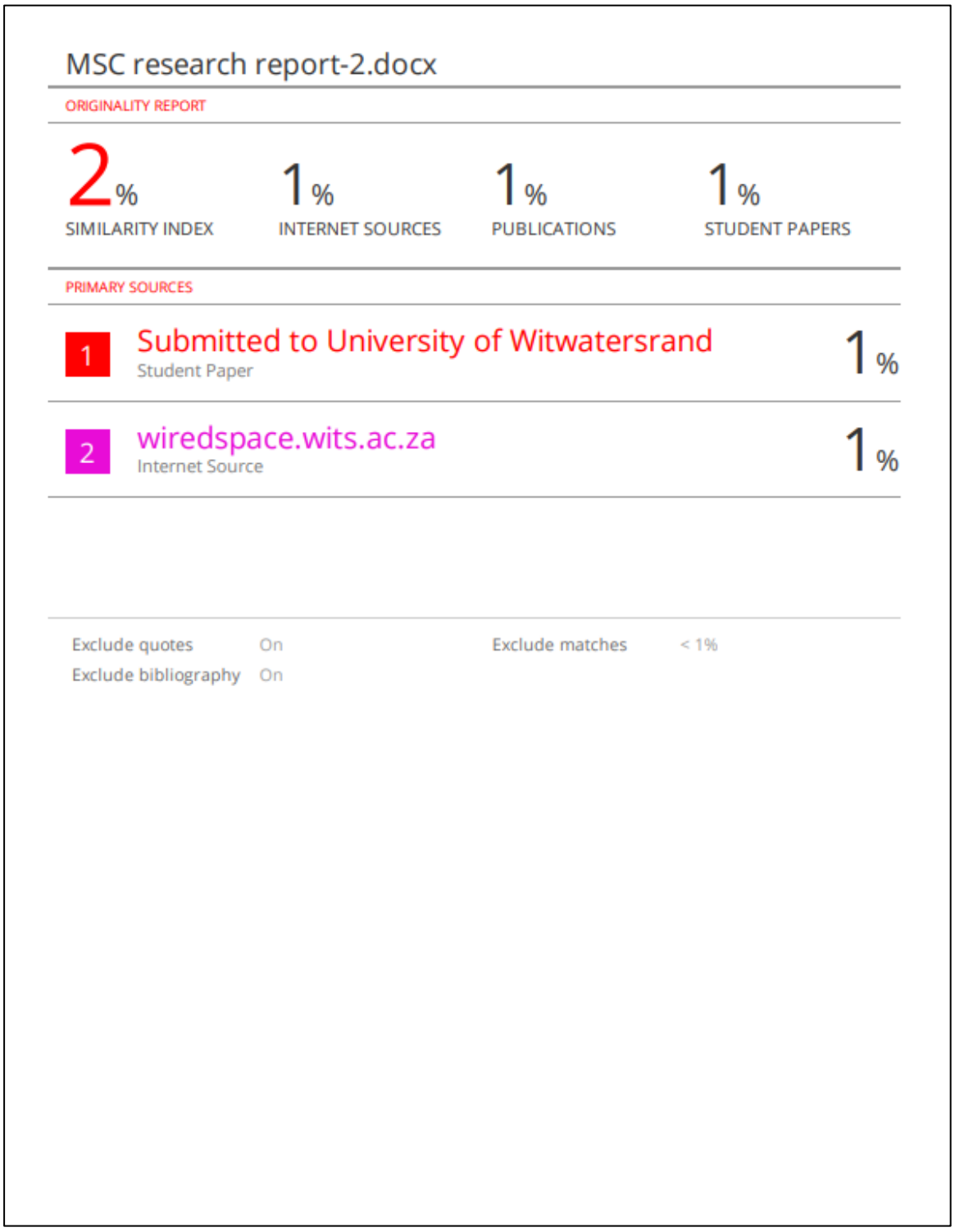
MM VANE
St Andrews hospital
Chief executive officer

GROWING KWAZULU-NATAL TOGETHER

Appendix H: Data collection form

De-Identified Number:	Age	Sex	Ethnicity	Named Previous Medical History. E.g.: HPT, Diabetes, etc	Does the patient Drink?	Does the patient smoke?	Does the patient chew carcinogenic agents?	Clinical Differential Diagnosis	Histopathology Report Diagnosis	Malignant/ Non-malignant

Appendix I: Turn-it-in Report



MSC research report-2.docx

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