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Profiling of oral squamous cell carcinoma in patients presenting to the Department of Oral Medicine and Periodontology Wits Oral Health

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TABLE OF CONTENTS

COVER PAGE .....

DECLARATION ..... **I**

DEDICATION ..... **II**

LIST OF FIGURES ..... **III**

LIST OF ABBREVIATIONS ..... **IV**

ABSTRACT……..…**V-VI**

INTRODUCTION **2**

LITERATURE REVIEW **4**

- **Epidemiology** **4**
- **Etiology** **6**
- **Pathogenesis** **13**
- **Investigations and Diagnosis** **17**

AIMS AND OBJECTIVES **20**

HYPOTHESIS **20**

MATERIALS AND METHODS **21**

- **Study design and sample** **21**
- **Inclusion criteria** **21**
- **Method** **21**
- **Data Collection** **23**

ETHICAL CONSIDERATIONS **24**

RESULTS **25**

DISCUSSION **32**

LIMITATIONS **36**

CONCLUSION **38**

REFERENCES **40**

APPENDIX 1 ..... **46**

APPENDIX 2 ..... **48**

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a malignancy of the epithelial cell layer.[1] The World Health Organisation (WHO) has defined cancer as the abnormal growth or division of cells beyond their normal anatomical boundaries leading to invasion of other bodily compartments or organ systems known as metastasis.[2] Two thirds of all OSCC cases documented in the world today present in advanced stages of the disease.[3,4] Local recurrence of the carcinoma is said to occur in up to thirty percent (30%) of cases, ten percent (10%) of cases will experience regional recurrence and up to twenty percent (20%) of cases will experience distant metastasis.[3,4] Oral squamous cell carcinoma (OSCC) of the lip, tongue, oral mucosa and gingiva present as a major health problem.

In 2012 as many as 690 000 new cases were documented worldwide.[5] Of these, 375 000 cases proved fatal.[5] OSCC makes up approximately 46% of total cancer mortality worldwide.[6] OSCC is also the 5th-8th most common malignancy known to man.

Two thirds of these cases occur in developing countries.[7] Access to health care facilities is a challenge that developing countries may face. South Africa should be basing health care protocols on local occurrences and statistics rather than those based on other countries with differing dynamics. It would be wise to redirect our efforts accordingly to achieve goals specific to our needs.

Understanding socio-economic, epidemiologic and pathognomonic parameters of our population gives us an informed advantage in managing major health care problems such as oral cancer.

Tobacco smoking and alcohol consumption form the two major causative factors for the development of OSCC. [8, 9] Understanding the prevalence of these causative agents within our population group may provide us with an idea of their contribution to this sinister disease.

Noting the exposure of citizens to other causative factors such as betel quid chewing, chronic sunlight exposure [7] or chemical pollution are all imperative in understanding a population's risk dynamic within our region.

Characterization of OSCC within this setting will provide information as to who is most at risk which in turn will inform intervention policies at all levels

LITERATURE REVIEW

Epidemiology

This heterogeneous disease (OSCC) shows a global prevalence for older Caucasian males over the age of 45 years [7] and is primarily associated with tobacco usage and alcohol consumption.[8, 9]

Other individuals at high risk of developing of OSCC, mostly of the lip, include those that are overexposed to ultraviolet radiation in hotter climates, as is the case for surfers, sunbathers, fisherman and farmers.[7] Populations unaccustomed to sun are at greater risk when exposed to sunlight.

The main intraoral site affected is the tongue.[7]The incidence, mortality, variation and site affected may vary widely.

The prevalence of OSCC is currently the fastest growing neoplasm worldwide.[10] Current literature indicates that OSCC of the lip condemns patients to a 95% five-year survival rate with the prognosis of lateral ventral tongue lesions being half as good with a 45% five-year survival rate.[7] Over the past several years there has been a significant decrease in the occurrence of OSCC in the USA and Canada and a marked increase in countries such as Portugal, France, Hungary, South America and South East Asia.[7, 11] This can possibly be attributed to more stringent tobacco and alcohol laws implemented in the US and Canada as well as heightened awareness of risk factors. In contrast, many eastern European

countries have experienced steadily increasing tobacco and alcohol sales. There has been a marked rise in young smokers and binge drinking since the 1980s, which is postulated to have played a significant role. [7]

In a European comparison, Eastern Europe has been shown to have an increased number of new OSCC cases compared to northern and southern Europe.[7] French citizens, in general, have a sevenfold higher chance of developing OSCC than Greeks.[7] It is estimated that 25% of all new OSCC cases worldwide originate in India.[7] This figure is closely followed by South American populations, particularly Brazilian, Argentinean and Uruguayan males, who have the third highest prevalence for OSCC.[7] Southeast Asia and India together contribute together well over 100 000 cases of OSCC per year, which can be understood by virtue of the sheer population size of over one billion citizens, many of whom are exposed to carcinogenic risk factors such as tobacco smoking and betel quid chewing. [7,6] A Libyan epidemiological study showed a mean occurrence of OSCC in males in the 5th and 6th decades of life, with the floor of the mouth being mostly affected.[13] Africa, interestingly, has produced little literature on prevalence numbers of OSCC. A paper published on the occurrence of OSCC development in Sudanese civilians, however, showed an alarmingly high prevalence of 66.5%.[14]

Etiology

Tobacco smoking and alcohol consumption are two major risk factors involved in the development of OSCC.[5] Tobacco smoking produces several known carcinogens such as tobacco specific nitrosamines (TSNAs), N-nitrosnornicotine, free radicals, and 4-methylnitrosamino-1-3 pyridal-1 butanone.[16] As carcinogenic exposure to somatic cells is increased, so the rate of mutation increases. [16] The carcinogens described above cause alterations in anti-oxidant enzymes, particularly glutathione-S-transferase (GST), glutathione reductase, superoxide dismutase, catalyse and glutathione peroxidise. [16] There is also an effect on lipid per oxidation and total Thiol metabolism. [16] These disruptive processes support the fact that smokers are twenty times more likely to develop OSCC. The risk is dose specific.[15,16]

Alcohol, or more specifically ethanol, consumption is also significant in OSCC development, especially as a synergistic partaker. Ethanol is oxidised to acetaldehyde, which is a suspected carcinogen.[15,16] The oxidation process is facilitated by alcohol dehydrogenases. The acetaldehyde is then further degraded to acetate, which is not a known carcinogen, by aldehyde dehydrogenases.[15,16] There is a fivefold increased risk of OSCC development associated with alcohol consumption.[5,16] The current consensus with regards to the contribution of alcohol in mouth wash is controversial and not yet conclusive as the relation of alcohol to OSCC is strongly dose dependant.

There is much evidence showing the synergistic effect of smoking and alcohol consumption.[16] Smoking increases the acetaldehyde burden when alcohol is consumed. Simultaneously, alcohol consumption increases the activity of pro-carcinogens present in tobacco. There is an increased metabolic activity by an induced cytochrome p450-2E1-dependant microsomal biotransformation system in the mucosa and liver. [5,16,28]

Areca nut or betel quid, known locally as "paan", is placed in the buccal mucosa and chewed as part of a cultural tradition mainly in India and other parts of Southeast Asia. [7,5,16,28] It is reported that up to 20% of the world's population has subscribed to this habit.[28] The areca nut causes a euphoric effect in the host. More importantly, it results in altered gene expression over various pathways. There is blockage of tumour suppressor genes by arecoline (an alkaloid contained within the areca nut). Arecoline causes a blockage in Tumour Suppressor Genes (TSGs) through a process known as hyper-methylation. [28] Dysregulation in p14, p15, and p16 occurs, as well as inhibition of the p53 gene and down regulation of DNA repair. At the same time, arecoline triggers DNA damage. Chewing betel quid is a particularly high risk habit since there is exposure to five separate carcinogens in the constructed chewable product. These include the leaf or vine, known as "piper betel", which contains betel oil, a liquid containing genotoxic phenols such as hydroxychavicol. The areca nut itself contains arecoline, which is carcinogenic. Additional carcinogens include

the fungus which grows on the nut (*aspergillus flavus*), the tobacco added to the product, which contains TSNAs, and finally the slaked lime or CaOH. The slaked lime breaks down the desmosomal attachment of tissues allowing easier absorption of the constituents leading to a heightened euphoric effect.

Caribbean populations such as Puerto Ricans also have abnormally high incidences of OSCC occurrence, this can be attributed to a prominent cigar-manufacturing industry and smoking culture.[7] Since cigar smoke is not inhaled but contained and swirled around in the oral cavity, the mucosa of the pharynx and lower respiratory system are less affected.

Another suspected aetiological risk factor is the use of an oral snuff known as toombak in North African countries.[7,27] Locals often combine toombak with varying amounts of sodium bicarbonate and other substances according to personal preference. [7,27] The Nigerian population have similar risk factors such as tobacco, kola nuts, alcohol and fuel sucking, which predispose them to OSCC.

OSCC has been shown to have a better prognosis in more affluent areas of the world where health care facilities are easily accessible and the disease is better understood. Providing clinicians with the armamentarium to make earlier diagnosis is therefore key in combating the disease.

We already know that OSCC formation is not only a function of exposure to risk factors such as smoking and alcohol but also of genetic susceptibility.[4,18,19] Patients presenting with syndromes or diseases that lead to carcinoma formation do so mainly because of a fundamental genetic instability.[4,3] Because such patients inherit single, mutant alleles, only three to four somatic mutations are needed for cancer development.[4,3] The number of clonal and non-clonal aberrations in the upper respiratory tract mucosa is also a factor of age, which explains OSCC prevalence in the elderly.[4,3] The genetic aberrations and subsequent cellular alterations are related to the level of exposure to carcinogens as well as the inherent inability to repair such DNA changes. [4,3] Consequently, we can describe this as a multi-step carcinogenesis.[4,18,19]

The genetic aberrations underlying the 'genetic progression model' may occur due to inactivation of TSGs by processes of mutation, deletion or methylation.[4,3] Oncogenes are activated by processes of mutation or activation.[4,3] Both inactivation of tumour suppressor genes and activation of oncogenes result in an overall uncontrolled growth of mutated cells.[4,3] Common genetic alterations for OSCC include the inactivation of the cyclin dependant kinase NZA (CDKNZA), inactivation of p53 located at 17p13, gain of chromosomal material at 3q26 and 11q13, and losses of chromosomal material at 3p21, 13q21 and 14q32.[5,3,4]

The literature suggests that OSCC in younger patients is aetiologically distinct from other OSCC cases considered.[4] OSCC in younger individuals has been shown to be more aggressive in many cases.[4] Since the known tobacco and alcohol risk factors are absent in these cases, it is necessary to consider the presence of other causative factors. Bodner *et al.* described in 2014 that the high occurrence of OSCC on the alveolar ridge in younger patients may be due to a high stem cell activity of the tooth-bearing regions. [4]

It is also necessary to consider the presence of viruses in the pathological aetiology of OSCC development. The relationship between Human Papilloma Virus (HPV) and OSCC is significant and was so noted when HPV DNA strands were found in OSCC specimens.[21] People having multiple sex partners are at a higher risk of developing OSCC [5,17] due to a higher chance of HPV contraction. The more virulent subtype is HPV16.

The relationship between oral health, periodontal disease and OSCC development has been documented.[20,21] Several theories of microbial interactions and inflammatory initiators of deregulation are proposed.[2] Two relatively newly discovered genotoxins, namely cytolethal distending toxin (CDT) and colibactin, have been associated with OSCC due to their ability to induce genomic instability, mutation and hence tumour progression.

The host defence has been shown to be crucial in the prevention of OSCC. Genetic, immune or dietary deficiencies may lead to a cascade of somatic cell

abnormalities which may be causative or contributory to OSCC development.[22] Conditions related to this group are drug addiction, nutrient deprivation, diabetes, Fanconi's anaemia, dyskeratosis congenital and scleroderma. Organ transplant patients are also at risk.[22]

It is important to note that the leukocytes constituting the body's defence system are crucial to survival. Without the action of the white blood cells, it is unlikely that we, as humans, would survive past infancy. [20] As bacteria enter the blood stream, the leukocytes engulf the bacteria or punch holes in the bacterial cell walls, thereby eliminating them. This "smouldering" inflammatory immune response which occurs long after the initial onslaught is now seen to be the cause of a more sinister problem. Several interleukins (IL) such as IL-6 and IL-9 as well as Matrix Metalloproteinases (MMPs) induce DNA damage and genomic instability with prolonged exposure[20]. Angiogenesis is promoted and thus the chance for tumour growth and progression. Much research is being done into controlling the immune response as an adjunct for cancer treatment. [20]

The literature provides strong evidence of the host diet in relation to OSCC development.[23] It is proposed that patients consuming increased amounts of fresh fruit and vegetables are at a lower risk of developing OSCC. [24,25] According to the literature, this is specifically true for yellow and orange fruits containing dietary antioxidants such as carotenoids and flavonoids, flavanones,

carotene, vitamin A, vitamin C and vitamin E and phytosterols. [25] Folate is also protective against OSCC development.

A mild iron deficiency and low glutathione levels are considered risk factors as they are associated with oxidative stress.[23] Smokers and drinkers can prevent OSCC development by up to 25% simply by consuming adequate quantities of fresh fruit and vegetables. [5,24] However, preserved fruit and vegetables are shown to be a significant risk factor in OSCC development. [5,25]

With OSCC proving fatal in over 50% of case [7,5], it is critical that health care providers gain a better understanding of OSCC presentation, epidemiological prevalence and regional specificity.

Pathogenesis

Several million cellular divisions occur daily, most of which are necessary to maintain homeostasis and normal physiologic functioning. However, several hundred thousand of these cellular divisions are potentially harmful in that the daughter cells may have undergone one or more genomic mutations.[4]

Mutations may occur at a number of places in the cell division cycle. Specialized check points exist within the cell cycle to systematically assess for any unwanted genetic aberrations which may have occurred during mitosis. These checkpoints are known as G_1/S and G_2/M. [16] These checkpoints are regulated closely by genes such as p53 and RB. The p53 gene, also known as the guardian of the human genome, is responsible for cell cycle inhibition in the event of an error in the cell replication process so that DNA repair may commence. [16] Consequently, it stands to reason that a mutation in the p53 gene or other similar controlling genes may lead to an inability of the gene to adequately control the cell cycle, leading to genomic instability and possible tumour development.[4,16]

Several exogenous and endogenous factors exist which may lead to genomic instability and hence tumour progression, making it a multifactorial disease. [4]

OSCC is defined by various other sources as a neoplasm that arises from multifocal areas of potentially malignant change. [4,18,19,27,28]

The term ‘oral cancer’ relates to all cancers involving the oral cavity, with the exception of the lip and neoplasms of the major salivary glands.[28] The term ‘potentially malignant’ has displaced ‘premalignant’ as it more accurately describes the nature and ability of these lesions progressing towards malignancy.[16,29]

As early as 1953, Slaughter had coined the term ‘field cancerization’ [27] which described OSCC as having a multicentre origin. This explained several significant clinical findings which were previously inexplicable. Slaughter stated that OSCC developed from a region or ‘field’ of genetically altered tissue that had undergone precancerous change rather than from a single cell that had become malignant.

Boudewijn and Braakhuis later expanded on Slaughter's theory of field cancerization by describing the genetic progression model. [18,19] This model describes the specific progressive genetic aberrations that occur within the host DNA. These genetic mutations and subsequent flaws in normal cellular function lead to the development and growth of a neoplasm which is clinically and histologically evident. [18,19]

The initial step in the genetic progression model involves early alteration of stem cells which presents clinically as a ‘patch’ formation[18,19]. The second step is the rapidly expanding ‘fields’ of genetically altered cells. Thirdly, a precursor

lesion develops within the field of genetically altered cells. Fourthly, a carcinoma arises with formation of a new precursor lesion. [27,18,19,28]

The clinical implications for the genetic progression model involve 'recurrence' of OSCC. This occurs in situations where there was incomplete removal of the carcinoma from the tissues, leaving malignant marginal cells behind. This is classified clinically as a tumour developing less than 2 cm away from the primary tumour in fewer than three years. In the situation where the entire tumour is removed with clear histological margins but the affected field still remains, one can expect a 'secondary field tumour' (SFT) arising from the same field as the primary tumour. This process may reoccur and give rise to a third and fourth tumour.[18,19] This is a significant problem since affected cell fields may be greater than 7cm wide in the oral cavity. [18,19] If the primary tumour and field are removed, the patient may still develop a 'secondary primary tumour' (SPT) unrelated to the initial tumour. [18,19] This is classified clinically as a tumour occurring more than 2cm away from the primary tumour after a minimum of three years. It is possible for a patient to develop a SPT in fewer than six months, in which case it is referred to as a 'synchronous secondary primary tumour' or otherwise. If the tumor occurs after six months it is termed a 'metachronous secondary primary tumour.' [18,19,28]

A more recent development is the ability to detect these abnormalities by using genetic markers, serum markers and salivary markers. The potential of these methods still has to be fully explored.

Investigations and Diagnosis

The ability to make a provisional clinical diagnosis is becoming increasingly valuable. Since an increased number of OSCC cases are presenting annually, health care workers would benefit from screening protocols that may aid in more rapid diagnosis of sinister lesions. The most important investigation of all is a detailed medical history. This often holds the secrets to the patients' condition before the clinical examination has taken place. Health care providers should spend time taking an extensive medical history which will direct them to a diagnosis. In 1980, Mashberg revised the process of using toluidine blue solution as an indicator of dysplasia.[30] It is important to note, however, that such an indicator is extremely sensitive to all rapidly dividing cells, but not specific to dysplastic cells. When the oral cavity is stained with the metachromatic toluidine blue solution, all tissues containing cells that are undergoing rapid cellular division are seen as darkly stained blue black patches. [30] This is true for malignant and healing tissues. Consequently, toluidine blue is indicative of dysplastic lesions, but it is not a means of diagnosis due to the chance of false positive readings.

Situations where false positive readings may be a reality are in cases of apthous ulcers or self-inflicted trauma of the mouth. One may also note the staining of surface cells constituting salivary gland openings. The process described by Mashberg, and later endorsed in a review by Scully and Bagan et al in 2008[31],

states that the process involves several steps. The patient is told to a) rinse with a 1% acetic acid (ethanoic acid) solution for 20 seconds; b) rinse with water twice for 20 seconds; c) rinse with 1cc-5cc of 1% toluidine blue solution for 20 seconds; d) rinse again with 1% acetic acid solution for 20 seconds, and e) rinse with water for approximately 60 seconds.

The process described above tempers the tissues and assists in the uptake of toluidine blue solution by the possibly dysplastic cells. The physiologic tendency of malignant cells to reflect light at differing wavelengths is known as birefringence. This property enables the clinician, with the help of various visual aids, to identify areas which are potentially malignant. The Velscope system[31] exploits this physiological trait of possibly malignant cells by displaying them as dark black patches among a sea of neon green healthy tissues.

Other optical spectroscopy systems are highlighted and described widely in the literature.[31] They include Raman spectroscopy, laser-induced fluorescence spectroscopy, light-induced fluorescence spectroscopy, elastic scattering spectroscopy, photo acoustic imaging, photon fluorescence, orthogonal polarization spectral (OPS) imaging, quantum dots, optical coherence tomography (OCT), trifocal spectroscopy, Doppler OCT, nuclear magnetic resonance spectroscopy, chromo endoscopy, narrow band imaging (NBI)m immune photo diagnostic techniques, differential path length spectroscopy, 2

photon fluorescence, second harmonic generation and Terahertz imaging.[31] Backscattering spectroscopy and low coherence spectroscopy have, however, been poorly reviewed and explored in clinical settings.[32]

It is noteworthy that the universal gold standard of diagnosis of OSCC is still the histopathological analysis of a biopsy sample taken adjacent and including the lesional tissue. The biopsy can be achieved incisionally, excisionally or using a brush.

AIMS AND OBJECTIVES

The aim of the study was to characterize the patient cohort by determining the most typical gender, race, age, site, predisposing factors, grade and size of lesion in the population group presenting to the Department of Oral Medicine and Periodontology Wits Oral Health. This will provide insight into the occurrence of the disease in the population group at Wits Oral Health Sciences during the specified period. This will also aid swift recognition and diagnosis of these lesions in future.

HYPOTHESIS

It was hypothesized that the epidemiological trends of OSCC in patients seen at the Wits Oral Health Services differed from other regions around the world due to a different risk model.

MATERIALS AND METHODS

Study design and sample

The study was designed as a retrospective study reviewing data within the Department of Oral Medicine and Periodontology. Seven hundred and thirteen (713) archived files from 1990 up to and including 2010 (twenty one year period) were analysed. Of these files, one hundred and seven (107) were found to represent OSCC cases.

Inclusion criteria

Of the one hundred and seven files, only those containing histological reports confirming diagnosis were included in the final sample. This left eighty one (81) computable files.

Method

A retrospective review of diagnosed OSCC cases from the Wits Department of Oral Medicine and Periodontology between 1990 and 2010 (21 year period) was performed. A final total of Eighty one (81) computable files from an original seven hundred and thirteen (713) files were assessed. Demographic, clinical and histological data such as age, gender, race, anatomical site of occurrence, alcohol consumption, smoking as a habit, snuff use, identifiable risk factors, systemic diseases, lymph node involvement, size of lesion and histological differentiation were obtained. Anatomical sites of the lesion were classified as described by the International Statistical Classification of Diseases[33], which

covers cancer of the tongue, gingivae, floor of the mouth, palate, and other unspecified parts of the mouth as well as related health problems.

The histological differentiation degree was classified as well differentiated (WD), moderately differentiated (MD) or poorly differentiated (PD) according to the World Health Organization (WHO) guidelines. [34]

Data Collection

The data was collected utilizing data collection sheets (see Appendix 1) and results were tabulated prior to entering them onto an Excel spreadsheet for commencement of data analysis. Data was categorized into categories such as age, gender, smoking, alcohol consumption, snuff use, dietary deficiencies, site and lymph node involvement. Two other categories were added for statistical benefit which included 'incomplete available clinical data' and 'no identifiable risk factors'. Given the relatively small sample size anticipated for the study, the focus was on descriptive analysis. Univariate statistics; mean, standard deviation, median, interquartile range for continuous variables, percentages and frequency distributions for categorical variables were presented for all key variables.

For further analysis, continuous variables (e.g. age, size of lesion) were categorised into clinically meaningful categories. Associations between variables were subjected to the chi-square test. Fisher's exact test was used for 2 x 2 tables or where the requirements for the chi-square test could not be met. The *strength* of the associations was measured by Cramer's V (for chi-square test) and the phi coefficient (for Fisher's exact test). Data analysis was carried out in SAS. A 5% significance level was used throughout, unless specified otherwise.

ETHICAL CONSIDERATIONS

Ethical clearance was granted (Ethics Approval # M140654) see Appendix 2.

RESULTS

Trends:

When considering the data obtained and categorizing it into five-year periods, the number of patients presenting with OSCC appears to have increased dramatically in the last decade of the study period. See fig 1.

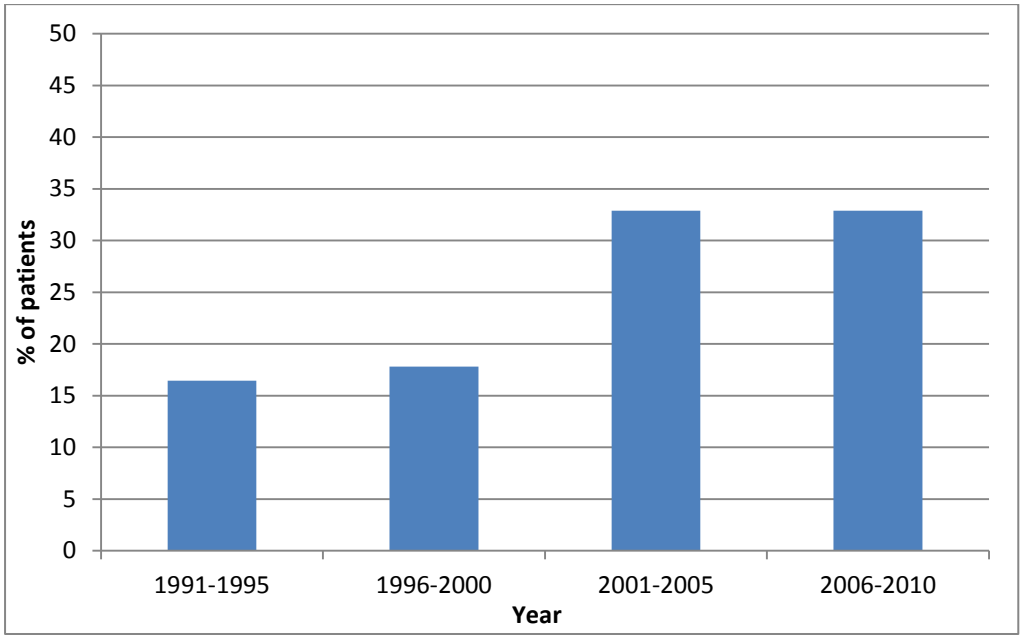

FIGURE1. A GRAPHICAL REPRESENTAION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF TIME

The age distribution was as shown in Figure 2, with the mean age of the patient at 56.3 years (sd 11.9y; range 24-79y; median 57.5y, interquartile range 50-64.5y).

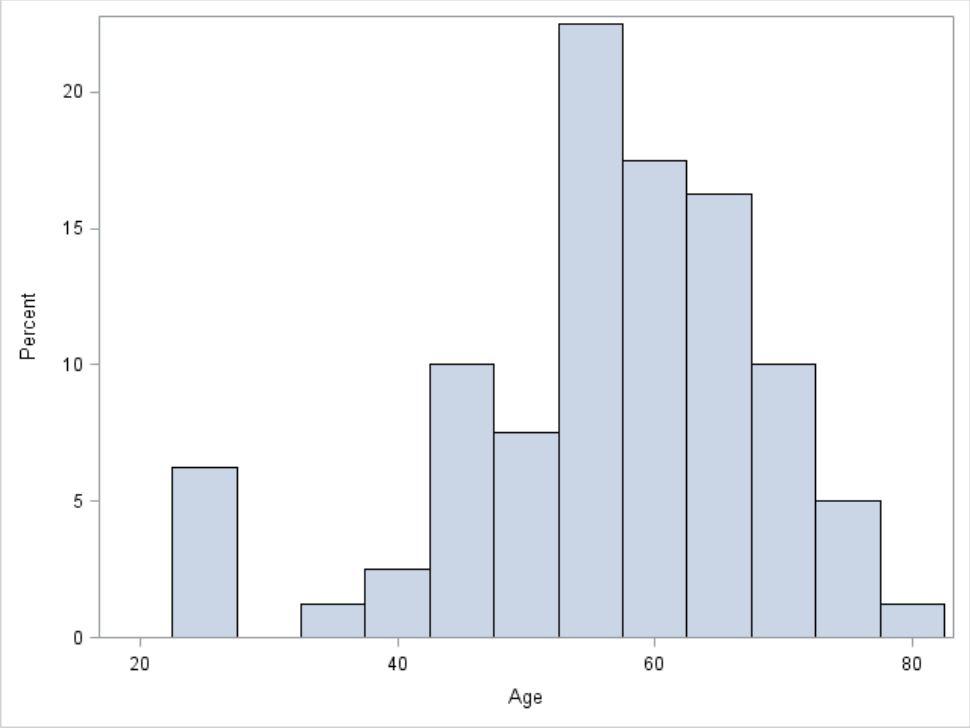

FIGURE 2. A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF AGE

Results showed that 73.8% of the study group was male. The majority of the patients (60.0%) were Black (Fig. 3).

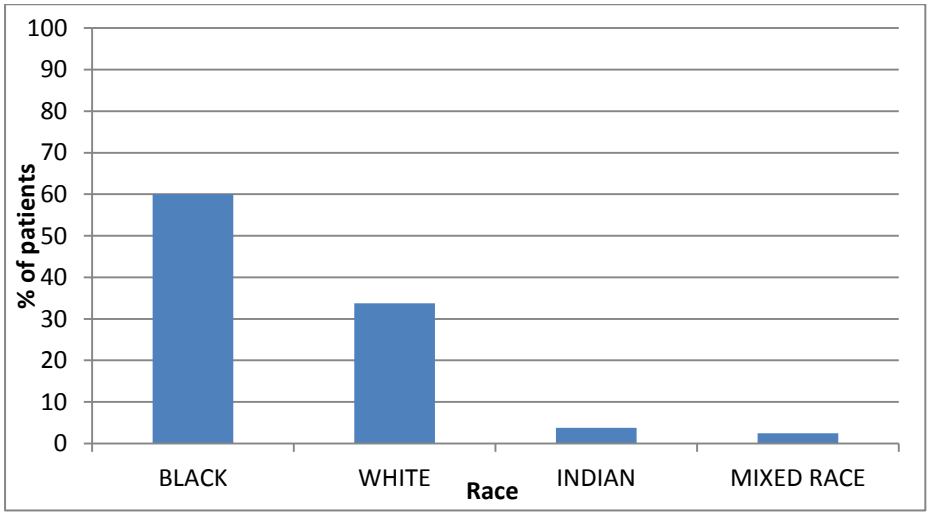

FIGURE 3. A GRAPHICAL REPRESENTAION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF RACE

Results showed that 68.8% of the patients' records were partially incomplete within the parameters of the inclusion criteria.

Risk Factors:

It was noted from the files containing alcohol data that 45.0% of the patients reported alcohol use (fig 4)

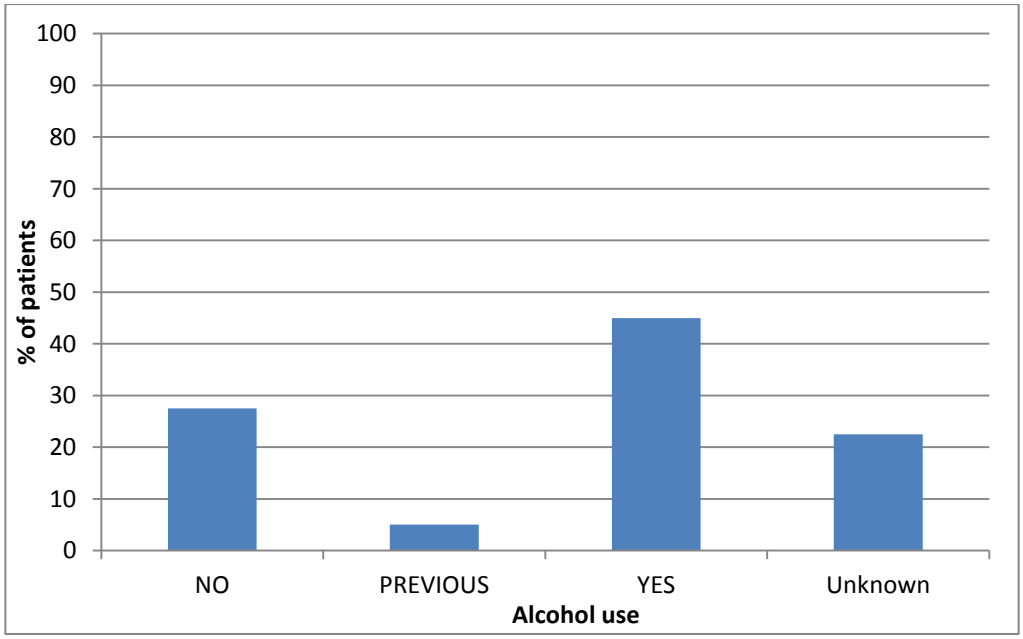

FIGURE 4. A GRAPHICAL REPRESENTAION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF ALCOHOL USE

It was noted that 72.5% of the patients were current smokers. This variable was categorised as light smoking (<10 per day) or heavy smoking (>= 10 per day). In 53.5% of cases, the patients smoked more than 10 cigarettes per day. One patient (1.3%) reported snuff use. There were no identifiable risk factors for 83.8% of the study group. Malnourishment was reported in 5.0% of the study

group. In 41.2% of the study group, systematic abnormalities or diseases were noted such as Fanconis anaemia, diabetes and congenital heart defects however there was no statistical significance found.

Presentation / Characteristics:

The majority of patients had one (43.8%) or two (38.8%) sites affected (Fig. 5).

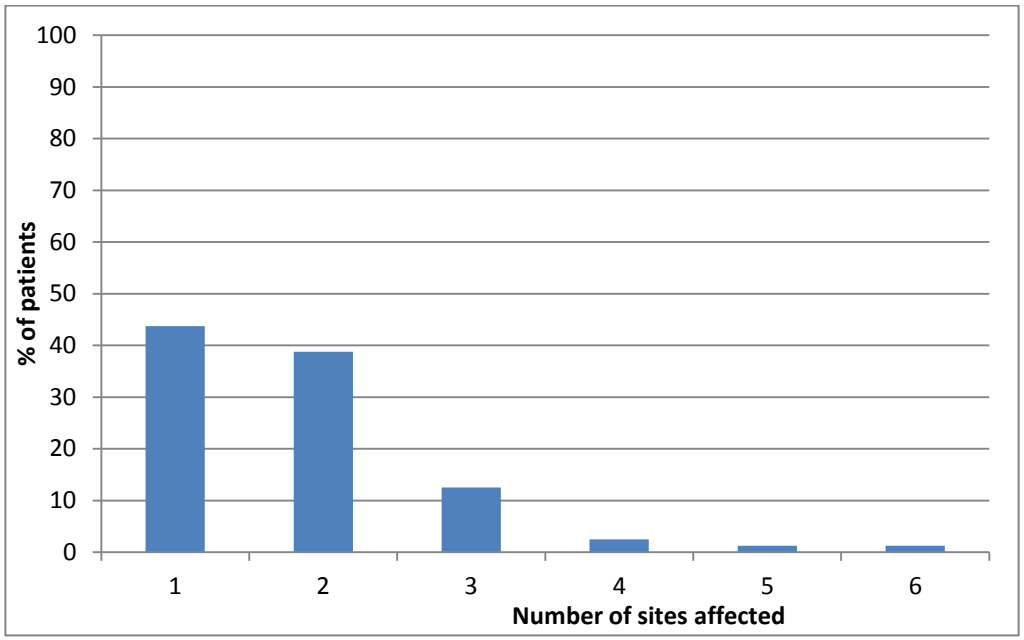

FIGURE 5. A GRAPHICAL REPRESENTAION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF NUMBER OF SITES AFFECTED

The floor of the mouth was most frequently affected (60.0% of patients). Note that percentages do not add to 100% since some patients had more than one site affected (Fig. 6).

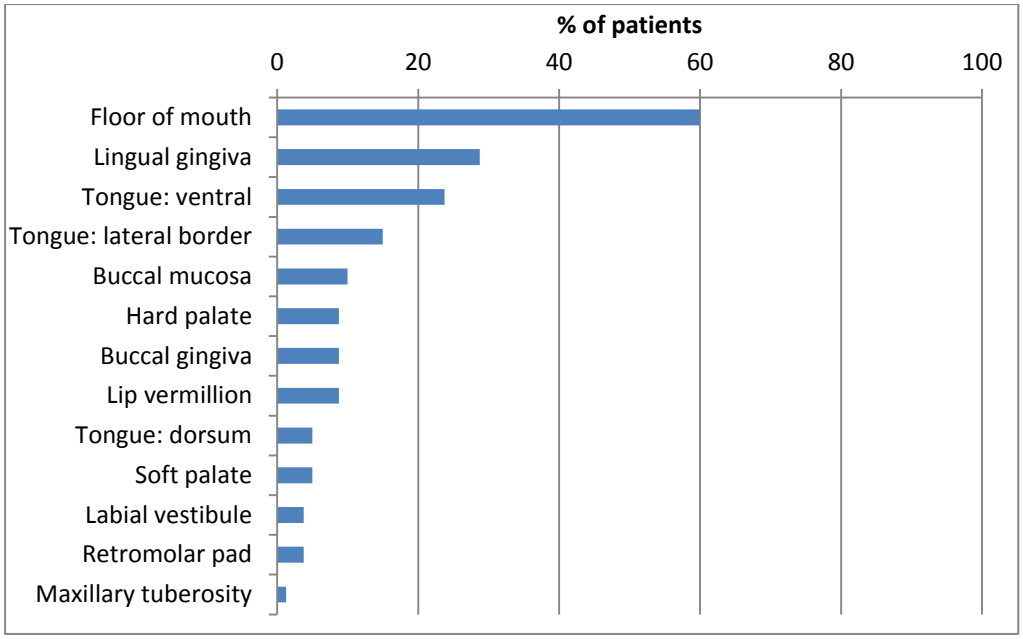

FIGURE 6. A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF ANATOMICAL SITE

The size of the lesion was unknown in 20% of the patients due to insufficient record keeping. The mean size of the lesion was 915mm^2 (sd 1 580; range 8-10 000; median 425, interquartile range 115-1 000mm^2). The distribution of sizes is shown in Figure 7.

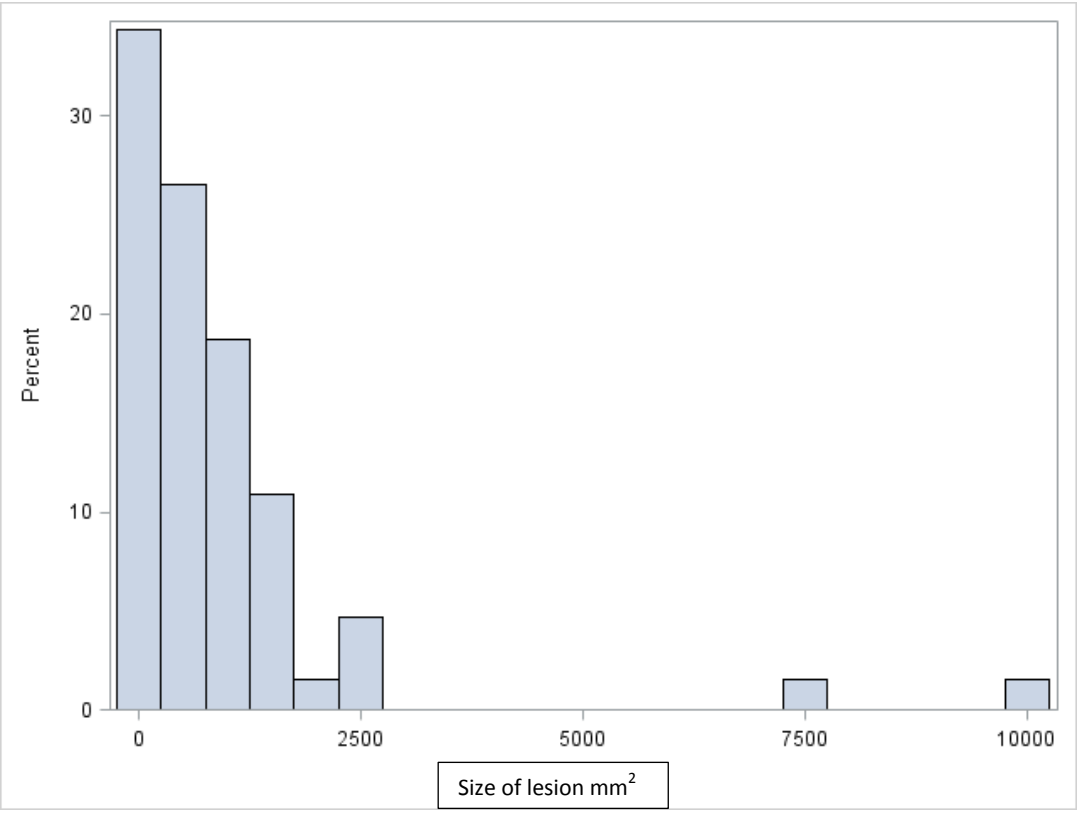

FIGURE 7 . A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF SIZE

The majority of patients (70%) had moderately differentiated lesions (Fig. 8).

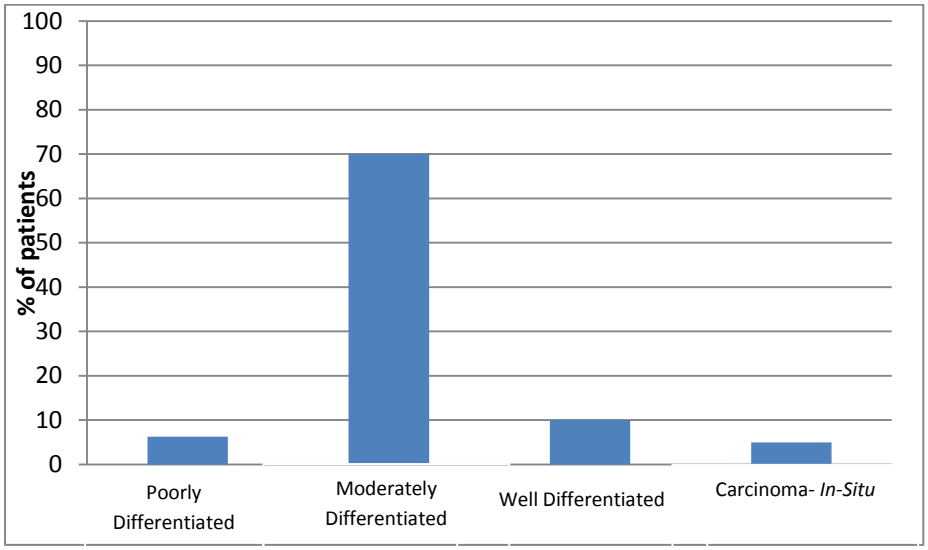

FIGURE 8 . A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF DIFFERENTIATION (POORLY DIFFERENTIATED, MODERATELY DIFFERENTIATED, WELL DIFFERENTIATED, CARCINOMA IN SITU)

In 43.8% of the patients, lymph node involvement was present. The submandibular lymph node was most frequently affected (91.4% of patients). Note that percentages do not sum to 100%, some patients had more than one site affected (fig 9).

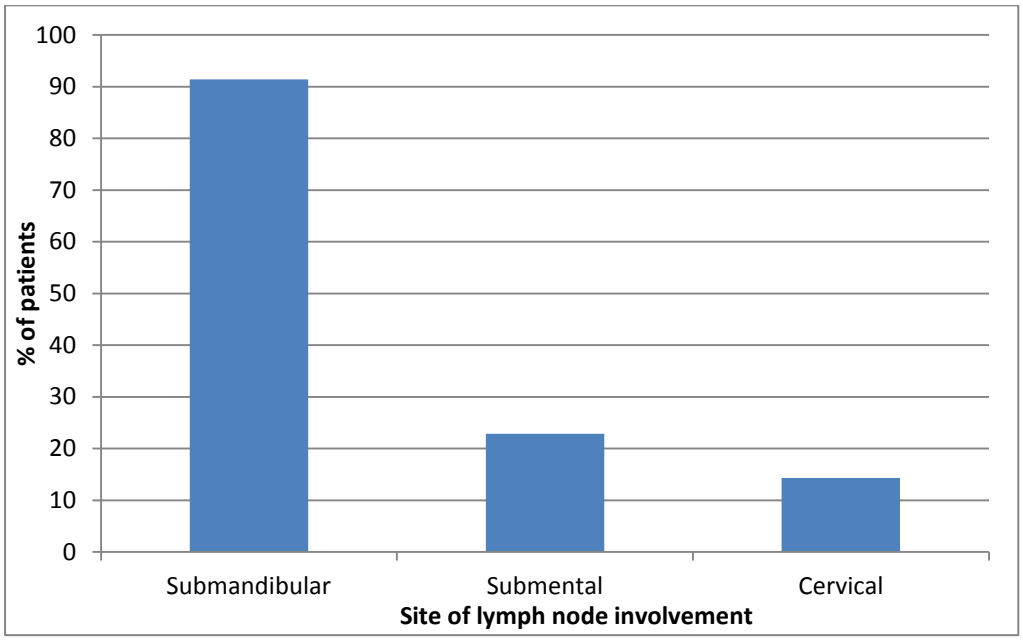

FIGURE 9 . A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS PRESENTING WITH OSCC AS A FUNCTION OF SITE OF LYMPH NODE INVOLVEMENT

Associations:

There were two significant associations made between variables in the study. A strong association between categorised size of lesion and year of presentation was made ($p=0.029$; phi coefficient=0.51): The proportion of small lesions decreased over time, while that of lesions sized between 101 and 1000 mm^2 increased with time (Fig. 10).

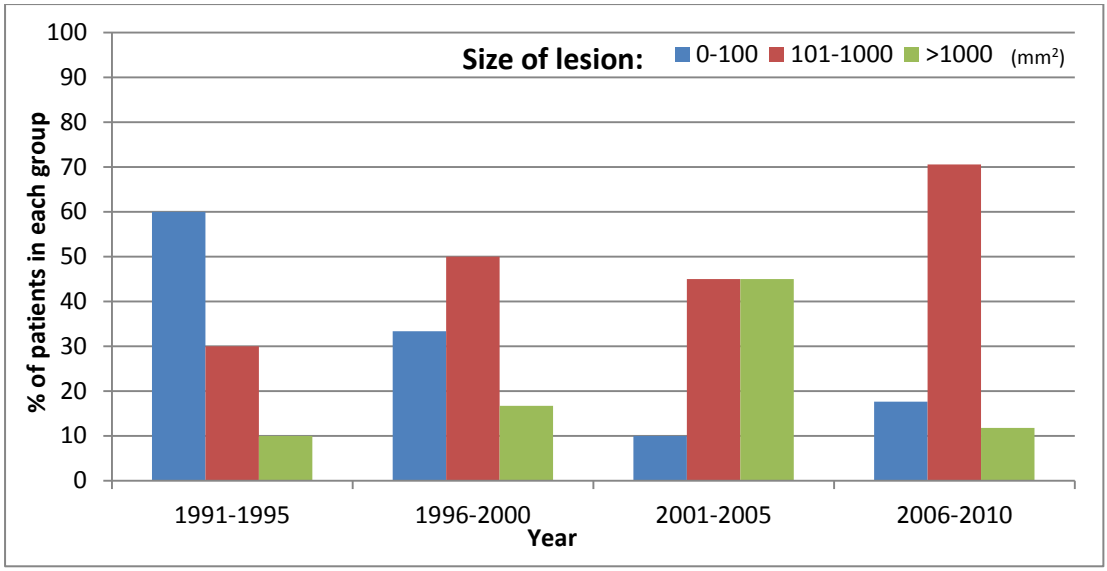

FIGURE 10 . A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS IN GROUPED LESION SIZES AS A FUNCTION OF TIME

A moderate association with size of lesion and age was made (p=0.027; phi coefficient=0.48): The size of the lesion increased with age (Fig. 11).

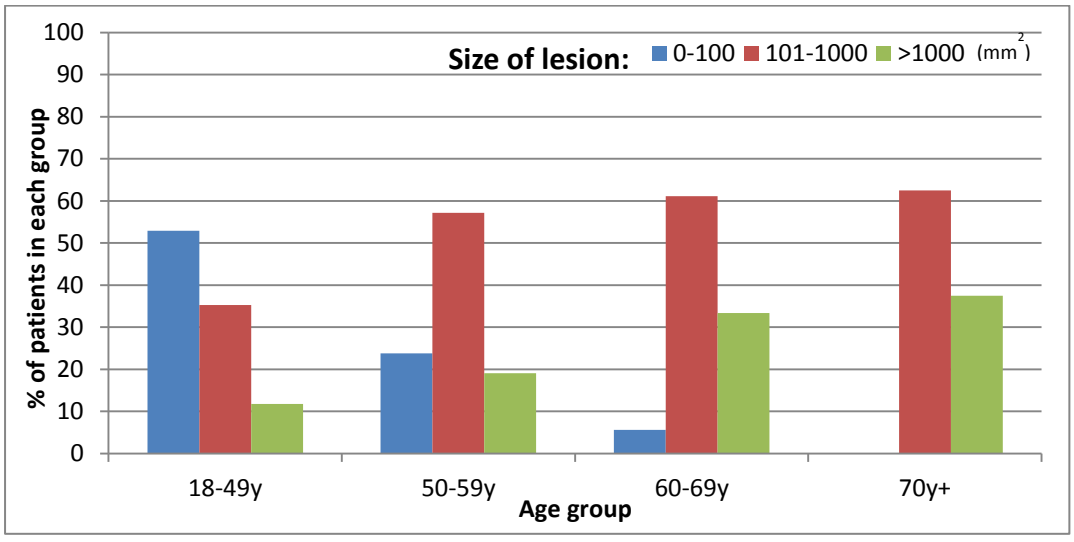

FIG 11. A GRAPHICAL REPRESENTATION OF PERCENTAGE OF PATIENTS IN GROUPED LESION SIZES AS A FUNCTION OF AGE

DISCUSSION

The study confirmed that the most affected individuals are males (73,8%) with an average age of 56.3 years. with the majority of lesions occurring on the floor of the mouth (60%). This concurs with the literature on global figures.[7,46] The study concluded that the most typical race however was Black and not Caucasian. This is expected, considering South Africa has a majority black population. The fact that alcohol and smoking were implicated in 45% and 72.5% of cases respectively reiterate their significance as risk factors in the aetiology in OSCC development and aligns this study with similar views held by others. [3,4]

The mean size of the lesion found on initial presentation was 915mm^{2,} which relates to a 30x30mm lesion. Since two thirds of all lesions worldwide present in their advanced stages, [12, 13] it is not an unusual finding that the majority of cases in this study were rather large moderately differentiated tumours (70%). There was lymph node involvement in 43.8% of cases, with the submandibular lymph node being the most commonly implicated lymph node group (91,4%). Interestingly, 43% of cases presented with a single site of involvement, whereas 38,8% of cases were found to have two or more sites involved. These sites may have been independent OSCC tumours or, more likely, secondary field tumours.

The proportion of small lesions decreased over time, while that of lesions sized between 101 and 1000 mm^2 increased over the 21-year period. This is an interesting finding, indeed since this indicates that lesions are larger on presentation in the more recent years of the study. This result may be due to poor access to health care facilities allowing lesions to increase in size before the condition takes priority and treatment is sought. Another possibility may be the implication of HIV in OSCC progression. Oral squamous cell carcinoma is already classified as an HIV associated malignancy along with other cancers of the head and neck.[35] Further research is required to accurately assess the influence of HIV on OSCC progression in South Africa.

Interestingly, another factor revealed by this study was that 5% of the cases reported malnourishment. This may have been caused by an inability to consume food effectively due to pain or size of the lesion. Malnourishment however does contribute to OSCC development [24,25,26] and hence it is difficult to distinguish clinically which came first.

Although the incidence of specific diseases was not recorded in this study, 41.2% of cases presented with one or more systemic disease or abnormality. These ranged from aquired to genetically predisposed congenital conditions which may or may not have affected the development of OSCC in this population group.

This study found that the average lesion size increased with age (Fig. 2). This is not uncommon as similar findings have been reported in the literature. For example, this is the case for a study done in Rio De Janeiro where approximately 50% of all the cases assessed were in age categories above 60 years old. [47]

LIMITATIONS

All appropriate files were reported on and included in the study within the specified period irrespective of the numbers, as the aim was to identify the specific profile of patient and lesion characteristics within the population group presenting to Wits Department of Oral Medicine and Periodontology.

The final sample size was a result of stringent selection criteria which ruled out many files due to incompleteness and missing supportive documentation

The impact of HPV and HIV were not considered in this study. Since files were handwritten, certain files were illegible and certain parameters regarding lesion specifics could not be assessed. Certain variables such as alcohol type or quantity were often not recorded adequately and hence quantifiable factors could not be extrapolated. Depth and height of the lesions were not recorded in majority of cases and hence only a surface area could be recorded rather than a volume.

It was speculated that patients underestimated the frequency of cigarettes smoked and quantity of alcohol consumed, however this is anecdotal.

The study also highlighted several other key issues that were not foreseen. These include issues concerning recording keeping. Certain file formats over a 21-year period offer a more extensive clinical record of cases examined than

others. This is extremely important as a retrospective study such as this is solely dependent on the accurate and extensive clinical data recorded on the file.

The lack of adequate history and examination protocols rendered many files fruitless and hence non-contributory within the confines of this study. The misplacement of histological records, incorrect diagnosis and no follow up appointments also further rendered many files as outliers.

CONCLUSION

Oral squamous cell carcinoma is a multifactorial disease of grave importance. Smoking and alcohol consumption appear to be the main aetiological factors in our region, which concurs with worldwide trends. Special consideration must be given to means of decreasing the amount of smoking and alcohol consumption amongst the population.

Contributing economic factors such as poor access to health care facilities and pathophysiologic factors such as HIV all increase the incidence of OSCC. By educating patients on the aetiology of OSCC and its clinical presentation, we can increase awareness. By making health care facilities more accessible, we can decrease the time between onset and diagnosis and consequently improve the prognosis. HIV management is essential in controlling the destruction of the immune system and consequently preventing the onset of multifactorial diseases like OSCC.

We can conclude that the hypothesis of this study was disproved and the most typical patient presenting to Wits Oral Health Sciences with OSCC matches global statistics despite a differing risk model. This is shown within the confines of this study as the most typical patient is a male between the 5th and 6th decades of life. Lesions most commonly occur on the floor of the mouth with submandibular lymph node involvement being the most frequently involved group of lymph nodes. It was found that 72.5% of patients reported a habit of

smoking and 45% of patients reported alcohol consumption. It was found that 45% presented with only 1 site affected and 70% of patients presented with a moderately differentiated lesion. Most importantly and unexpectedly we found that the average lesion size has increased over the last 10 years of the study. This highlights our failed efforts as clinicians to bridle this sinister disease and we should heed the fact that this may signify a serious future health care problem.

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APPENDIX 1

Data collection sheet:

1) Case study Number:

2) Patient age:

3) Gender:

4) Smoker:

Frequency:

5) Snuff Use:

Frequency:

6) Alcohol consumption:

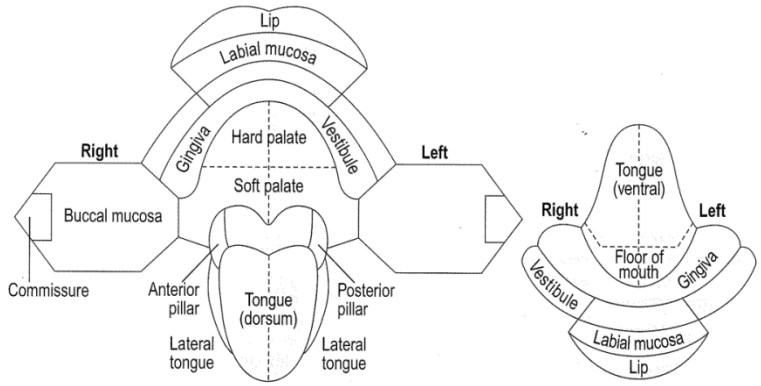
Frequency:

7) No identifiable risk factor

8) Incomplete available clinical data

9) Dietary deficiencies or abnormalities:

10) Site:



11) Lymph node involvement

12) Site of lymph node involved

13) Size of Lesion (mm^2)

14) Degree of Differentiation

APPENDIX 2

R14/49 Dr Rhoodie Garrana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140654

NAME: (Principal Investigator)	Dr Rhoodie Garrana
DEPARTMENT:	Oral Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Profiling of Oral Squamous Cell Carcinoma Patients Presenting to the Wits Dept of Oral Medicine and Periondontology
DATE CONSIDERED:	27/06/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof S Shangase
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/07/2014

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 Secretary in Room 10004, 10th floor, Senate House, University.

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.**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES