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HEAD AND NECK LYMPHOMAS: A 20 YEAR RETROSPECTIVE REVIEW OF CASES DIAGNOSED IN AN ORAL PATHOLOGY UNIT, JOHANNESBURG, SOUTH AFRICA

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

Master of Science in Dentistry

in the branch of Oral Pathology

Johannesburg, March 2016

DECLARATION

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

.....

Nasreen Alli

4th day of March 2016

DEDICATION

To my parents and husband

ABSTRACT

Introduction: Lymphomas are the most frequent non-epithelial oral and maxillofacial malignancy. Non-Hodgkin lymphoma (NHL), though not common in the oral cavity is reported with increasing frequency in patients with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). An increased risk of lymphoma development is also seen in persons with primary immunodeficiency and connective tissue diseases and patients on cytotoxic immunosuppressive treatment. With South Africa looming as a country with the highest incidence of HIV and AIDS worldwide, an epidemiologic study would provide valuable insight into head and neck lymphomas in a defined South African population.

Aim: This retrospective review is aimed at evaluating the frequency and clinico-pathologic characteristics of patients diagnosed with head and neck lymphoma at the Department of Oral Pathology, University of the Witwatersrand, Johannesburg over the 20 year period, 1993-2012.

Methods: Histopathology reports of patients diagnosed with lymphomas of the head and neck were reviewed. Epidemiological data including the demographic, clinical, laboratory, and histological parameters for each patient were recorded. Variables included, amongst others age, gender, site, size of tumour, histologic subtype of lymphoma and year of diagnosis. Lymphomas were classified according to the 2008 World Health Organisation classification of tumours of lymphoid neoplasms.

Results: There were 504 patients (2.24%) with head and neck lymphomas. The median age was 39 years and the age range was 2 to 100 years. The male:female ratio was 1.13:1. The cervical lymph node was the most common anatomic site (115 cases) and the maxilla (60 cases) was the most common extranodal site. Plasmablastic lymphoma (159 cases) was the most common histologic subtype followed by diffuse large B-cell lymphoma

(155 cases). The most common Hodgkin's lymphoma (HL) was nodular sclerosing HL (21 cases). Ninety percent of cases were NHLs and ten percent were HL. Seventy-three percent of cases were extranodal and twenty-seven percent were nodal in origin. A mass/swelling was found to be the most common clinical feature and B symptoms only occurred in one patient.

Conclusion: This study confirmed the increase in head and neck lymphoma frequency over the 20 year period, contrary to that found in Western countries, which show a decline in incidence with highly active antiretroviral therapy. Oral and maxillofacial lymphomas occurred predominantly in the third decade with a strong male bias. Most were extranodal, presenting as ulcerated painful swellings. This study serves as a baseline for future head and neck lymphoma studies, especially in a South African setting.

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ABBREVIATIONS

TERMINOLOGY	ABBREVIATION
Acquired immune deficiency syndrome	**AIDS**
Anaplastic lymphoma kinase	**ALK**
Anti-retroviral therapy	**ART**
Burkitt lymphoma	**BL**
Central nervous system	**CNS**
Chronic lymphocytic leukaemia	**CLL**
Classic Hodgkin's lymphoma	**CHL**
Diffuse large B-cell lymphoma	**DLBCL**
Epstein-Barr virus	**EBV**
Extranodal	**EN**
Follicular lymphoma	**FL**
Hepatitis C virus	**HCV**
Highly active anti-retroviral therapy	**HAART**
Hodgkin's lymphoma	**HL**
Human herpes virus 8	**HHV8**
Human immunodeficiency virus	**HIV**
Human T-cell lymphotrophic virus	**HTLV**
Human T-cell lymphotrophic virus 1	**HTLV-1**
Male:Female	**M:F**
Mucosa-associated lymphoid tissue	**MALT**
Nodal	**N**
Non-Hodgkin's lymphoma	**NHL**
Not otherwise specified	**NOS**
Plasmablastic lymphoma	**PBL**
Small lymphocytic leukaemia	**SLL**
Waldeyer's tonsillar ring	**WR**
World Health Organisation	**WHO**
United States of America	**USA**

CHAPTER 1

1.0 INTRODUCTION

Lymphomas comprise a diverse group of neoplasms, affecting the lympho-reticular system, originating from cells of the immune system at different stages of their differentiation and eventually resulting in varying histology, immunophenotypes, genetic abnormalities and clinical findings (Agrawal, Agrawal & Kambalimath 2011; Zini et al. 2012). Non-Hodgkin's lymphomas (NHLs) can arise from either B cells, T cells or NK cells, but arise more frequently from B cells (Cawson & Odell 2002), and plasmacytoma is a special clinical entity that occurs primarily in the bone marrow (Scherfler et al. 2012). However, despite their cell type, all lymphomas are malignant and can range from being relatively indolent to highly aggressive in nature (Cawson & Odell 2002; Zini et al. 2012). All lymphoid neoplasms are referred to as monoclonal as they are derived from a single transformed cell (Kumar, Abbas & Aster 2007).

Over the last decade, great progress has been made in formulating an internationally recognised classification for lymphoid neoplasms. The widely accepted World Health Organisation (WHO) classification of haemato-lymphoid neoplasms includes the morphologic, phenotypic, genotypic and clinical features of each entity. This classification separates lymphoid neoplasms into Hodgkin's lymphoma (HL), NHL and lymphoid leukaemia and thereby encompassing the solid and circulating phases of lymphoma and lymphoid leukaemia (Huh 2012). As traditionally known and for simplification purposes, lymphomas are referred to as HL and NHL (Kumar, Abbas & Aster 2007).

A number of NHL histotypes do not originate from lymph nodes and arise from sites that do not normally contain lymphoid tissue (Bussu et al. 2013). These are referred to as primary extranodal lymphomas (Bussu et al. 2013). According to Kemp et al. (2008), up to 40% of NHLs occur at extranodal sites and about 2-3% of these extranodal lymphomas occur in oral sites.

Lymphomas were thought to be exceptionally uncommon in the mouth but to frequently affect the cervical lymph nodes (Cawson & Odell 2002). However, with the acquired immune deficiency syndrome (AIDS) pandemic over the last few years, lymphomas may now account for almost 2% of oral neoplasms (Cawson & Odell 2002). Apart from human immunodeficiency virus (HIV) and AIDS, an increased risk of developing a lymphoma is also seen in persons with primary immunodeficiency diseases, those with connective tissue diseases, especially rheumatoid arthritis and Sjögren's syndrome, and patients on cytotoxic immunosuppressive treatment (Cawson & Odell 2002).

Lymphomas are the most frequent non-epithelial malignant tumours in the oral and maxillofacial region and they can present as nodal disease, extranodal or a combination of both (Zini et al. 2012). Following the gastrointestinal tract, the head and neck region is said to be the second most frequent site for extranodal lymphomas (Bussu et al. 2013; Agrawal, Agrawal & Kambalimath 2011). HL is known to present as nodal disease whereas NHL may develop extranodally (Agrawal, Agrawal & Kambalimath 2011). HL and NHL each display distinct morphological characteristics, biological behaviour, epidemiological and prognostic features, with varying responses to treatment (Oluwasola et al. 2011).

HL is characterised by the presence of distinct Reed-Sternberg giant cells, a feature that sets HL apart from NHL, and which in involved nodes are generally greatly outnumbered by non-neoplastic inflammatory cells (Kumar, Abbas & Aster 2007). HL has a fairly good prognosis. NHL in itself is a diverse group of lymphoid malignancies and is approximately nine times more common than HLs (Walter et al. 2015). Due to the great diversity of NHL, its prognosis and treatment varies. Treatment involves radiation and/or chemotherapy and depending on the cell type, a specific chemotherapy regime must be followed (Wilson & Wright 1986).

NHL is not commonly seen in the oral cavity but has been reported with some frequency in patients with AIDS (Basavaraj et al. 2012). Some studies state that malignant lymphomas are the second most frequent malignancy of the oral cavity and maxillofacial region following squamous cell carcinoma (Kemp et al. 2008; Scherfler et al. 2012) while others say it ranks third following squamous cell carcinoma and salivary gland neoplasms (Triantafillidou et al. 2012; Kolokotronis et al. 2005). Some of the other sites affected in the head and neck region include Waldeyer's tonsillar ring (WR), the orbit(s), paranasal sinuses, nasal cavity, salivary glands and larynx.

Lymphomas make up approximately 10-12% of all malignancies in paediatric patients (Gualco et al. 2010). Of this, approximately 4-7% is HLs and 7-10% is NHLs (Gualco et al. 2010). Childhood NHL differs from adult NHL in biological behaviour, staging system, disease types, treatment and outcome (Gualco et al. 2010). NHLs in adults are often low to intermediate grade, whereas the majority of NHLs in children are high grade (Gualco et al. 2010). Over the past two decades, the incidence of NHL among children

younger than 15 years, has remained almost constant, while there has been a slight increase in incidence for the age group 15-18 year olds (Gualco et al. 2010).

Whilst there have been various global epidemiological reports on head and neck lymphomas, each focusing on different epidemiologic variables including amongst others age, gender, anatomic site (Bussu et al. 2013; Iguchi et al. 2012), there is a dearth in the literature regarding African and more especially South African studies on head and neck lymphomas.

Furthermore, numerous reports in the literature reflect on the increase in head and neck lymphomas with the HIV and AIDS pandemic (Chetty, Sudi & Abayomi 2012; Agrawal, Agrawal & Kambalimath 2011; Brower 2011), and with South Africa looming as a country with the highest incidence of HIV and AIDS (Granich et al. 2015) worldwide, a study of this nature would provide valuable and novel insight on the epidemiology of head and neck lymphomas within a South African population. Due to the change in disease incidence, patterns and virulence over the past two decades, a retrospective study of this nature will help us evaluate how Africa and South Africa compare to the rest of the world in terms of disease.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 Terminology: Head and neck lymphomas

Terminology pertaining to lymphomas encountered in the oral and maxillofacial region varied considerably in the literature, with studies using terms ranging from head and neck lymphomas to cranio-maxillofacial lymphomas (Bussu et al. 2013; Scherfler et al. 2012). Similar to our study, most international studies on head and neck lymphomas generally encompassed all lymphomas of the head and neck region encountered in the oral and maxillofacial pathology diagnostic unit (Hart et al. 2004; Scherfler et al. 2012; Triantafillidou et al. 2012). Although this study was performed in an oral pathology unit, where the referral cases are mostly oral, perioral and orofacial as well as salivary gland neoplasms, the odd cases of lymphomas of the larynx, orbit and scalp diagnosed within the unit were included in the study as part of the head and neck group of lymphomas.

Kolokotronis et al. (2005) in their study, excluded jaw NHLs as they felt it should be discussed with lymphomas of the bone. However, the only study with specific inclusion and exclusion criteria was the South African study by Chetty, Sudi & Abayomi (2012) that excluded central nervous system (CNS), thyroid, laryngeal, nasal and paranasal lesions as well as the so-called 'grey-zone' lymphomas and precursor lymphoid neoplasms. Their inclusion criteria included the oral cavity (all areas from the lips anteriorly and extending posteriorly up to, but excluding the oropharynx). Jaw lesions were included and skin lesions of the head and neck were included as primary cutaneous lesions.

2.2 Epidemiology

2.2.1 Lymphoma incidence in the West and Asia

According to Huh (2012) the lack of a standardised classification system, has had a great negative impact on the epidemiological study of malignant lymphomas worldwide and has therefore prevented important global comparison and analysis. However, the general consensus with the information at hand is that malignant lymphomas are more common in the developed countries (Europe, North America, Australia and New Zealand) and less common in the developing countries (Asia and Africa), with the exception of Burkitt lymphoma (BL) in its endemic population (Huh 2012). East Asia has one of the lowest incidence rates (Huh 2012). Globally, the incidence of malignant lymphoma has shown to increase by 3-4% over the past four decades, however during recent years, some stabilisation has been noticed in the developed countries (Huh 2012).

The NHL incidence has been on the increase since 1970 in all populations (Huh 2012). However, in the West especially the United States of America (USA), the steady increase of 3-4% each year started to show a slight decrease to 1-2% by the mid 1990 (Huh 2012). While in Asia (Korea) a consistent increase was seen with no stabilisation (Huh 2012).

In comparison to NHL, HL has a consistently lower incidence rate globally, which is either decreasing or static (Huh 2012). The reason for this however is not known (Huh 2012). On the other hand, an increase in the HL incidence has been observed in the female population (Huh 2012). This increase in HL in the Korean female population has been attributed to females delaying motherhood and childbearing, linking this to being a means of protection against HL (Huh 2012).

Due to this new female trend, the HL incidence is expected to increase further (Huh 2012). It is also important to note the effects of environmental factors on lymphomagenesis. This is highlighted by the difference in incidence in genetically similar ethnic populations (Koreans and Chinese) living in diverse environments, as illustrated by Huh (2012) in the example of resident Koreans versus migrant Koreans in the USA. The risks of lymphoma development associated with a particular geographic area in a specific ethnic group would be dependent on the age at migration, duration of residence and residential neighbourhood (Huh 2012). This was further illustrated by Clarke et al. (2011) as cited by Huh (2012) who found significantly higher rates of follicular lymphoma (FL), small lymphocytic lymphoma (SLL) and nodular sclerosing HL in Asians born in the USA when compared with foreign born Asians.

Various international studies have been published on lymphomas of the head and neck (Bussu et al. 2013; Iguchi et al. 2012; Beasley 2012). Previous reports show that lymphomas contributed about 5% of all head and neck malignancies (Iguchi et al. 2012; Scherfler et al. 2012). However, a recent large scale USA database on head and neck cancers has shown lymphomas to have an incidence rate of 12.4% (Cooper et al. 2009 as cited by Iguchi et al. 2012). Iguchi et al. (2012) showed a similar incidence rate of head and neck lymphomas of 15.1%. This data is in keeping with the overall increase in the incidence of malignant lymphomas worldwide (Huh 2012).

Over the past 30 years, the incidence of NHL has increased drastically in the USA as well as in other countries; however the USA has higher incidence rates compared to many other countries (Chiu & Weisenburger 2003). The difference is evident especially for FL cases in Western countries compared to developing countries as well as in China and Japan

(Chiu & Weisenburger 2003). The reason for these international differences has been attributed to geographic differences in aetiological and host factors.

Generally however, the increase in the incidence of NHL is not well understood. Possible reasons for this increase include improved diagnostic techniques, HIV and AIDS, immunosuppressive therapies, immunodeficiency, infections [Epstein-Barr virus (EBV), Human T-cell lymphotrophic virus (HTLV), Hepatitis C virus (HCV)], familial aggregation, blood transfusion, diet, agricultural and pesticide exposures, occupation, genetic susceptibility and lifestyle factors (Chiu & Weisenburger 2003).

2.2.2 Lymphoma incidence in Africa

According to Oluwasola et al. (2011), NHL is quite rare in most African countries; however there is a higher incidence in North and sub-Saharan Africa due to the high number of BL cases in kids in the tropical regions of Africa. In 1976, Ibadan (Nigeria) reported one of the highest incidences of lymphoma cases globally, to the International Agency for Research on Cancer (Oluwasola et al. 2011). However, the incidence of BL from the 1960s, 1970s and 1980s to 1990s has decreased from 50% to 37% and to 19.4% in the 1990s (Oluwasola et al. 2011). This decrease was attributed to malaria control, better living conditions and possibly a decline in EBV infection (Oluwasola et al. 2011).

A recent retrospective study in Ibadan from 1991-2005, also showed a decrease in the number of cases from 58 cases in 1991 to 24 cases in 2005 (Oluwasola et al. 2011). The decrease was seen in both HL and NHL (Oluwasola et al. 2011). The authors of this study do however err on the side of caution and in their study limitations mention possible

variables as to whether the study is a true reflection of the study population or not (Oluwasola et al. 2011).

A study carried out by Ogwang et al. (2011) was aimed at assessing the accuracy of clinical and local pathology diagnosis of BL by using an outside pathology review diagnosis team. This was in the hope of understanding the limitations in histopathology practice in a resource-constrained region (Uganda). Uganda is endemic for BL and due to the high number of patient cases, diagnosis is frequently assumed during clinical consultation and during epidemiologic studies (Ogwang et al. 2011).

Accurate histopathology diagnosis is critical for patient care and just as important for cancer registration and epidemiologic studies (Ogwang et al. 2011). In Africa, less than 50% of cancers are diagnosed using histopathology methods (Ogwang et al. 2011). Due to the common presentation of BL in Africa, diagnosis is frequently clinically diagnosed and sometimes confirmed only by aspiration cytology (Ogwang et al. 2011).

Some of the findings of this study included amongst other factors small biopsy size, inadequate tissue preservation and suboptimal tissue fixation creating challenges in accurate diagnosis by local pathologists (Ogwang et al. 2011). Laboratory procedures are rarely supervised and there is a lack of written standardised operational procedures which forms a norm in developed countries (Ogwang et al. 2011).

There is also a shortage of pathologists in Uganda and most pathologists in these resource-constrained areas may not have been adequately trained and do not have the expertise in

NHL; more specifically in the histopathologic characteristics and anatomic presentation of BL (Ogwang et al. 2011).

A study carried out in Malawi and Uganda which confirmed significant associations between HIV and BL was reanalysed by a review team who found no statistically significant association between HIV and BL (Ogwang et al. 2011). This placed enormous doubt on the validity of the two studies (Ogwang et al. 2011).

Similarly, a review committee did not find 100% diagnostic accuracy in previously diagnosed BL cases reported by Ogwang et al. (2011). This study concluded that there is an urgent need to improve histopathological diagnosis in Africa prior to carrying out further more in depth clinical and epidemiologic studies (Ogwang et al. 2011).

South African statistics are presumed to be more accurate, as South Africa is not as resource-constrained as some of the other African countries, and South Africa holds a worldwide reputation as a quality producer of internationally sought after medical specialists (Cassim & Ruggunan 2014). Perhaps, an exception would be in rural areas where cancers may go undiagnosed due to poor access to adequate healthcare facilities, therefore compromising the accuracy of the statistics. To the best of our knowledge no study has been done in South Africa to reanalyse or reassess previously reported studies.

2.3 Aetiology

2.3.1 Epstein-Barr virus (EBV)

EBV infection is strongly associated with the adult population and it is said that about 90% of the people living in developed countries show evidence of previous EBV infection by

the time they are 40 years. Immunocompromised patients, such as AIDS patients, are at increased risk of developing EBV associated primary brain lymphomas as well as other high grade B-cell NHLs. Almost all endemic BL cases (Africa and New Guinea) have evidence of EBV; however, the sporadic cases (USA and other developing countries) show EBV in less than 20% of patients (Chiu & Weisenburger 2003). EBV is seen in many lymphoma cases, for example extranodal NK/T-cell lymphoma (nasal type), however it is thought that most EBV infections are secondary infections as a result of reactivation of the latent virus in the immunocompromised patients (Chiu & Weisenburger 2003; Beasley 2012). EBV infection is thought not to have a great impact on the increasing NHL incidence (Chiu & Weisenburger 2003; De Roos et al 2013).

2.3.2 Human T-cell lymphotrophic virus (HTLV)

Cleghorn et al. (1995) (as cited by Chiu & Weisenburger 2003) stated that if patients are infected with human T-cell lymphotrophic virus-1 (HTLV-1), especially during the early childhood years, there is a great possibility of adult T-cell leukaemia/lymphoma developing. The modes of transmission of this virus include blood transfusion, sexual contact and breastfeeding (Chiu & Weisenburger 2003). Due to the rarity of this virus which leads to its rare T-cell subtype and its special geographic distribution (Japan, Central and South America, Africa, New Guinea and Caribbean Islands) it is thought that this is not the main cause leading to the rising NHL incidence (Chiu & Weisenburger 2003; Hennessy, Hanrahan & Daly 2004; Huh 2012).

2.3.3 Hepatitis C virus (HCV)

According to some authors, there is an association between HCV and low grade B-cell NHLs in many cases. However, epidemiologic studies have not found any conclusive link between these two entities and the recent HCV increase cannot explain the NHL pattern which began more than 30 years ago (Chiu & Weisenburger 2003).

2.3.4 Immunodeficiency

Congenital and acquired forms of immunodeficiency are said to be the biggest known contributing factor to increase the risk of NHL. NHL is the most common malignancy in young individuals with the following conditions: Wiskott-Aldrich syndrome, ataxia telangiectasia, X-linked lymphroproliferative syndrome or combined immunodeficiency. EBV seems to be an important cofactor. Congenital immunodeficiency conditions are rare and do not contribute much to the rising incidence of NHL (Chiu & Weisenburger 2003).

Patients on immunosuppressive therapy following bone marrow or organ transplantation are 30-50 times at greater risk of developing NHL. B-cell lymphomas have been seen to regress when the immunosuppressive drugs are stopped, however in some cases they can turn into aggressive NHLs. Persistent EBV infection is what feeds this malignant process. However, EBV associated NHLs are rare and do not explain much of the NHL increase in general (Chiu & Weisenburger 2003).

Malignant lymphoma affects 5% to 10% of HIV positive patients, and HIV infected individuals are more than 100 times at risk of developing NHLs compared to healthy individuals (Chiu & Weisenburger 2003; Folk et al 2006). In fact, Ota et al (2014) reported the incidence of malignant lymphoma to be 60 to 200 fold greater in HIV infected

persons when compared to the general uninfected patient population. HIV associated lymphomas are generally high grade neoplasms of B-cell lineage, mostly diffuse large B-cell lymphoma (DLBCL), immunoblastic or Burkitt subtypes and often affect extranodal sites, such as the brain (Chiu & Weisenburger 2003; Folk et al 2006; Ota et al 2014).

HIV associated NHL is due to inadequate immune surveillance of oncogenic herpes viruses such as EBV and human herpes virus 8 (HHV8), together with inadequate immune regulation and chronic antigenic stimulation as a result of other infections. HIV associated NHL affects a small number of individuals and is not responsible for the NHLs in older individuals and females (Chiu & Weisenburger 2003).

Patients with diseases of the immune system are also at increased risk of developing NHL (Chiu & Weisenburger 2003). These conditions include: Sjögren's syndrome, rheumatoid arthritis, coeliac disease and systemic lupus erythematosus (Chiu & Weisenburger 2003; Zhong 2006). The above conditions are rare and are not thought to contribute much to the rise in NHL incidence (Cawson & Odell 2008; Chiu & Weisenburger 2003).

2.3.5 Familial aggregation

A positive family history of haemato-lymphoid neoplasms has very often been shown to increase the NHL risk by two to three times. This association is said to be stronger than the other proposed risk factors. Lymphomas can also occur within families as a result of common environmental factors such as occupational exposure and pesticides. One report found that a low intake of vitamin C and carotene lead to an increased risk of NHL, especially in individuals with a positive family history of mainly haemato-lymphoid neoplasms. Another report found an association between alcohol consumption and an

increased risk of NHL, however this was only found to affect males with a positive family history of haemato-lymphoid neoplasms. These findings show a link between NHL and genetic and environmental factors. Familial predisposition accounts for less than 5% of NHL cases and does not explain the rapidly increasing NHL incidence (Chiu & Weisenburger 2003).

2.3.6 Blood transfusion

Blood transfusion as a cause of NHL shows contradictory findings in the literature and further investigation on this subject is required to come to a definitive conclusion (Chiu & Weisenburger 2003).

2.3.7 Agricultural and pesticide exposures

The use of phenoxyacetic acid herbicides, fertiliser and organophosphate insecticides has been shown to lead to increased NHL risk. Pesticides specifically have been shown to be linked to SLL and FL (Chiu & Weisenburger 2003).

2.3.8 Occupation

Numerous occupations including pathologists, chemists, anaesthesiologists, dry cleaners, petroleum refinery workers, rubber workers, benzene workers and farmers have been linked to the increased incidence of NHL. The common agents in the abovementioned occupations include exposure to chemicals that are said to lead to increase in NHL incidence. One study reported occupational exposure to account for up to 11% of NHLs. The general public may also be exposed to many chemicals but at much lower doses (Chiu & Weisenburger 2003).

2.3.9 Genetic susceptibility

Genetic susceptibility is associated with genes relevant to metabolic enzymes as well as genes relevant to immune function (Chiu & Weisenburger 2003).

2.3.10 Lifestyle factors

Consumption of fruits, vegetables rich in carotene and vegetables of the cabbage family have shown a decreased risk of developing NHL, while consumption of meat, fat and animal protein are associated with increased risk of NHL. Contradictory information has been found with alcohol consumption, cigarette smoking, use of hair dyes, exposure to UV radiation, physical activity and the risk of NHL. Newer epidemiologic studies including the role of lifestyle factors on NHL have also been inconclusive (Chiu & Weisenburger 2003).

The AIDS epidemic, improved access to medical care and enhanced diagnostic tools are said to only account for one-third of the rise in the NHL incidence (Chiu & Weisenburger 2003; Zhong 2006). The cause for the remaining fraction of the increase in the NHL incidence is not entirely understood, however the abovementioned factors are said to play some role in the aetiology of NHLs (Chiu & Weisenburger 2003).

2.4 Age range of lymphomas

Both HL and NHL have a wide age range (Farman, Nortje & Wood 1993). HL has two peaks: 15-35 years and after 50 years (Etemad-Moghadam et al. 2010). NHL affects individuals of any age and its incidence increases throughout life (Kolokotronis et al. 2005). However, it is more common in adulthood than in childhood (Etemad-Moghadam et al. 2010) and is rare before the age of ten years and peaks in the seventh decade of life

(Farman, Nortje & Wood 1993). A study by Etemad-Moghadam et al. (2010) entitled "Head and neck NHL: a 20 year demographic study of 381 cases" found an age range of seven months to 98 years. It is age ranges like these that lead to a younger mean age like 46.3 years in this case. However, in most NHL studies the mean age is above 50 years (Söderholm et al. 1990; Kolokotronis et al. 2005; Kemp et al. 2008). NHL is typically a disease of the elderly, with the median age of most subtypes being in the sixth or seventh decade (Huh 2012). However, the exception is BL and precursor NHL (Huh 2012).

The incidence of NHL increases in males and females (at a lower rate than males) but continues in males, and in females it decreases at 80 years and over (Huh 2012). Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma), FL and NK/T-cell lymphoma usually affect a younger age group when compared to the other mature NHLs (Huh 2012).

HL differs from NHL in that it has many specific age-incidence trend curves, which are dictated by the socio-economic status of a population (Huh 2012). In underdeveloped countries, an early childhood peak is seen and mixed cellularity classic HL is the prevalent subtype (Huh 2012). This peak is followed by an adult peak of > 50 years of age (Huh 2012). Mixed cellularity classic HL is associated with socio-economically disadvantaged children, which are at increased risk of early childhood infection, and the older adult population that are immunocompromised as a result of age or HIV and AIDS (Huh 2012). In developed countries, a young adult peak is observed with nodular sclerosis classic HL being the prevalent subtype (Huh 2012). This peak is followed by an older adult peak (Huh 2012). The nodular sclerosis classic HL subtype is associated with a higher socio-economic background and therefore leading to delayed exposure to childhood infections, resulting in a young adult peak (Huh 2012).

2.5 Gender distribution

Lymphomas usually have a slight male predominance (van der Waal et al. 2005) and this is seen in many studies (Bussu et al. 2013; Iguchi et al. 2012). However some head and neck and oral NHL studies have found equal sex distribution (Bennett et al. 1974 as cited by Hart et al. 2004) while others have found no significant sex predilection (Urquhart et al. 2001 as cited by Kemp et al. 2008).

NHL has a male predominance with the exception of MALT lymphoma and nodular sclerosis classic HL, which have a female predominance (Huh 2012). HL has an overall male predominance; however the different age groups have specific gender predominance (Huh 2012). In developed countries, the young adult peak and prevalent nodular sclerosis classic HL subtype is associated with a female predominance (Huh 2012). In developing countries, the early childhood peak and prevalent mixed cellularity classic HL subtype is associated with a male predominance (Huh 2012).

Anatomic sites also have specific gender predominance, for example the salivary glands and thyroid gland are said to show a predominance of NHL in females (Vega, Lin & Medeiros 2005). This could be due to the fact that MALT lymphoma is a common subtype in both these sites (Beasley 2012).

2.6 Clinical features

Clinical features are usually related to the affected anatomic site. However, the typical clinical appearance is that of a growing mass that may or may not be ulcerated with the lesions generally being asymptomatic but pain, fever or weight loss can occur (Etemad-

Moghadam et al. 2010; Kemp et al. 2008; Triantafillidou et al. 2012). Triantafillidou et al. (2012) found that the oral lesions often show rapid growth and can spread to affect the underlying bone. Kolokotronis et al. (2005) in his study found that the overlying tissues appeared either normal in colour, red or red-blue.

2.7 B symptoms/systemic symptoms

Lymphomas can cause generalised systemic symptoms, which can be seen in both HL and NHL and it generally indicates a poorer prognosis. B symptoms include systemic symptoms such as night sweats, more than 10% weight loss over the past six months, unexplained fever greater than 38ºC, fatigue and pruritus (Kolokotronis et al. 2005; Triantafillidou et al. 2012). B symptoms are more common in HLs compared to NHLs (accounting for 41% and 27% respectively) (Triantafillidou et al. 2012). It is rare in NHL patients and is said to co-exist in approximately 15-20% of patients (Kolokotronis et al. 2005). van der Waal et al. (2005) mentioned that B symptoms hardly occur in the oral cavity. Most NHL studies of the head and neck region showed the incidence of B symptoms to be between 8-16% (Hart et al. 2004; Kolokotronis et al. 2005; van der Waal et al. 2005).

2.8 Radiographic features

Determining if the lymphoma originated from hard or soft tissue can pose a challenge; however clinical or radiographic bone involvement does assist in determining the site of origin (Kemp et al. 2008). Kemp et al. (2008) used radiographic imaging (to indicate bone destruction) in their study in order to confirm the site of origin to be bone even if there was soft tissue involvement. Radiographic images of NHLs of the jaw are non-specific, usually showing diffuse bone destruction, either as a solitary defect, lowering of alveolar bone

margin or disappearance of lamina dura (Kolokotronis et al. 2005; Zhong 2006). Other radiographic findings include a mixed radiolucent-radiopaque appearance due to osteoblastic activity and bone resorption (Kolokotronis et al. 2005). Triantafillidou et al. (2012) described radiographic intra-osseous lesions to appear as radiolucent areas, either multilocular or unilocular and with diffuse borders.

2.9 Most common anatomic site

Due to the findings of various studies, it has been accepted that WR is the most common extranodal site in the head and neck region (Kolokotronis et al. 2005; Scherfler et al. 2012; van der Waal et al. 2005). The tonsils have been found to be the most common sub-site within WR (Kolokotronis et al. 2005; Etemad-Moghadam et al. 2010; Hart et al. 2004; Jacobs & Hoppe 1985). Following WR, the oral cavity and salivary glands are the most common sites for lymphomas of the head and neck region (Kolokotronis et al. 2005; Etemad-Moghadam et al. 2010; Jacobs & Hoppe 1985). The palate is the most common oral site and the parotid gland followed by the submandibular gland is the most commonly involved salivary gland (Kolokotronis et al. 2005).

2.10 Most common histological subtype

Various authors have found DLBCL to be the most common NHL subtype of the head and neck region (Ota et al. 2014; Scherfler et al. 2012; Iguchi et al. 2012; Kolokotronis et al. 2005).

2.10.1 Lymphomas of B-cell origin

The majority of the primary extranodal NHLs are of B-cell lineage, however the cause of this is unknown (van der Waal et al. 2005). Hashimoto et al. (1982) (as cited by Sirsath et

al. 2014) concluded that lymphomas of B-cell origin are the most common histological subtypes of the oral cavity. Histological NHL subtypes of B-cell origin are said to be quite common in the head and neck region and the subtypes include DLBCL, MALT lymphoma, mantle cell lymphoma, FL, BL/leukaemia and SLL/chronic lymphocytic leukaemia (CLL) (Triantafillidou et al. 2012).

2.10.1.1 Diffuse large B-cell lymphoma (DLBCL)

DLBCL is a clinical and biological heterogeneous subtype (Cabanillas 2011). It has two large categories: Activated B-cell type (associated with poor prognosis) and Germinal centre B-cell type (associated with good prognosis) (Cabanillas 2011). It is well known that DLBCL is the most common aggressive lymphoma (Hennessy, Hanraham & Daly 2004), however it is treatable and has a variable clinical course of painful or painless swelling, either with or without ulceration (Triantafillidou et al. 2012). The aggressive lymphomas usually affect the proliferating precursor lymphocytes (centroblasts, immunoblasts, lymphoblasts) (Hennessy, Hanraham & Daly 2004).

According to van der Waal et al. (2005), DLBCL accounts for about 40% of adult lymphomas and according to Scherfler et al. (2012) it accounts for about 20-30% of all NHLs in adults and occurs in about 40% of extranodal sites. Xie, Pittaluga & Jaffe (2015) reported DLBCL as the most common lymphoma, representing 30-40% of adult NHL worldwide. DLBCL develops in 2-8% of patients with CLL (Triantafillidou et al. 2012).

Most intra-oral soft tissue and jaw lymphomas are DLBCLs (Triantafillidou et al. 2012). Approximately 70-80% of lymphomas of WR are DLBCLs and this is more so for patients

with localised disease (Triantafillidou et al. 2012). In the Western countries, DLBCL is a common lymphoma subtype of the sinonasal tract (Kanumuri et al. 2014).

DLBCL is also the most common lymphoma subtype of the head and neck region in immunocompetent individuals however other subtypes do occur (Sirsath et al. 2014). The broad heading of "DLBCL" encompasses a large number of entities based on distinct clinical, pathologic or biologic features (WHO classification of tumours of haematopoietic and lymphoid tissues (2008) as cited by Xie, Pittaluga & Jaffe (2015)). These include amongst others:

- EBV-positive DLBCL of the elderly

  This subtype affects the elderly (over 50 years). Patients are EBV positive and one of the common sites affected is the tonsil (Bacon 2010).

- Primary DLBCL of the CNS

  These are aggressive lymphomas of the brain appearing as single or multiple lesions (Bacon 2010). Those affecting the immunocompromised patients are EBV positive as well (Bacon 2010).

2.10.1.2 Plasmablastic lymphoma (PBL)

This is an aggressive B-cell neoplasm that shows plasmacytic differentiation, originates in the oral cavity and tends to involve the gingiva and can infiltrate bone (Vega, Lin & Medeiros 2005). The WHO classification (Stein et al. 2008) lists PBL as a variant of DLBCL. Due to the relatively high frequency of PBLs in South Africa, especially in HIV-positive individuals (Chetty et al. 2003; Chetty, Sudi & Abayomi 2012), I have chosen to discuss this entity separately.

This NHL subtype has been said to classically present as a lymphoma of the oral cavity, and is associated with HIV and AIDS or immunosuppression and EBV positivity (Bacon 2010; Elyamany, Al Mussaed & Alzahrani 2015). Sirsath et al. (2014) reported that the rate of EBV positivity is almost 100% in oral HIV associated PBLs and that PBL is the most common subtype in immunocompromised patients. In their study half the patients with PBL were HIV positive. According to Kemp et al. (2008) this is a rare subtype and fewer than 60 cases have been reported in the literature. EBV association with PBLs is greater than with HHV8 (Castillo, Pantanowitz & Dezube, 2008). Whilst there have been isolated reports of HHV8 infection in PBLs (Goedhals, Beukes & Hardie, 2008), HHV8 is continuously absent in most PBLs (Sirsath et al. 2014).

PBLs have been reported to occur in immunocompetent patients as well as in HIV negative patients (Elyamany, Al Mussaed & Alzahrani 2015). In addition to the oral cavity PBL is also increasingly being described in several others sites, such as the gastrointestinal tract, omentum, lung, nasal and paranasal regions, testes, bones, soft tissue, lymph nodes, bone marrow, skin, CNS and sacrococcygeal area (Elyamany, Al Mussaed & Alzahrani 2015). PBL has a poor prognosis with most patients dying within 2 years from initial presentation, and there are very few long-term survivors (Elyamany, Al Mussaed & Alzahrani 2015).

2.10.1.3 Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma)

Extranodal marginal zone lymphoma is commonly called MALT lymphoma when they affect mucosa-associated lymphoid tissue (Kemp et al. 2008). They usually occur in tissues with chronic inflammation and sometimes chronic reactive hyperplastic lesions due to their genetic aberrations (Kemp et al. 2008). Typically however, they occur as a result

of Sjögren's syndrome, rheumatoid arthritis or Hashimoto's thyroiditis and occur at sites that produce lymphoid tissue due to autoimmune diseases or infections (Kemp et al. 2008).

The gastrointestinal tract is the most common site for MALT lymphomas, followed by the salivary glands (14%), head and neck (14%) and the ocular adnexa (12%) (Triantafillidou et al. 2012). The common sites for MALT lymphomas in the head and neck region are the parotid gland, thyroid gland, WR and ocular adnexa (especially the conjunctiva) (Hosokawa et al. 2012). Some authors have found the ocular adnexa to be the most common extranodal site for MALT lymphomas, accounting for up to 60-70% of cases (as cited by Triantafillidou et al. 2012). MALT lymphomas have a tendency to involve other extranodal sites however the bone marrow is not often involved (Vega, Lin & Medeiros 2005).

MALT lymphomas are said to have a smooth course and spread slowly (Triantafillidou et al. 2012). They are characteristically low grade and indolent in nature and therefore occur over prolonged periods (Hosokawa et al. 2012). Transformation of low grade MALT lymphomas to high grade MALT lymphomas, namely DLBCL can occur (Vega, Lin & Medeiros 2005). MALT lymphomas have a female predilection with a 1.4:1 female to male ratio and a mean age of 64 years (Hosokawa et al. 2012). Head and neck MALT lymphomas usually involve many organs at the same time, therefore increasing the risk of recurrences when local measures are used for treatment (Etemad-Moghadam et al. 2010). Due to the indolent nature of this subtype, the prognosis is usually good in majority of the non-disseminated cases (Etemad-Moghadam et al. 2010); even though occasional studies have reported high rates of recurrences with this subtype (Vazquez et al. 2015).

2.10.1.4 Mantle cell lymphoma

Mantle cell lymphoma is a rare NHL subtype, which mostly presents as nodal disease (Kemp et al. 2008). Extranodal involvement is rare (Kemp et al. 2008). Mantle cell lymphoma is aggressive in nature (Bacon 2010). It has a fairly poor prognosis and mostly occurs in males in the seventh or eighth decade of life (Bussu et al. 2013). Generalised lymphadenopathy is usually the presenting feature at diagnosis (Kemp et al. 2008). Intra-oral mantle cell lymphoma is rare, with the first cases occurring in the palate reported by Chang et al. (2003) (as cited by Kolokotronis et al. 2005) and Kolokotronis et al. (2005). According to Bacon (2010) in most patients that develop extranodal mantle cell lymphoma, the common anatomic site that is affected is WR.

2.10.1.5 Follicular lymphoma (FL)

It is well known that FL is the most common indolent lymphoma (Hennessy, Hanraham & Daly 2004). Indolent lymphomas usually affect the non-dividing mature lymphocytes (Hennessy, Hanraham & Daly 2004). In the USA, FL has been found to be the most common NHL subtype, mostly with nodal involvement, and extranodal involvement being rare (Kemp et al. 2008). Even though it has an indolent nature, FL can transform to aggressive DLBCL and this accounts for approximately 40% of cases (Kemp et al. 2008). According to Armitage & Weisenburger (1998) (as cited by Scherfler et al. 2012), FL is the second most common form of NHL and often shows a nodal presentation. Most patients present with disseminated disease at diagnosis (Scherfler et al. 2012), and many patients with FL relapse several times (Hennessy, Hanraham & Daly 2004).

2.10.1.6 Burkitt lymphoma (BL)

BL can be divided into three categories: endemic cases in Africa, sporadic cases around the world and HIV associated cases (Kemp et al. 2008). It is usually extranodal and commonly occurs in children and young adults (Kemp et al. 2008). Endemic BL typically affects the jaws and sporadic BL usually affects the abdomen (Kemp et al. 2008). EBV is very closely associated with endemic BL, occurring in almost every case however, it only occurs in 25% of the other BL groups (Kemp et al. 2008). EBV has been consistently found in the tumour tissue of endemic BL in Africa and New Guinea (Zhong 2006). A similar highly aggressive form of BL can be seen in adults (Kemp et al. 2008). It is quite uncommon and is termed Burkitt-like lymphoma (Kemp et al. 2008), with morphological features in-between that of DLBCL and BL (Kemp et al. 2008).

2.10.1.7 Small lymphocytic lymphoma (SLL)/chronic lymphocytic leukaemia (CLL)

SLL and CLL have the same phenotype and genotype, with the only difference being their degree of lymphocytosis (Kemp et al. 2008). It commonly affects patients older than 50 years of age (Kemp et al. 2008). Although indolent in nature, transformation to DLBCL occurs in about 30% of cases and is termed Richter syndrome (Kemp et al. 2008). It is not common for SLL/CLL alone to develop an extranodal mass (Bacon 2010).

2.10.1.8 Plasma cell tumours

Plasma cell tumours include plasma cell myeloma, solitary plasmacytoma of bone and extra-osseous plasmacytoma. The plasmacytomas are rare, and plasma cell myeloma has a poor prognosis (Kemp et al. 2008). Plasma cell tumours rarely occur below the age of 40 years (Kemp et al. 2008). According to González et al. (1991) (as cited by Scherfler et al. 2012), 12-15% of plasma cell myeloma cases first occur in the jaw bones and oral cavity.

2.10.1.8.1 Extra-osseous plasmacytomas

Eighty percent of extra-osseous plasmacytomas occur in the head and neck with 4% being non-epithelial neoplasms of the nasopharynx, nasal cavity and paranasal sinuses (Vega, Lin & Medeiros 2005). This subtype has a male predominance and usually occurs in patients over the age of 40 years with its peak in the sixth decade of life (Vega, Lin & Medeiros 2005). Any site in the head and neck can be primarily involved however the common primary sites involved include the tonsil, sinus, nose and nasopharynx (Vega, Lin & Medeiros 2005). EBV is usually not present in this subtype (Vega, Lin & Medeiros 2005).

2.10.2 T-cell and NK-cell lymphomas

Mature T-cell and NK-cell neoplasms make up a small percentage of NHL cases worldwide (Kemp et al. 2008). Extranodal NK/T-cell lymphomas are often associated with EBV (Kemp et al. 2008). It is commonly seen in Asia and South America (Kemp et al. 2008). The palate and the nasal cavity are the most common affected sites and while it does occur at other sites, it is a rare finding (Kemp et al. 2008). T-cell lymphomas commonly occur nodally but may present extranodally (Bacon 2010).

2.10.3 Anaplastic large cell lymphoma (ALCL)

ALCL has two subtypes:

- ALCL CD30-positive ALK-positive (ALK is the protein anaplastic lymphoma kinase)
- ALCL CD30-positive ALK-negative

Both subtypes are said to be aggressive, however ALCL ALK-positive affects younger individuals up to 30 years of age and ALCL ALK-negative affects patients with an average age of 60 years (Hennessy, Hanraham & Daly 2004). ALK-positive ALCL usually affects extranodal sites such as bone, soft tissues and lung (Bacon 2010).

2.11 Nodal versus extranodal lymphomas

Extranodal lymphomas of the head and neck are uncommon (Beasley 2012). However, the head and neck is a more common site for extranodal NHLs than primary HLs, which are usually nodal (Beasley 2012).

2.12 Lymphomas of Waldeyer's Ring (WR)

WR is made up of the tonsil, nasopharynx and base of the tongue (Beasley 2012). Approximately 50% of all extranodal NHLs of the head and neck occur in WR (Vega, Lin & Medeiros 2005). There is a male predilection and it usually affects patients over 50 years of age (Vega, Lin & Medeiros 2005). These lymphomas usually present as a mass or an ulcer with pain, altered hearing and airway obstruction (Vega, Lin & Medeiros 2005). The tonsils are affected in more than half the cases, followed by the nasopharynx and the base of the tongue (Vega, Lin & Medeiros 2005). Beasley (2012) found the tonsil and the nasopharynx to be the most common sites affected in adults and children respectively. He also found that involvement of the base of the tongue only is rare.

Of the WR lymphomas, 80-90% are NHL of B-cell lineage and DLBCL is the most common subtype (Vega, Lin & Medeiros 2005). However, other subtypes do occur but to a lesser extent. Other lymphoma subtypes that have occurred in this anatomic site include MALT lymphoma, peripheral T-cell lymphoma, FL and mantle cell lymphoma (Vega, Lin

& Medeiros 2005). HL rarely occurs at this site (Vega, Lin & Medeiros 2005). If it does, the frequent subtypes are lymphocyte-rich classic HL and nodular sclerosing subtypes (Vega, Lin & Medeiros 2005).

WR consists of normal mucosa-associated lymphoid tissue however; MALT is not the most common subtype (Vega, Lin & Medeiros 2005). It is possible that these lymphomas are under diagnosed due to the fact that many DLBCLs are of MALT origin and lymphomas of WR as a result of lymphoepithelial lesions, cannot be said to be of MALT origin (Vega, Lin & Medeiros 2005).

2.13 Lymphomas of the salivary glands

Lymphocytes are not normally found in salivary tissue however, they do occur when there is inflammation (Vazquez et al. 2015). Of the extranodal lymphomas of the head and neck, 12% occur in the salivary glands (Beasley 2012). The parotid gland is affected in 80% of cases, followed by the submandibular gland (16%), the sublingual gland (2%) and the minor salivary glands (2%) (Vega, Lin & Medeiros 2005). Symptoms of salivary gland lymphomas include a painful or painless mass and occasionally facial nerve palsy (Vega, Lin & Medeiros 2005). MALT lymphoma and DLBCL are the most common histological subtypes (Vega, Lin & Medeiros 2005). Salivary gland lymphomas of MALT origin can be either low grade lymphomas or DLBCLs (Vega, Lin & Medeiros 2005). Most salivary gland lymphomas are low grade B-cell subtypes with T-cell subtypes being very rare (Beasley 2012). Low grade MALT lymphoma has been found to be the most common subtype to affect the salivary glands (Beasley 2012).

The peak incidence for salivary gland lymphomas is the seventh decade (Beasley 2012). Adults are mainly affected with a male:female (M:F) ratio of 1:2 (Vega, Lin & Medeiros 2005; Kojima et al. 2007 as cited by Etemad-Moghadam et al. 2010), however, some studies found an almost equal sex distribution (Roh, Huh & Moon 2007; Dunn et al. 2004 as cited by Etemad-Moghadam et al. 2010). The reason for the female predominance is not really known however, what is known is that of the total percentage of patients affected by autoimmune diseases, 78% are women (Vazquez et al. 2015). This includes Sjögren's syndrome which could possibly be the cause (Vazquez et al. 2015).

Myoepithelial sialadenitis (a benign lymphoepithelial lesion which is a reactive salivary gland infiltrate of Sjögren's syndrome) is said to be a precursor lesion of NHL and can lead to MALT lymphoma (Vega, Lin & Medeiros 2005; Beasley 2012). It has been found that 20% of patients with salivary gland lymphomas have Sjögren's syndrome (Vega, Lin & Medeiros 2005). Patients with the above mentioned conditions are approximately 43.8 times more at risk of developing NHL compared to normal healthy individuals (Vega, Lin & Medeiros 2005). Patients not suffering from Sjögren's syndrome generally are affected by the FL subtype (Beasley 2012).

The parotid gland has many lymph nodes around the gland as well as within the parenchyma and therefore lymphomas of salivary glands may be nodal or extranodal in origin (Vega, Lin & Medeiros 2005). Salivary gland lymphomas arising in Warthin's tumour are rare and have been reported in only about 20 cases (Vega, Lin & Medeiros 2005). The histological subtypes associated with Warthin's tumour include DLBCL, FL and SLL, with MALT lymphoma being quite rare, and commonly occurring as nodal disease (Vega, Lin & Medeiros 2005).

2.14 Lymphomas of the jaws

NHL of the jaws is quite rare (with the exception of BL) however; it is the most frequent site of osseous lymphomas compared to all the other craniofacial bones (Djavanmardi et al. 2008). They have an incidence rate of about 5% in extranodal sites (Etemad-Moghadam et al. 2010). Lymphomas of the jaws are usually seen in adults between the ages of 40-50 years (Djavanmardi et al. 2008). These neoplasms may be either primary, with the jaw being the site of origin of the lymphoma or secondary, as a result of metastatic disease (Djavanmardi et al. 2008).

According to Kolokotronis et al. (2005), there is conflicting data with regards to the prevalence of lymphomas in the jaw. Agrawal, Agrawal & Kambalimath (2011) stated that the maxilla is the most prevalent jaw site. Of the mandibular tumours, 8% are primary NHLs and these account for approximately 0.6% of all NHLs (Djavanmardi et al. 2008). More than 50% of BL cases occur in the mandible and about 15% of them occur as non-endemic disease (Djavanmardi et al. 2008).

Some of the common signs and symptoms include continuous pain and ulceration of the oral mucosa, tumour mass on gingiva, mobile teeth, post-extraction mass in socket, neurological disorders (e.g. paraesthesia) and cervical lymphadenopathy (Djavanmardi et al. 2008; Kolokotronis et al. 2005). Radiographically, ill-defined borders are seen and bone lysis is noted in about 80% of cases (Djavanmardi et al. 2008).

2.15 Lymphomas of the orbit and conjunctiva

The ocular adnexa are the second most common site for head and neck lymphomas (Vega, Lin & Medeiros 2005). They usually affect elderly individuals and have a slight female predilection (Vega, Lin & Medeiros 2005). Orbital involvement is seen in 60-70% of cases, followed by the conjunctiva in 10-20% of cases (Vega, Lin & Medeiros 2005). Bilateral involvement occurs in 10-15% of cases (Vega, Lin & Medeiros 2005).

Clinical features include swelling, pain, proptosis, opthalmoplegia, distorted vision, conjunctival chemosis and slow onset erythema (Triantafillidou et al. 2012; Vega, Lin & Medeiros 2005). Systemic symptoms are rare however; they are more often seen in patients with diffuse and high grade lymphomas (Gerbino et al. 2014). Majority of these lymphomas are low grade (Gerbino et al. 2014). MALT lymphomas comprise 60-70% of the lymphomas involving these sites (Vega, Lin & Medeiros 2005). Other common subtypes include FL, DLBCL, mantle cell lymphoma and lymphoplasmacytic lymphoma (Gerbino et al. 2014). MALT lymphomas have the best prognosis whereas mantle cell lymphomas are usually fatal (Gerbino et al. 2014). Common sites for dissemination of orbital lymphomas include lymph nodes, bone marrow, the skin and spleen (Gerbino et al. 2014). There is said to be an association between Chlamydia psittaci and ocular lymphomas as well as a regression following antibiotic therapy (Vega, Lin & Medeiros 2005).

2.16 Lymphomas of the larynx

Lymphoma of the larynx is a rare entity (Vega, Lin & Medeiros 2005). However, some of the subtypes frequently found at this site include plasmacytoma, MALT lymphoma and DLBCL (Vega, Lin & Medeiros 2005). Symptoms of laryngeal lymphomas are dysphonia,

dysphagia, cough, hoarseness or even the feeling of a lump in the throat (Vega, Lin & Medeiros 2005). Plasmacytoma at this site presents as a unilateral, smooth, non-ulcerated mass and commonly occurs in the epiglottis (Vega, Lin & Medeiros 2005).

2.17 Sinonasal tract lymphomas

Sinonasal tract lymphomas are rare neoplasms of the head and neck region (Kanumuri et al. 2014). In the Western countries DLBCL is a common subtype of this site and is more common in the paranasal sinuses and rare in primary nasal neoplasms (Abbondanzo & Wenig 1995; Fellbaum, Hansmann & Lennert 1989; Woo et al. 2004 and Cuadra-Garcia et al. 1999 all cited by Kanumuri et al. 2014). A study by Kanumuri et al. (2014) was consistent with what is reported in the literature (Abbondanzo & Wenig 1995; Fellbaum, Hansmann & Lennert 1989; Woo et al. 2004 and Cuadra-Garcia et al. 1999 all cited by Kanumuri et al. 2014), with DLBCL accounting for 65.9% of the paranasal lymphomas and 34% of the nasal cavity lymphomas. DLBCL is usually less aggressive compared to the other subtypes found in this site (Abbondanzo & Wenig 1995 and Logsdon et al. 1997 as cited by Kanumuri et al. 2014) however; they have non-specific clinical presentations that differ between patients and geographic locations (Kanumuri et al. 2014).

The sinonasal area has a complex anatomy due to the many critical structures in its surrounding, such as the orbit and cranial nerves, and is prone to local spread of disease (Kanumuri et al. 2014). Primary neoplasms of the nasal cavity have a very poor prognosis (Hatta et al. 2001 as cited by Kanumuri et al. 2014). The study by Kanumuri et al. (2014) differed from other reports in the literature as it showed that patients with nasal cavity involvement and paranasal sinus involvement had similar survival rates.

Many lymphoma subtypes have a male predominance however, with sinonasal tract lymphomas the gender predominance is unclear (Kanumuri et al. 2014). Two studies found a male predominance while one found a female predominance (Kanumuri et al. 2014). Signs and symptoms of sinonasal lymphomas include facial swelling, nasal obstruction, bloody discharge or visual disturbances, and B symptoms can occur (Kanumuri et al. 2014). Extranodal dissemination is the frequent cause of fatality especially with primary lymphomas of the nasal cavity which have a poor prognosis (Kanumuri et al. 2014). However, due to the subtle symptoms of sinonasal tract lymphomas, they can be mistaken for benign inflammatory conditions such as upper respiratory tract infections and allergic rhinitis; this being seen more common in paediatric patients (Kanumuri et al. 2014).

2.18 Extranodal NK/T-cell lymphoma-nasal type

Extranodal NK/T-cell lymphoma as referred to as "lymphoma of nasal type" is the most common histological subtype of the nasal cavity and paranasal sinuses however, other subtypes do occur (Triantafillidou et al. 2012). A few cases of NK/T-cell lymphoma-nasal type can be found in primary non-nasal sites (Coha et al. 2014). This lymphoma subtype has a tendency to involve various extranodal sites, especially the nasopharynx, nasal cavity and palate (Vega, Lin & Medeiros 2005).

It is said that most of these neoplasms are of NK-cell lineage and a few of T-cell origin and thereby the name (Vega, Lin & Medeiros 2005). The median age is usually around 50 years and has a slight male predominance (Coha et al. 2014). The common symptoms of this subtype are nasal mass, nasal obstruction, chronic rhinorrhoea or epistaxis (Coha et al. 2014; Beasley 2012). Some of the primary sites affected include the nasopharynx, nasal

cavity, paranasal sinuses, larynx and tonsils (Coha et al. 2014). Spread of tumour to the hard palate, orbit, soft tissue and bone can occur (Coha et al. 2014). This subtype is responsible for extensive destruction of the vasculature as well as tissue necrosis and has an aggressive clinical course (Coha et al. 2014). Metastasis to regional nodes and distant organs is also reported (Coha et al. 2014). Common metastatic sites include the gastrointestinal tract, lungs, skin and testes (Coha et al. 2014). Bone marrow is not usually affected (Vega, Lin & Medeiros 2005). CNS involvement is rare (Beasley 2012). Relapse remains localised but generally occurs at extranodal sites (Beasley 2012; Vega, Lin & Medeiros 2005).

This subtype is commonly seen in South and Central America as well as East Asia (Beasley 2012) and is rare in the European population (Coha et al. 2014). A strong genetic/racial predisposition is linked to this subtype due to the high incidence in Asians that migrated to North America (Beasley 2012). There is a strong link with this subtype and EBV (Beasley 2012). A high frequency of the hepatitis B-cell carrier has been found in some areas where this lymphoma subtype is highly prevalent (Beasley 2012). An association between this subtype and haemophagocytic syndrome was also found (Vega, Lin & Medeiros 2005).

2.19 Cutaneous lymphomas of the head and neck

Certain histological subtypes of primary cutaneous lymphomas are seen more often than others in the head and neck region and these include some subtypes of DLBCL, MALT lymphoma and primary follicle-centre lymphoma (Vega, Lin & Medeiros 2005). Cutaneous DLBCLs in the head and neck region probably represent cutaneous expression of systemic lymphoma (Vega, Lin & Medeiros 2005).

2.20 Geographic variances

The frequency and subtype distribution of lymphomas varies according to geographic location (Iguchi et al. 2012; Huh 2012). Geographic variances in lymphoma incidence ratio in Japan as compared to that in Western countries include a lower incidence ratio in HL, and a higher incidence ratio of T/NK-cell lymphomas (especially adult T-cell leukaemia/lymphoma and extranodal NK/T-cell lymphoma nasal type) (Iguchi et al. 2012). The incidence of HL in Japan is rare (4-7% of all lymphomas) compared to Western countries which have a reported incidence of about 40-45% (Iguchi et al. 2012). The incidence of T/NK-cell lymphoma (15-20%) in Asia is also reported to be higher when compared to reports in Western countries (5-10%) (Iguchi et al. 2012). The 3.3% HL incidence and 18% T/NK-cell lymphoma incidence reported by the Japanese study (Iguchi et al. 2012) is in keeping with that of previous reports. In a similar manner to head and neck reports, recent Japanese large scale surveys on lymphomas of the entire body showed an HL incidence of 4-7% and T/NK-cell lymphoma ratios of 19-25% (Iguchi et al. 2012). However, B-cell lymphomas accounted for the most number of cases in both studies (Iguchi et al. 2012).

In the Western population, DLBCL accounts for most of the sinonasal tract lymphomas; more commonly in the paranasal sinuses and less commonly in the nasal cavity (Kanumuri et al. 2014). However in Asia, NK/T-cell lymphomas are more common in the sinonasal area (Kanumuri et al. 2014). The Asian population has shown distinctly higher frequency rates of the subtypes T/NK-cell lymphoma and MALT lymphoma, and lower rates of FL and SLL/CLL when compared to the Western world (Huh 2012). The lower rates of the 3 subtypes cannot be explained, however the higher rates of MALT lymphoma in the Asian

population and T/NK-cell lymphoma in the south-eastern Japanese population stems from the high frequency of Helicobacter pylori and HTLV-1 respectively (Huh 2012).

It is also important to note the role of environmental factors as an aetiological factor in lymphoma formation (Huh 2012). An NHL study of Asians residing in the USA, grouped Asians into two categories: USA-born Asians and foreign born Asians (Huh 2012). The study found USA- born Asians to have higher incidence rates of FL, SLL/CLL and nodular sclerosis classic HL. This study supports the role of environmental factors in the aetiology of malignant lymphoma (Huh 2012).

2.21 HIV and AIDS and lymphomas

Lymphomas are one of three AIDS-defining cancers (Brower 2011) and can be the first manifestation of HIV (Sirsath et al. 2014). These HIV associated lymphomas account only for 22-26% of the total number of lymphoma cases (Sirsath et al. 2014). Over 80% of lymphomas that occur in HIV positive patients are high grade, mature lymphomas of B-cell origin of both germinal centre and activated B-cell subtypes (Sirsath et al. 2014). These subtypes include DLBCL, BL, PBL, primary DLBCL of the CNS and primary effusion lymphoma (Sirsath et al. 2014).

The relationship of CD4 count to the risk of developing an HIV associated lymphoma differs according to the lymphoma subtype (Sirsath et al. 2014). Primary CNS lymphomas mostly occur in the setting of very low CD4 counts ($<50mm^3$) while germinal centre DLBCLs and BLs usually occur in patients with higher CD4 counts (Sirsath et al. 2014).

The increase in this cancer is due to limited access to anti-retroviral therapy (ART) and prevention programs and therefore people in Africa that are affected with AIDS, have a five times higher risk of developing lymphomas (Brower 2011). Developing countries have thus shown an increase in lymphoma cases due to the poor highly active anti-retroviral therapy (HAART) coverage of patients, late commencement of treatment and incomplete viral suppression (Brower 2011).

In general, there is minimal reported epidemiologic data on the relationship between HIV and AIDS and lymphoma incidence in Africa (Oluwasola et al. 2011). African cancer statistics need to be utilised with caution as only eight African countries keep cancer registries, and record keeping is not very efficient (Brower 2011). A Nigerian study done on the association between HIV and the incidence of lymphoma cases showed that from 1991 to 2001, the HIV incidence increased from 1.8% to 5.8% and then decreased to 4.4% in 2005 (Oluwasola et al. 2011). However a study on the lymphoma incidence during the same period showed a decrease from 58 cases to 24 cases and surgical biopsies dropped from 1.4% to 0.7% (Oluwasola et al. 2011). This suggests that the HIV epidemic did not influence the lymphoma incidence (Oluwasola et al. 2011). This finding was attributed to the fact that out of the high number of HIV positive patients in Nigeria, only a very small portion of patients receive HAART treatment, while the bulk of the patients have a very short survival rate due to acquiring opportunistic infections (Oluwasola et al. 2011). Therefore there is not much opportunity for a lymphoma to develop (Oluwasola et al. 2011).

The risk of CNS NHL in an AIDS patient is increased by 5000 times, of DLBCL by 100-140 times, of BL by 100 times, and of PBL and HL by 10 times (Huh 2012).

Approximately 50% of the HIV positive DLBCL cases are EBV positive and about 30% of the HIV positive BL cases are EBV positive (Huh 2012), and there is almost 100% EBV positivity in HIV positive PBL cases (Sirsath et al. 2014). HAART has shown to decrease the incidence of HIV related lymphomas in recent years (Huh 2012). However, HL has shown an increasing incidence since the use of HAART in HIV patients, indicating that HL requires a healthy immune system to thrive (Huh 2012). HIV associated PBL cases have a very high male predominance and a median CD4 count of about 178 cells/mm^3 (Sirsath et al. 2014).

2.22 Head and neck lymphomas in South Africa

A study carried out in Western Cape, South Africa investigated the trends of prevalence and the pathological spectrum of head and neck lymphomas at the Tygerberg referral hospital over a five year period, as well as a possible relationship with HIV (Chetty, Sudi & Abayomi 2012). This study showed that there was an overall increase in NHL cases over the 5 year period, which tied up with a similar increase in the HIV prevalence as well, and concluded that the suboptimal management using ART in HIV positive patients may have a direct link. DLBCL was the largest category of NHL (32%), followed by HL (27%), FL (10%) and PBL (8%). PBL and BL were only seen in HIV positive patients. Head and neck lymphomas presented as nodal disease in 64% of cases and as extranodal disease in 37% of cases. The limitation of this study included the failure to determine HIV status in all records (Chetty, Sudi & Abayomi 2012).

2.23 Lymphomas of children and adolescents

Head and neck neoplasms are quite uncommon in childhood (Khademi, Taraghi & Mohammmadianpanah 2009). However, lymphomas are the most common solid tumour

of the head and neck region in children (Dubey et al. 1998). The incidence of lymphomas varies according to geographic location with equatorial Africa having a lymphoma incidence rate of 50% due to the high incidence of BL (Dubey et al. 1998). Non-endemic BL areas have a childhood incidence rate of about 10% (Roh, Huh & Moon 2007; Dubey et al. 1998; Khademi, Taraghi & Mohammmadianpanah 2009). The incidence of childhood malignancies, including lymphomas is on the increase in developed countries (Roh, Huh & Moon 2007). The trend in the Asian population is not known; however EBV which is closely related to certain lymphomas, such as NK/T-cell lymphomas is endemic in East Asia (Roh, Huh & Moon 2007).

The literature clearly shows that malignant lymphomas comprise two distinct entities (HL and NHL), and highlights the differences in their incidence, demographics, clinical features, geographic distribution, their association with different anatomic sites and its association with HIV. The differences in developed and developing countries are also emphasised. The results of this study will be compared to that of the literature to determine how South Africa compares to the rest of the world.

CHAPTER 3

3.0 AIM

The aim of this retrospective review is to evaluate the frequency and clinico-pathologic characteristics of patients diagnosed with head and neck lymphoma at the Department of Oral Pathology, University of the Witwatersrand, Johannesburg over the 20 year period, 1993-2012.

3.1 STUDY OBJECTIVES

- To determine the total number of lymphoma cases diagnosed per annum during the study period and to evaluate the overall frequency and prevalence of lymphoma cases over the 20 year period, 1993 – 2012
- To determine the frequency and prevalence of each subtype
- To determine the percentage of HL versus NHL cases
- To evaluate the male:female ratio in each sub-type
- To determine the age range within each sub-type
- To determine the percentage of nodal to extranodal sites of the diagnosed cases
- To evaluate anatomical sites involved and their frequency
- To analyse the histological type/subtype of all the head and neck lymphomas within the sample in the defined 20 year study according to the 2008 WHO classification of haemato-lymphoid malignancies

CHAPTER 4

4.0 MATERIALS AND METHODS

4.1 Study design and population

This is a retrospective study of all histologically confirmed head and neck lymphomas diagnosed in the Department of Oral Pathology, University of the Witwatersrand, Johannesburg, South Africa over a 20 year period, from the 1 January 1993 until the 31 December 2012.

The study sample is thought to be reflective of the greater Johannesburg and surrounding areas. The Department of Oral Pathology provides a regional wide diagnostic service to the Charlotte-Maxeke Johannesburg Hospital as well as to municipal community clinics, and other provincial hospitals within the greater Johannesburg Metropolitan and surrounding areas, including amongst others the Chris Hani-Baragwanath and Helen Joseph Hospitals. These hospitals are tertiary academic and community referral centres for a large portion of the Gauteng population and serve both low and middle socio-economic persons with and without medical insurance. Data collected in this retrospective analysis was fairly representative, minimising the possibility of bias when compared to a cross-sectional study.

4.2 Data collection

The histopathology reports of patients diagnosed with lymphomas of the head and neck were reviewed in great detail. Epidemiological data including the demographic, clinical, laboratory, and histological parameters for each patient were recorded on a standardised

data capture sheet (Appendix 1). Variables included, amongst others, the age of patient, gender, site involved, size of tumour, type of lymphoma (final histological diagnosis) and year diagnosed.

Lymphomas were classified according to the 2008 WHO Classification of Tumours of Lymphoid Neoplasms (refer to Appendix 2) (Swerdlow et al. 2008). For simplification purposes and as traditionally described, lymphomas were divided into two main groups: HL and NHL. The NHLs were further divided into B-cell, T & NK-cell neoplasms and precursor and mature/peripheral subtypes. HLs were sub-classified into nodular lymphocyte predominant category and classic HL (CHL). CHL was further subdivided into: nodular sclerosing, mixed cellularity, lymphocyte rich and lymphocyte depleted. All lymphoma subtypes were correlated with age, gender and sites involved.

4.3 Statistical analysis

The data was entered into Microsoft® Excel® spread sheets, and then transferred to the statistical software programme Statistica for statistical analysis under the guidance of a biostatistician. The Chi-square test was used to assess the trends amongst the categorical variables, such as amongst others gender, nodal versus extranodal, and HL versus NHL. The level of significance was set at 0.05.

4.4 Ethical considerations

There was no direct contact with any of the patients during this retrospective study and patient records and slides were given study numbers in order to maintain patient confidentiality. The protection of the rights of human research subjects was respected.

Ethical clearance (M131043) was granted by the Human Research Ethics Committee at the University of the Witwatersrand, Johannesburg, South Africa (Appendix 3).

CHAPTER 5

5.0 RESULTS

5.1 Number of cases

A 20 year review of the archives in the Oral Pathology Unit, University of Witwatersrand revealed a total of 22 459 patients referred to the Unit during the period 1993-2012. Of the 22 459 oral pathology cases, 504 of these patient cases (2.24%) were head and neck lymphomas. The annual number of oral pathology cases, total number of lymphoma cases and the annual percentage of lymphoma cases are shown in Table 5.1 and Figure 5.1.

5.2 Age

Age was recorded in 498 patients out of the 504 patients. The median age was 39 years and patients ranged in age from 2 to 100 years.

5.3 Gender

Gender was recorded in 503 patients out of the 504 patients. 267 patients (53%) were male, 236 (46.8%) were female and one patient had an unknown gender (0.2%) (M:F ratio = 1.13:1).

Table 5.1 Number and percentage of lymphoma cases per annum from 1993-2012

Year	Oral pathology cases (*n*)	Lymphoma cases (*n*)	Lymphoma cases (%)
1993	725	6	0.83
1994	602	3	0.50
1995	824	2	0.24
1996	661	3	0.45
1997	636	3	0.47
1998	442	2	0.45
1999	1066	8	0.75
2000	1134	13	1.15
2001	1184	21	1.77
2002	1382	19	1.37
2003	1477	30	2.03
2004	1380	29	2.10
2005	1294	25	1.93
2006	1086	32	2.95
2007	1004	32	3.19
2008	1124	38	3.38
2009	1618	62	3.83
2010	1471	56	3.81
2011	1788	62	3.47
2012	1561	58	3.72
TOTAL	**22 459**	**504**	**2.24**

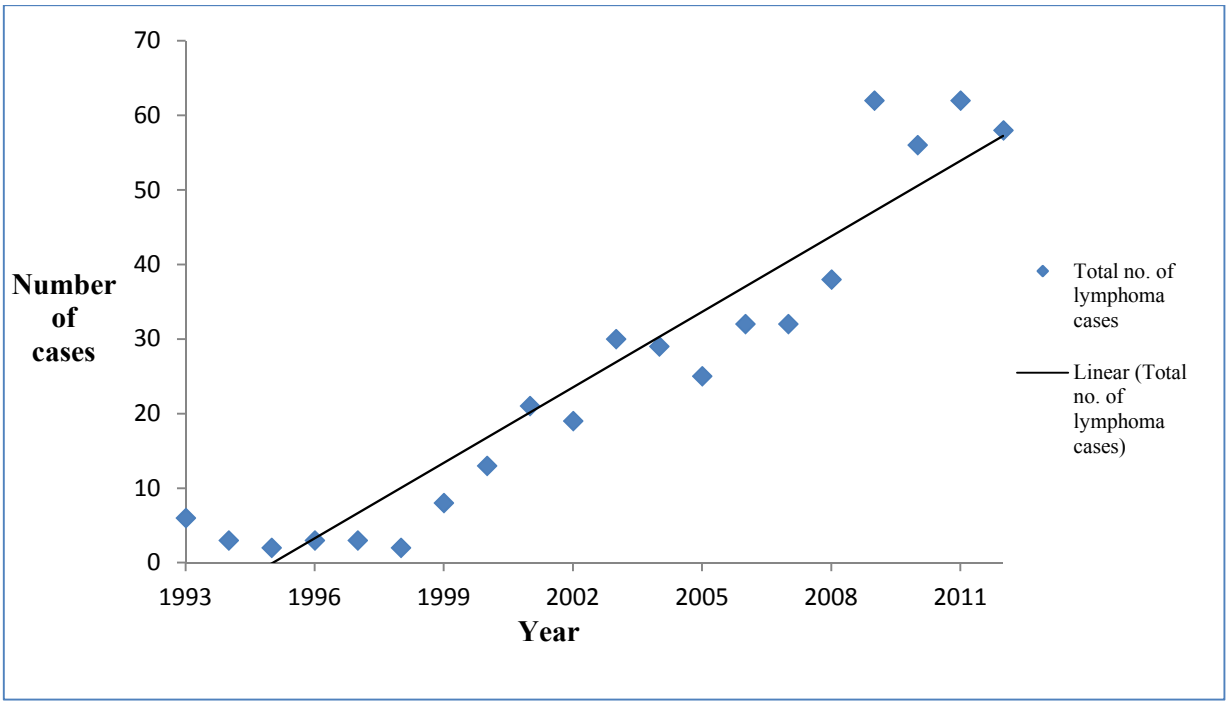

Figure 5.1 Comparison of number of lymphoma cases per annum from 1993-2012

5.4 Anatomic site

The anatomic sites are shown below in Table 5.2 and Figure 5.2. Of the 504 lymphoma cases, 57% of cases (287 cases) were intra-oral sites and 43% of cases (217 cases) were extra-oral.

Table 5.2 Anatomic sites of occurrence of the head and neck lymphomas

Anatomic site	Lymphoma cases (*n*)	Percentage (%)
Cervical lymph node	115	22.82
Maxilla	60	11.90
Palate	49	9.72
Mandible	42	8.33
Gingiva	41	8.13
Buccal mucosa	33	6.55
Maxillofacial lymph node	22	4.37
Salivary gland	18	3.57
Waldeyer's ring	17	3.37
Nasal cavity	16	3.17
Paranasal sinuses	12	2.38
Posterior nasal space	10	1.98
Neck	9	1.79
Oral cavity (NOS)	7	1.39
Jaw (NOS)	7	1.39
Tongue	7	1.39
Floor of mouth	6	1.19
Buccal vestibule	6	1.19
Submandibular area	6	1.19
Face	4	0.79
Oropharynx	3	0.60
Lip	3	0.60
Pharynx	2	0.40
Larynx	2	0.40
Orbit	1	0.20
Alveolus	1	0.20
Tonsillar fossa area	1	0.20
Submental area	1	0.20
Scalp	1	0.20
Parapharynx	1	0.20
Retromolar mucosa	1	0.20

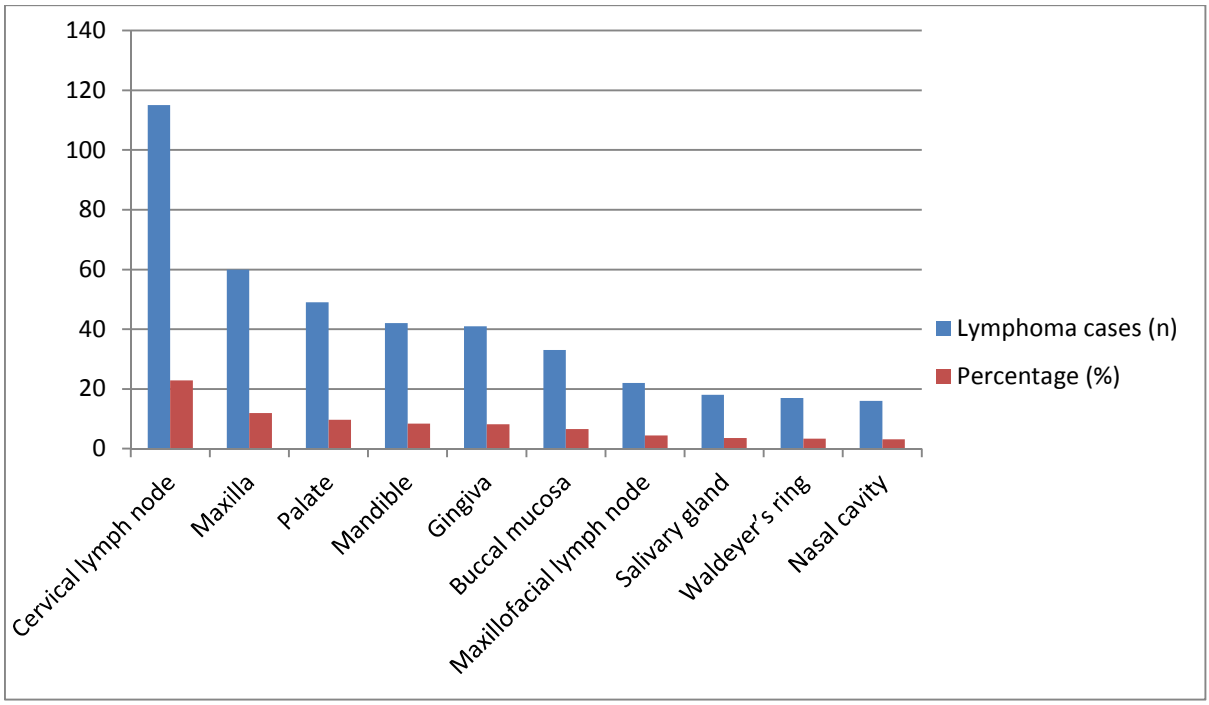

Figure 5.2 Comparison of the ten most common anatomic sites of the head and neck lymphomas

5.5 Lymphoma subtypes

Table 5.3 and Figure 5.3 show the lymphoma subtypes diagnosed within the study period, the number of cases (*n*) and percentage (%) of each case.

Table 5.3 Head and neck lymphoma subtypes diagnosed within the study period, 1993-2012

Lymphoma subtype	Number of cases (*n*)	Percentage (%)
Plasmablastic lymphoma	159	31.55
Diffuse large B-cell lymphoma	155	30.75
Burkitt lymphoma	28	5.56
Nodular sclerosing classic HL	21	4.17
Nodular lymphocyte predominant HL	16	3.17
Plasma cell myeloma	15	2.98
Mixed cellularity classic HL	14	2.78
Peripheral T-cell lymphoma (NOS)	12	2.38
Small lymphocytic lymphoma	11	2.18
Follicular lymphoma	10	1.98
Anaplastic large cell lymphoma	10	1.98
NK/T-cell lymphoma (nasal type)	10	1.98
MALT lymphoma	9	1.79
Solitary plasmacytoma of bone	7	1.39
Extra-osseous plasmacytoma	7	1.39
Burkitt-like lymphoma	6	1.19
Mantle cell lymphoma	5	0.99
B-cell NHL (NOS)	2	0.40
Acute undifferentiated leukaemia	2	0.40
Marginal zone lymphoma	1	0.20
T-cell lymphoma (NOS)	1	0.20
T-cell rich B-cell NHL	1	0.20
T-cell acute lymphoblastic lymphoma	1	0.20
Lymphoblastic lymphoma (NOS)	1	0.20
Total	**504**	**100**

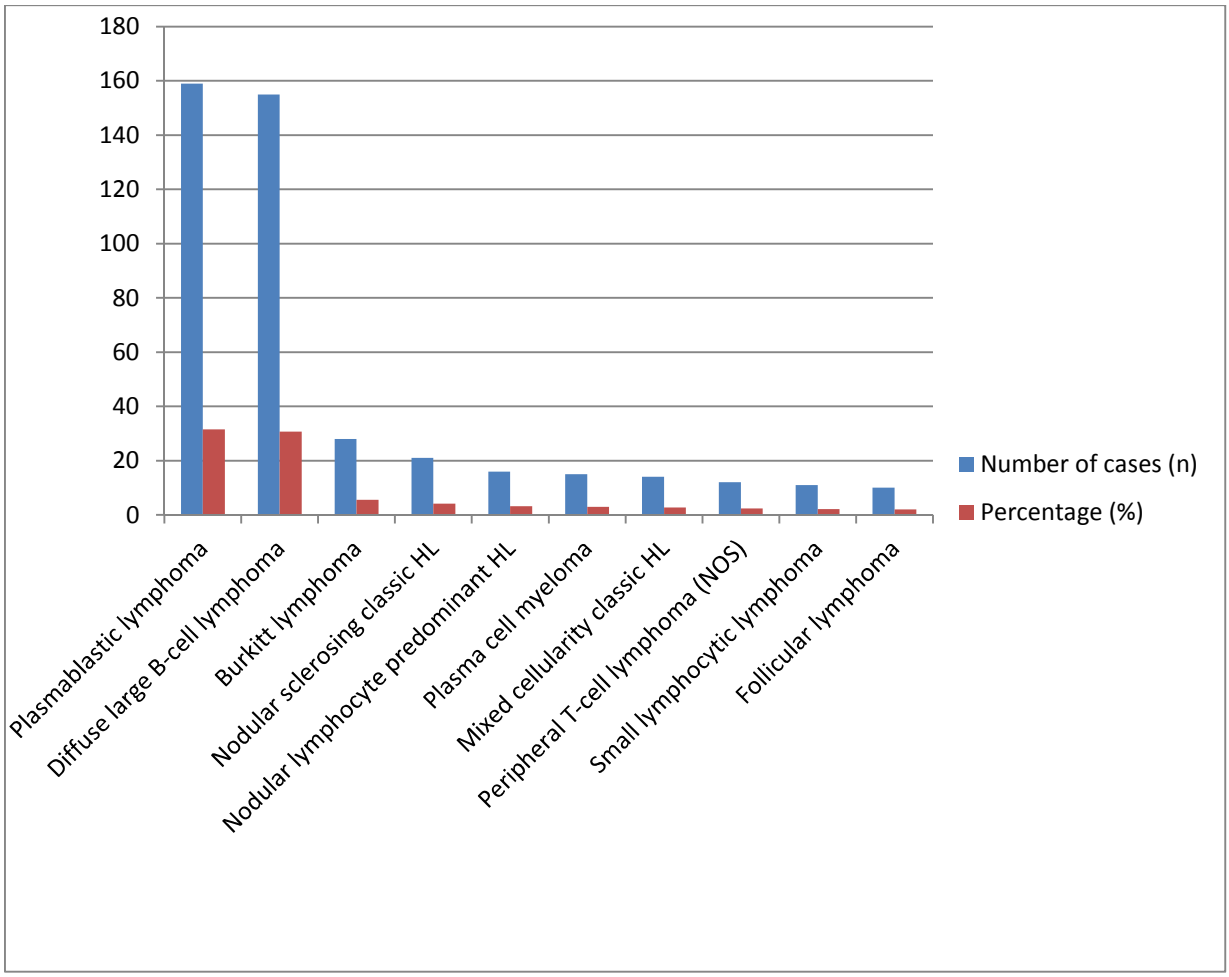

Figure 5.3 Comparison of the ten most common head and neck lymphoma histological subtypes

5.6 NHL versus HL

Of the 504 lymphoma cases, 453 patients (90%) had NHL and 51 patients (10%) had HL (Figure 5.4 and Table 5.4).

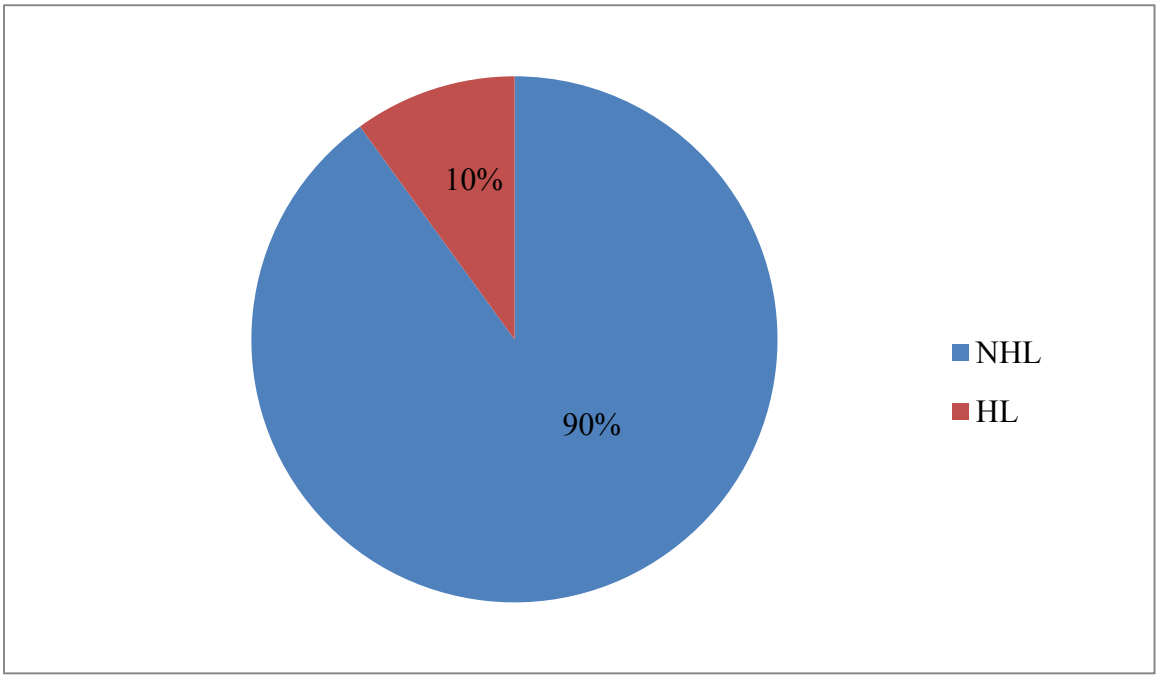

Figure 5.4 Comparison of percentage of NHL versus HL

Table 5.4 Distribution of the number of head and neck NHL and HL lymphoma subtypes

Lymphoma subtype	Number of cases (*n*)	Percentage (%)
Non-Hodgkin lymphoma		
Plasmablastic lymphoma	159	31.55
Diffuse large B-cell lymphoma	155	30.75
Burkitt lymphoma	28	5.56
Plasma cell myeloma	15	2.98
Peripheral T-cell lymphoma (NOS)	12	2.38
Small lymphocytic lymphoma	11	2.18
Follicular lymphoma	10	1.98
Anaplastic large cell lymphoma	10	1.98
NK/T-cell lymphoma (nasal type)	10	1.98
MALT lymphoma	9	1.79
Solitary plasmacytoma of bone	7	1.39
Extra-osseous plasmacytoma	7	1.39
Burkitt-like lymphoma	6	1.19
Mantle cell lymphoma	5	0.99
B-cell NHL (NOS)	2	0.40
Acute undifferentiated leukaemia	2	0.40
Marginal zone lymphoma	1	0.20
T-cell lymphoma (NOS)	1	0.20
T-cell rich B-cell NHL	1	0.20
T-cell acute lymphoblastic lymphoma	1	0.20
Lymphoblastic lymphoma (NOS)	1	0.20
Hodgkin lymphoma		
Nodular sclerosing classic HL	21	4.17
Nodular lymphocyte predominant HL	16	3.17
Mixed cellularity classic HL	14	2.78
Total	**504**	**100**

Of the 453 NHL cases:

- 416 cases were of B-cell origin (91.83%)
- 35 cases were of NK/T-cell origin (7.73%)
- 1 case was of ambiguous lineage (0.22%)
- 1 case was of unknown origin (0.22%)

The 453 NHL cases were further categorised:

- ✓ 1 case of ambiguous lineage (0.22%)
- ✓ 2 cases being precursor neoplasms (0.44%)
- ✓ 450 cases being mature neoplasms (99.34 %)

From all the NHL cases (453 cases), 448 patients had known ages. The median age was 40 years and the age range was 2 to 100 years. From the 51 HL cases, 50 patients had ages recorded. The median age was 30 years and the age range was 12 to 58 years.

Of the 453 NHL patients, 244 (53.86 %) were males and 208 (45.92 %) were females and one patient had an unknown gender (0.22%). Of the 51 HL patients, 23 (45%) were males and 28 (55%) were females. There was no statistically significant difference between the percentage of males and females in NHL and HL (p=0.23).

The most common NHL was PBL (31.55%) and the most common HL was nodular sclerosing classic HL (4.17%). Of all the NHLs the most common lymphoma of B-cell origin was PBL (31.55%) and the most common lymphoma of T-cell origin was peripheral T-cell lymphoma (NOS) (2.38%).

5.6.1 B-cell lymphomas

Of the 159 PBLs, 104 patients (65.41%) were male and 55 patients (34.59%) were female. The median age was 39 years with an age range of 11 to 84 years. PBLs occurred more commonly intra-orally, with132 cases (83.02%) occurring in oral sites and 27 cases (16.98%) in extra-oral sites; 31 cases (19.50%) occurred in the maxilla, 26 cases (16.35%) in the palate, 22 cases (13.84%) in the gingiva, 18 cases (11.32%) in the mandible, 17 cases (10.69%) in the buccal mucosa, 5 cases each (3.14%) in the cervical lymph node, nasal cavity and the oral cavity (NOS), 4 cases each (2.52%) in the posterior nasal cavity and paranasal sinuses, 3 cases each (1.89%) in the floor of the mouth and the buccal vestibule, 2 cases each (1.26%) in the salivary glands, lip, maxillofacial lymph node, face and tongue, and 1 case each (0.63%) in WR, pharynx, alveolus, jaw (NOS), larynx and submandibular area.

DLBCL occurred in 155 cases, 74 patients (47.74 %) were male, and 80 patients (51.61%) were female and one patient had an unknown gender (0.65%). Of the 155 DLBCL cases, age was documented for 152 patients. The median age was 40 years with an age range of 3 to 92 years.

Oral involvement was seen in 71 DLBCL cases (45.81%), and 84 cases (54.19%) occurred in extra-oral sites. These included 43 cases (27.74%) occurring in the cervical lymph nodes, 14 cases (9.03%) in WR, 12 cases (7.74%) in the gingiva, 11 cases each (7.10%) in the palate, salivary glands and maxillofacial lymph nodes, 7 cases each (4.52%) in the maxilla and the mandible, 6 cases (3.87%) in the neck, 5 cases (3.23%) in the buccal mucosa, 4 cases (2.58%) in the posterior nasal space, 3 cases each (1.94%) in the nasal cavity, buccal vestibule, jaw (NOS), submandibular area and the tongue, 2 cases (1.29%)

in the oropharynx, and 1 case each (0.65%) in the floor of the mouth, paranasal sinuses, oral cavity (NOS), pharynx, tonsillar fossa area, face and larynx.

BL occurred in 28 cases of which 6 cases were atypical BL. Of the 28 BL cases, 13 patients (46.43%) were male and 15 (53.57%) were female. Age was recorded in 27 patients. The median age was 28 years and the age range was 2 to 59 years. Orally, there were 22 (78.57%) BL cases, and 6 cases (21.43%) occurred in extra-oral sites; 9 cases (32.1%) occurred in the mandible, 6 (21.4%) in the maxilla, 3 (10.7%) in the buccal mucosa, 2 each (7.1%) in the jaw (NOS) and cervical lymph nodes, and 1 each (3.6%) affecting the gingiva, maxillofacial lymph node, submandibular area, posterior nasal space, paranasal sinuses and oral cavity (NOS).

Plasma cell myeloma occurred in 15 patients, 7 patients (46.67%) were male and 8 (53.33%) were female. Age was recorded in all 15 patients. The median age was 52 years and the age range was 26 to 77 years. Orally, there were 11 cases (73.33%), and 4 cases (26.67%) occurred at extra-oral sites; 5 cases (33.33%) occurring in the maxilla, 3 (20%) in the mandible, 2 (13.33%) in the paranasal sinuses and 1 each (6.67%) in the palate, buccal mucosa, nasal cavity, gingiva and the scalp.

SLL occurred in 11 patients, with 6 patients (54.55%) being male and 5 patients (45.45%) female. Age was recorded in all patients. The median age was 62 years and the age range was 24 to 85 years. This subtype occurred in 4 oral sites (36.36%) and 7 (63.64%) extra-oral sites, and 5 cases (45.45%) occurred in the cervical lymph nodes, 2 (18.18%) in the tongue and 1 each (9.10%) in the maxilla, maxillofacial lymph node, jaw (NOS) and parapharynx.

FL occurred in 10 patients, 6 males (60%) and 4 females (40%). All patient ages were recorded. The median age was 54 years and the age range was 36 to 82 years. This subtype occurred in 2 oral sites (20%) and 8 extra-oral sites (80%), and 6 cases (60%) occurred in the cervical lymph nodes and 2 each (20%) in WR and the maxillofacial lymph nodes.

MALT lymphoma occurred in 9 patients, 2 males (22.22%) and 7 females (77.78%). Age was recorded in all 9 patients. The median age was 61 years and the age range was 46 to 78 years. This subtype occurred in 5 oral sites (55.56%) and 4 extra-oral sites (44.44%), and 4 cases (44.44%) occurred in the salivary glands, 3 (33.33%) in the palate and 1 each (11.11%) in the buccal mucosa and mandible.

Solitary plasmacytoma of bone occurred in 7 patients, 3 males (42.86%) and 4 females (57.14%). Age was recorded in all 7 patients. The median age was 50 years and the age range was 12 to 100 years. All 7 cases occurred in the oral cavity, with 3 cases (42.86%) occurring in the maxilla and 2 each (28.57%) in the palate and mandible.

Extra-osseous plasmacytoma occurred in 7 patients, 3 males (42.86 %) and 4 females (57.14%). Age was recorded in all 7 cases. The median age was 52 years and the age range was 42 to 65 years. This subtype occurred in 4 oral sites (57.14%) and 3 extra-oral sites (42.86%), and 3 cases (42.86%) occurred in the nasal cavity, 2 (28.57%) in the gingiva and 1 each (14.29%) in the maxilla and the retromolar mucosa.

Burkitt-like lymphoma occurred in 6 patients, 1 male (16.67 %) and 5 females (83.33%). Age was recorded in all 6 patients. The median age was 32 years and the age range was

5 to 59 years. This subtype occurred in 3 oral sites (50%) and 3 extra-oral sites (50%), and 1 case each (16.67%) occurred in the cervical lymph node, buccal mucosa, orbit, mandible, paranasal sinuses and the submandibular area.

Mantle cell lymphoma occurred in 5 patients, 4 males (80%) and 1 female (20%). Age was recorded in all 5 patients. The median age was 57 years and the age range was 41 to 73 years. This subtype occurred in 2 oral sites (40%) and 3 extra-oral sites (60%), and 2 cases (40%) occurred in the cervical lymph nodes and 1 case each (20%) in the buccal mucosa, lip and posterior nasal space.

B-cell NHL (NOS) occurred in 2 patients, both patients being female. The median age was 38.5 years and age range was 33 to 44 years. Both cases occurred in oral sites, one case in the mandible and one in the floor of the mouth.

Marginal zone lymphoma occurred in 1 patient which was a female. She was 88 years old and it occurred in an extra-oral site which was the cervical lymph node.

5.6.2 T-cell lymphomas and NK/T-cell lymphomas

Peripheral T-cell lymphoma (NOS) occurred in 12 patients, with 4 patients (33.33%) being male and 8 patients (66.67%) female. Age was recorded in all patients. The median age was 35.5 years and the age range was 11 to 55 years. This subtype occurred equally in oral and extra-oral sites (6 cases each [50%]), and 2 cases each (16.67%) were found in the cervical lymph node, palate and maxilla and 1 case each (8.33%) in the neck, nasal cavity, gingiva, maxillofacial lymph node, submental area and oropharynx.

Anaplastic large cell lymphoma occurred in 10 patients, 8 males (80%) and 2 females (20%). Age was recorded in 9 patients. The median age was 24 years and the age range was 4 to 60 years. This subtype occurred in 6 oral sites (60%) and 4 extra-oral sites (40%), and 3 cases (30%) occurred in the cervical lymph nodes, 2 each (20%) in the buccal mucosa and gingiva and 1 each (10%) in the maxilla, floor of mouth and neck.

NK/T-cell lymphoma (nasal type) occurred in 10 patients, 6 males (60%) and 4 females (40%). All ages were recorded. The median age was 36.5 years and the age range was 16 to 61 years. This subtype occurred in 4 oral sites (40%) and 6 extra-oral sites (60%), and 3 cases (30%) occurred in the nasal cavity and 2 each (20%) in the palate, maxilla, paranasal sinuses and 1 case (10%) in the face.

T-cell lymphoma (NOS) occurred in a single patient, a 69 year old female in an oral site, the maxilla. T-cell rich B-cell NHL occurred in a single patient, a 31 year old male in an extra-oral site, a salivary gland.

5.6.3 HL

Nodular sclerosing CHL occurred in 21 cases, 7 patients (33.33%) were male and 14 (66.67%) were female. The median age of the 21 patients was 32 years and the age range was 12 to 47 years. All 21 cases (100%) occurred in extra-oral sites, 20 cases (95.24%) occurred in the cervical lymph nodes and 1 case (4.76%) occurred in a maxillofacial lymph node.

Nodular lymphocyte predominant HL occurred in 16 patients, with 10 patients (62.5%) being male and 6 (37.5%) female. Age was recorded in 15 out of the 16 patients. The

median age was 27 years and the age range was 14 to 51 years. All 16 cases (100%) occurred at extra-oral sites, 13 (81.25%) affecting the cervical lymph nodes and 3 (18.75%) affecting the maxillofacial lymph nodes.

Mixed cellularity CHL occurred in 14 patients, with 6 patients (42.86%) being male and 8 (57.14%) female. Age was recorded in all patients. The median age was 33 years and the age range was 17 to 58 years. This subtype occurred in 3 oral sites (21.43%) and 11 (78.57%) extra-oral sites; 11 cases (78.57%) occurred in the cervical lymph node and 1 each (7.14%) in the palate, buccal mucosa and neck.

5.6.4 Precursor lymphoid neoplasms

T-cell acute lymphoblastic lymphoma occurred in a single 14 year old female patient in an extra-oral site, a cervical lymph node.

Lymphoblastic lymphoma (NOS) occurred in a single 12 year old female patient in an oral site, the palate.

Acute undifferentiated leukaemia (of ambiguous lineage) occurred in 2 patients and both were males. Age was recorded in both patients. The median age was 27 years and the age range 26 to 28 years. This subtype occurred in 1 oral site (50%) and 1 extra-oral site (50%), and 1 case each (50%) occurred in the buccal mucosa and paranasal sinuses.

5.7 Nodal versus extranodal sites

Of the 504 head and neck lymphoma cases noted, 137 cases (27%) were of nodal origin and 367 cases (73%) were of extranodal origin (Figure 5.5). Out of the 137 nodal cases,

64 patients (46.72%) were male and 73 patients (53.28%) were female. From the 367 extranodal cases, 203 patients (55.3%) were male and 163 patients (44.4%) were female and one patient had an unknown gender (0.3%). There was no statistically significant difference found in the percentage of males and females in nodal and extranodal sites (p=0.1).

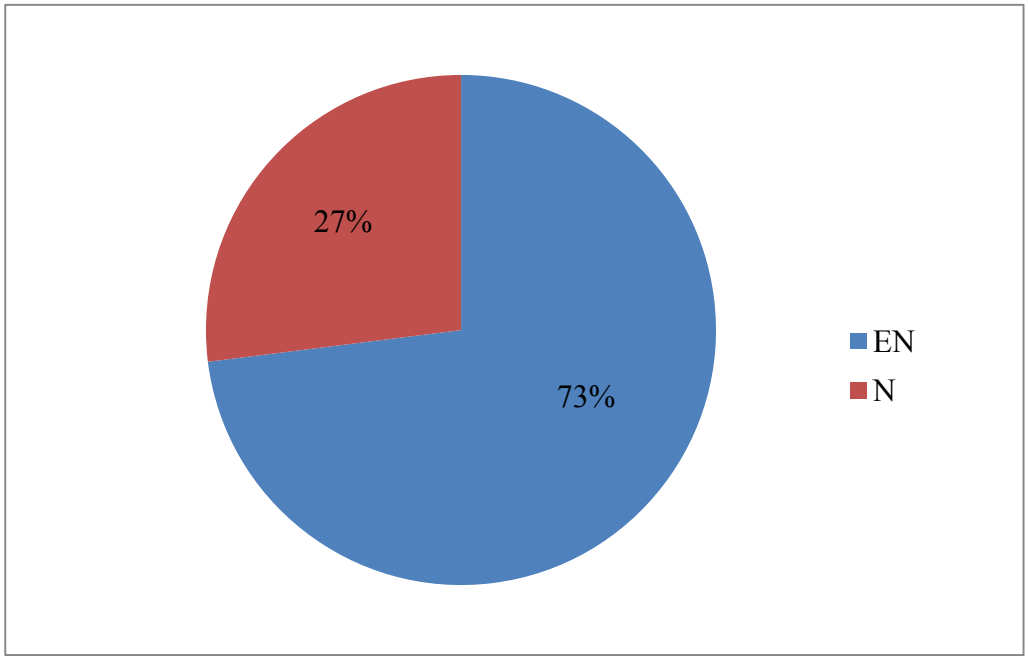

Figure 5.5 Percentage comparison of nodal (N) versus extranodal (EN) head and neck lymphomas

Of the 137 cases of nodal origin, 89 cases (64.96%) were NHL and 48 cases (35.04 %) were HL. Of the 367 extranodal cases, 364 cases (99.18 %) were NHL and 3 cases (0.82%) were HL. There was a statistically significant difference between the percentage of NHL and HL cases of nodal and extranodal origin (p=0.00)

5.8 Clinical Features

The most common clinical presentation was a swelling. In almost all the cases, the neoplasm was described as a swelling/mass or lump. Ulceration was noted in 57 cases (11.31%) of patients and 36 cases (7.14%) complained of pain. The duration of symptoms ranged from 6 days to 10 years. The nodal lesions ranged in size from 0.3x0.3x0.1cm to 12x7x6cm while the extranodal lesions ranged in size from 0.3x0.2x0.2cm to 15cm.

5.9 B symptoms

There was only one patient in this study that had reported B symptoms. It was a 43 year old female with FL of a facial lymph node. The patient also had hepatosplenomegaly.

5.10 Subtype and gender distribution and age analysis of anatomic sites

5.10.1 Waldeyer's ring

Of the 17 cases that occurred in WR, 10 (58.82%) occurred in the tonsils, 6 (35.29%) in the nasopharynx and 1 (5.88%) in the base of the tongue. 10 cases (58.82%) occurred in males and 7 (41.18%) in females. Age was recorded in all 17 patients. The median age was 46 years and the age range was 29 to 92 years. Of the 17 cases, 14 (82.35%) were DLBCL, 2 (11.76%) were FL and 1 (5.88%) was a PBL.

5.10.2 Salivary glands

Of the 18 cases, 15 cases (83.33%) occurred in the parotid gland and 3 (16.67%) in the submandibular gland. Gender was recorded in 17 patients, 5 (27.78%) males, 12 (66.67%) females and one patient had an unknown gender (5.56%). Age was recorded in all 18 patients. The median age was 44.5 years and the age range was 3 to 76 years. Of the

18 cases, 11 (61.11%) were DLBCLs, 4 (22.22%) were MALT lymphomas, 2 (11.11%) were PBLs and 1 (5.56%) was a T-cell rich B-cell NHL.

5.10.3 Lymphomas of the jaw

There were 109 cases which occurred in the jaws, 60 (55.05%) in the maxilla, 42 (38.53%) in the mandible and 7 (6.42%) were not otherwise specified. Of the 109 cases, 64 (58.72%) patients were male and 45 (41.28%) were female. Age was recorded in all the maxillary cases. The median age was 41 years and the age range was 5 to 100 years. Age was recorded in 40 of the 42 mandibular cases. The median age was 36.5 years and the age range was 2 to 78 years. Age was recorded in all 7 of the jaw (NOS) cases. The median age was 28 years and the age range was 6 to 63 years.

5.11 HIV status

HIV status was recorded in 218 patients (43.25%) of the 504 patients and the HIV status in the remaining 286 patients (56.75%) was unknown. In the 218 patients in which the HIV status was known, 199 patients (91.28%) were HIV positive and 19 (8.72%) were HIV negative.

5.12 EBV status

EBV status was recorded in 157 (31.15%) of the 504 cases and the EBV status in the remaining 347 (68.85%) patients was unknown. Of the 157 patients, 61 (38.85%) were EBV positive and 96 (61.15%) were EBV negative.

5.13 Metastasis, recurrence and second neoplasms

Metastasis occurred in 12 out of the 504 cases. Of the 12 patients, 5 had PBLs, 2 had DLBCLs, and there was 1 each with SLL, anaplastic large cell lymphoma, peripheral T-cell lymphoma (NOS), NK/T-cell lymphoma and mixed cellularity CHL.

Recurrence occurred in 5 of the 504 cases. Two of these patients had FL and 1 each had extra-osseous plasmacytoma, mantle cell lymphoma and nodular sclerosing HL.

Of the 504 patients, 4 developed another neoplasm either before or after the lymphomas were diagnosed. Two patients had a history of lip and tonsillar carcinoma and later developed PBL and FL respectively. The third patient had FL of the cervical lymph node and later developed keratinising squamous cell carcinoma of the skin. The last patient had DLBCL of the mandible and carcinoma of the cervix.

CHAPTER 6

6.0 DISCUSSION

6.1 Frequency over the 20 year period

As predicted this study showed an overall increase in the number of lymphoma cases diagnosed over the 20 year period. Although this is in keeping with global trends, the reasons for the increase in a South African population may differ. Changes in disease patterns, trends and virulence over the past few decades may be contributing factors.

This increasing head and neck lymphoma frequency pattern is in keeping with that of literature worldwide (Iguchi et al. 2012, Huh 2012). The frequency pattern of this study was similar to the consistent increase noted in Asia (Korea) with no stabilisation, as well as to that of the Western Cape study (Chetty, Sudi & Abayomi 2012) and differed from that of the developed countries which have shown some stabilisation in recent years (Huh 2012).

While reasons such as the AIDS epidemic, improving diagnostic accuracy and reporting, a new globally accepted classification system, an aging population and the increase in cancer-causing behaviours are all contributing factors, this only accounts for 50% of the global increasing trend and most plausible explanations remain unexplained (Huh 2012). South Africa is said to have one of the lowest percentages (25%) of HAART coverage in HIV patients in the African continent (Brower 2011). This puts the remaining 75% of the AIDS affected patients at a higher risk of acquiring this AIDS-defining cancer. Chetty, Sudi & Abayomi (2012), in their study carried out in the Western Cape, found the

commencement of HAART not to have an impact on the lymphoma frequency. They attributed these findings to inadequate HAART coverage, delay in starting ART, high viral loads and late presentation of disease. They also considered socio-economic factors such as lack of education, poverty, accessibility to healthcare services and female dependence on partners to be some of the other contributing factors. These reasons may also form part of the contributing factors in the rise in the number of lymphoma cases found in this study.

Biologic agents that have been associated with the aetiology of malignant lymphomas include EBV, HHV8, hepatitis B and C virus, *helicobacter pylori*, autoimmune disease, exposure to certain organic chemicals and pharmaceuticals (Huh 2012). The current study raises the possibility of a link between the increase in the frequency of lymphoma in the study cohort and EBV and HIV status.

6.2 Comparison to studies in developed European countries

Seven reports from the Northern (Finland, United Kingdom), Southern (two from Greece, Italy) and Western (Germany, Netherlands) Europe were compared to this study (Söderholm et al. 1990; Hart et al. 2004; Triantafillidou et al. 2012; Kolokotronis et al. 2005; Bussu et al. 2013; Scherfler et al. 2012; van der Waal et al. 2005). Six of the studies evaluated NHLs of either the oral cavity only or the head and neck region. One study evaluated both HLs and NHLs of the head and neck region as did the current study.

The aim of most of these studies was to analyse, describe or evaluate the clinical signs and symptoms, presenting features and the histological subtypes, in a similar manner to that of this study. The number of cases varied with the largest sample size being 190 patients with extranodal lymphomas of the head and neck, over a 30 year period (Hart et al. 2004).

These European studies comprised of relatively small sample sizes compared to the 504 cases in this study. This is most possibly due to the fact that this study included both HL and NHL and was over a larger study period compared to the other studies.

Studies on NHL showed mean ages, ranging from lowest to highest, to be 52; 54.5; 59; 64 and 64 years (Söderholm et al. 1990; Triantafillidou et al. 2012; van der Waal et al. 2005; Scherfler et al. 2012; Kolokotronis et al. 2005), with one study reporting a median age of 65 years (Hart et al. 2004). The mean age in the head and neck lymphoma study was 59 years (Bussu et al. 2013).

Our study showed the median age of the NHL cases to be 40 years and the median age of the overall head and neck lymphoma cases to be 39 years which is much lower than the reported ages noted in the developed European countries. The lower limit of the ages ranged from 1 to 27 years (Scherfler et al. 2012; Kolokotronis et al. 2005) and the upper limit ranged from 81 to 93 years (Triantafillidou et al. 2012; Bussu et al. 2013). This was in keeping with the age range of this study which was 2 to 100 years for the NHL cases as well as the overall lymphoma age range.

In the developed European countries, three studies showed a slight male predominance (van der Waal et al. 2005; Triantafillidou et al. 2012; Bussu et al. 2013) as did this study however, three other reports also showed a slight female predominance (Hart et al. 2004; Scherfler et al. 2012; Kolokotronis et al. 2005). Bussu et al. (2013) showed a nodal to extranodal ratio of 1:1.94, whilst in the current study a slightly higher ratio of 1:2.7 was evident.

Six of the European studies found the most common clinical feature to be a swelling/mass (Scherfler et al. 2012; Kolokotronis et al. 2005; Triantafillidou et al. 2012; van der Waal et al. 2005; Hart et al. 2004; Söderholm et al. 1990). Two reports showed ulceration to be the second most common feature (Kolokotronis et al. 2005; van der Waal et al. 2005) while one study found pain to be the second most common symptom (Hart et al. 2004). Two studies found dysphagia to be the most common and third most common clinical symptom (Bussu et al. 2013; Hart et al. 2004). The current study recapitulated these findings of a swelling or mass to be the most common clinical feature followed by ulceration and pain.

Three studies found the jaw bones and soft tissue of the jaws to be the most common anatomic site (Scherfler et al. 2012; Söderholm et al. 1990; van der Waal et al. 2005), a finding which coincides with that of the current study in which the jaw bones was the most common extranodal site. However, three other reports found the tonsils to be the most common extranodal site (Bussu et al. 2013; Hart et al. 2004; Kolokotronis et al. 2005) and two studies found this site to be followed by the salivary glands (Bussu et al. 2013; Hart et al. 2004).

DLBCL was the commonest subtype in four of the studies (Bussu et al. 2013; Hart et al. 2004; Kolokotronis et al. 2005; Scherfler et al. 2012) and ranked second to MALT lymphoma in a single report (Triantafillidou et al. 2012). This study found DLBCL to be the second most common subtype. Other common subtypes (in the European studies) following DLBCL were MALT, FL and mantle cell lymphoma. These were the most common subtypes, even though the order in which they were ranked in each study varied. A similar pattern was not seen in this study.

6.3 Comparison to developed North American countries

Two North American studies one from Boston and the other from Stanford were analysed (Kemp et al. 2008; Jacobs & Hoppe 1985). The one included NHL of the oral cavity only and the other included extranodal NHL of the head and neck (Kemp et al. 2008; Jacobs & Hoppe 1985). The study samples were relatively small, 40 and 156 patients respectively compared to 453 NHL cases analysed in this study.

Mean ages of 53 and 71 years noted in the two North American studies (Jacobs & Hoppe 1985; Kemp et al. 2008) were much higher than the median age of 40 years in patients with NHL in the present study. The lower limit of the age ranges was 16 and 35 years respectively (Jacobs & Hoppe 1985; Kemp et al. 2008). Jacobs & Hoppe (1985) excluded patients below the age of 16 years in their study, however Kemp et al. (2008) did not state any age exclusion and showed a much higher lower age limit (35 years) compared to the lower age limit of 2 years noted in the present study. The upper limit of the age range in patients with NHL in this study was 100 years, which was higher than the 81 and 89 years found in the North American studies (Jacobs & Hoppe 1985; Kemp et al. 2008). Similar to the current study, Jacobs & Hoppe (1985) found a slight male predominance whilst Kemp et al. (2008) found a slight female predominance.

Like the present study, Kemp et al. (2008) found swelling and ulceration to be the most common clinical features. Jacobs & Hoppe (1985) reported 12% of patients with B symptoms which differed from this study, in which only 1 patient (0.2%) showed B symptoms. In both this study and that of Kemp et al. (2008), the jaw bones followed by the palate were the most common anatomic sites, whilst in the study by Jacobs & Hoppe (1985) WR followed by the salivary glands were the most common sites.

The B-cell to NK/T-cell ratio found in the study by Kemp et al. (2008) (49:1) was far higher than that found in this study (11.88:1). The most common subtype in their study was DLBCL followed by FL, extranodal marginal zone lymphoma and plasma cell tumours while this study found PBL to be the most common subtype followed by DLBCL, BL and plasma cell tumours, when considering only the NHLs.

6.4 Comparison to developed Middle East and Asian countries

Reports from Iran, Israel and Japan that were analysed and compared to the findings of this study, included a study on NHL of the head and neck, a study on oral and pharyngeal lymphoma and one of lymphoid neoplasms of the head and neck (Etemad-Moghadam et al. 2010; Zini et al. 2012; Iguchi et al. 2012). The incidence rate of lymphomas noted in each study was 0.48%, 5.7% and 15.1% respectively.

The mean age of the head and neck NHL study was 46.3 years which was slightly higher than the median age (40 years) of the NHL cases in this study (Etemad-Moghadam et al. 2010). The two lymphoma studies reported mean and median ages of 59.5 years and 66 years respectively (Zini et al. 2012; Iguchi et al. 2012) which were far higher than the median age of 39 years in this study. The age ranges of the Iranian (7 months - 98 years) and the Israeli study (2- 97 years) were very similar to that of this study (2- 100 years) however, it differed from the Japanese study (17- 89 years) which had a much higher lower age limit and a slightly lower upper age limit (Etemad-Moghadam et al. 2010; Zini et al. 2012; Iguchi et al. 2012). The M:F ratio of this study (1.13:1) was almost the same as that of the Israeli study (1.1:1) however, the ratio was much lower than the Iranian (2.2:1) and Japanese (2.3:1) studies (Zini et al. 2012; Etemad-Moghadam et al. 2010; Iguchi et al. 2012).

The nodal to extranodal ratio found in the Iranian study (1:0.36) was lower than that found in this study (1:2.7) (Etemad-Moghadam et al. 2010). The HL to NHL ratio of the Israeli (1:25) and Japanese studies (1:29) was far higher than that found in this study (1:9). The B-cell to NK/T-cell lymphoma ratio of 11.88:1 in this study was higher than that of the Japanese study (4.3:1) and much lower than that of the Israeli study (48.5:1) (Iguchi et al. 2012; Zini et al. 2012).

As seen in the present study, the most common clinical feature recorded in the Iranian population was a local mass (Etemad-Moghadam et al. 2010). WR was found to be the most common anatomic site in all three studies accounting for 36%, 36% and 67.5% of cases (Etemad-Moghadam et al. 2010; Zini et al. 2012; Iguchi et al. 2012). This differed from the present study that found cervical lymph nodes to be the most common overall anatomic site and the maxilla to be the most common extranodal site. WR only accounted for 17% of cases in this study.

PBL (31.55%) was the most common histological subtype followed by DLBCL (30.75%) in this study, whilst DLBCL was the most common histological subtype in the Iranian (65%) and Japanese (54.9%) populations (Etemad-Moghadam et al. 2010; Iguchi et al. 2012).

6.5 Comparison to a developing Asian country

A retrospective study on primary NHLs of the oral cavity in South India over an approximate 10 year period showed only seven cases of NHLs compared to the 453 NHL cases found in this 20 year retrospective study (Sirsath et al. 2014). Similar to this study

which showed a median age of 40 years in patients with NHL, the median age was 43.2 years. The ages ranged from 29 to 65 years compared to 2 to 100 years found in this study. The lower age limit of their study (29 years) was much higher than that in this study (2 years) and the upper age limit (65 years) was much lower than that of this study (100 years). Similar to our study, a slight male predominance was noted in their study.

Like the present study, all patients in the South Indian study presented with a slow growing ulcerative mass (Sirsath et al. 2014). Similarly no patients showed B symptoms in their study compared to the single patient in our study with B symptoms. The most common anatomic site in their study was the anterior two-thirds of the tongue which differed from our study, in which the maxilla was the most common oral site.

Comparable to the current study, the study by Sirsath et al. (2014) found the most common histological subtypes to be PBL followed by DLBCL. Unlike their study that found peripheral T-cell lymphoma (NOS) to be the third most common NHL, this lymphoma ranked fifth in our study.

6.6 Comparison to a South African study

Similar to our study (Gauteng Province, South Africa) a 5 year retrospective study (2003-2007) on head and neck lymphomas was carried out in a South African population in the Western Cape (Chetty, Sudi & Abayomi 2012). The total number of lymphoma cases in this study was 242. The M:F ratio of 1.08:1 found in the Western Cape study was similar to the 1.13:1 found in the present study.

The nodal to extranodal lymphoma ratio in this study was 1:2.7 compared to their 1:0.58. The HL to NHL ratio of this study (1:9) was much higher than that of their study (1: 2.57). DLBCL ranked first in the Western Cape study and second in this study however the frequency of DLBCL in both studies was similar; namely 30.75% in this study and 32% in the Western Cape. There were 23.55% more PBLs in the present study compared to the Western Cape study, whilst their study found 17% more HLs and 8.02% more FLs than this study.

Whilst the cervical lymph nodes were the most common site in both the studies, this was much higher in the Western Cape study (64%) compared to our study (22.82%). Oral sites accounted for 25% of cases in the Western Cape compared to 57% in this study. Salivary gland lymphomas accounted for 3.57% of cases in this study and this was slightly lower than their 5% of cases.

HIV status was known in 43.25% of cases in this study compared to 80% of known HIV cases in the Western Cape. Our study found slightly more HIV positive cases (39.48%) than the Western Cape study (35%), whilst they showed more HIV negative cases (45%) compared to the negative cases (3.77%) in our study. This is however probably due to the fact that the number of patients with a known HIV status was almost double when compared to our cohort of patients with known HIV status.

6.7 Study limitations and strengths

Chiu & Weisenburger (2003) attributed only a third of the lymphoma increase to the possible causative factors with the reasons for the increase in the remaining two-thirds of cases to be unknown. Their reasoning however is not based on African nor especially South African statistics, where the incidence rates of HIV and AIDS continue to be the highest in the world (Granich et al. 2015). Whilst the Western Cape study confirmed an association between the HIV epidemic and increase in the frequency of the head and neck lymphoma, the probable relationship between HIV and AIDS as a reason for the increase of NHL noted in this study cannot be confirmed due to the unknown HIV status of a large number of patients in the cohort analysed.

This lack of information proved to be a limitation of the study as regards drawing any association between HIV and AIDS and head and neck lymphomas. This information as well as data regarding CD4 count and viral load is mandatory for future studies of this nature. A further limitation noted was the under reporting of cases due to various reasons, compromising adequate data collection and rendering the data not a true representation of the larger population. Technical and non-technical bias may also pose as a limitation to this study.

Furthermore, information regarding HIV and EBV status as well as whether the tumour was part of a generalised multifocal process or a primary tumour was not always available resulting in incomplete data. Also as a result of modern diagnostic aids such as immunohistochemistry and molecular diagnostic techniques, as well as more recent classification systems, there is a possibility that some of the earlier reported diagnoses may

have been inaccurate or incorrect, and may have changed with the adjunctive use of immunohistochemistry and molecular diagnostic techniques.

It is important to note that this study is only a description of the frequency of lymphomas diagnosed in a defined Oral Pathology Unit. In this regard the study does not represent a true reflection of the frequency of the various head and neck lymphoma subtypes seen by pathologists in the greater Johannesburg area.

This study included both HL and NHL with the aim of having a general overview of the lymphomas occurring in the head and neck region and more specifically the oral cavity. Perhaps inclusion of only B-cell non-Hodgkin's lymphomas in the study would have rendered the study more focussed.

A major strength of this 20 year retrospective study is that it offers an overview of the head and neck lymphomas seen in a defined population sample in South Africa. Furthermore, it provides a baseline or reference for future head and neck lymphoma studies to be carried out, especially in South Africa.

CHAPTER 7

7.0 CONCLUSION

This study confirmed the increase in head and neck lymphoma frequency over the 20 year period found in a defined South African population within the Department of Oral Pathology, University of the Witwatersrand, Johannesburg. A finding which is contrary to that found in Western countries, which have shown a decline in the lymphoma frequency with the advent of HAART.

Head and neck lymphomas represent 2.24% of the total number of oral pathology cases diagnosed in the Department of Oral Pathology; 90% of the total number of lymphomas being NHL and 10% HL. PBL, DLBCL and BL represent the three most common histological subtypes. The reason for the strong predilection of PBL for the oral cavity remains unknown.

Lymphomas of the oral and maxillofacial region occurred over a wide age range with predominance for the third decade and a strong male bias. Even though the male to female ratio and age range differed in each subtype; most lymphomas occurred in males and ranged in age from 2 to100 years (median, 39 years).

Head and neck lymphomas are predominantly extranodal (73%), usually presenting as ulcerated painful swellings. The most common anatomic site was the cervical lymph node, with the maxilla being the most common extranodal site.

The high prevalence of HIV in certain lymphoma categories provides a strong indication, all be it circumstantial evidence of the pivotal role of HIV and AIDS in the pathogenesis of this lymphomas, especially PBL, DLBCL and BL. Further research elucidating the molecular oncogenic pathway of both HIV and EBV is recommended.

Future studies should include long term prospective analyses on NHL patients with a strict ART regime on early and late diagnosed HIV and AIDS patients in order to monitor and evaluate the effect of a strict ART regime on the incidence of AIDS-related cancers. This would provide a major breakthrough in the study of lymphomas in the HIV and AIDS era. Such findings could motivate healthcare workers and patients in ensuring compliance with ART as well as ensuring government and non-governmental organisations to assist in providing services in the heart of communities and rural areas in order to reduce the morbidity and mortality associated with AIDS-related cancers.

Further investigation into the aetiological factors of lymphomas, with emphasis on risk factors, lifestyle and medical history is needed (Zini et al. 2012). Insight on the causative factors of the disease will contribute in reducing the annual number of fatalities caused by this neoplasm.

Furthermore, in view of the increasing lymphoma incidence there is a need for a uniform reporting system in order to establish accurate epidemiologic comparisons in different populations and countries. This will provide an improved prognostication of oral and maxillofacial lymphomas and will be most valuable for both clinicians and pathologists.

CHAPTER 8

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CHAPTER 9

9.0 APPENDICES

9.1 APPENDIX 1: DATA COLLECTION SHEET

Head and neck lymphomas: a 20 year retrospective review of cases diagnosed in an Oral Pathology Unit, Johannesburg, South Africa

Pathology report no. _____ **Date**

D	D	M	M	Y	Y

Age ____ **Gender** Male | Female

HIV Status Positive | Negative

EBV Status

Positive	Negative	Type of test

Lymphoma-Histological Type/Subtype:

Hodgkin		
Subtype		
Non-Hodgkin		
B cell		
Subtype		
T cell		
Subtype		
Additional information:		

Clinical appearance:

_____

Anatomic Site	Size	Nodal/ Extranodal lymphoma	Metastatic/ Primary/ Second/ unknown site	Presence of Systemic disease: e.gbone marrow involvement
Gingiva				
Palate				
Tongue				
Buccal mucosa				
Tonsils				
Pharynx				
Maxillary Sinus				
Salivary glands				
Parotid gland				
Submandibular gland				
Sublingual gland				
Nasopharynx				
Cervical lymph node				
Other:				

Local RG findings: _____
Systemic RG findings: _____
Additional General information:
_____

9.2 APPENDIX 2: WHO CLASSIFICATION OF LYMPHOID NEOPLASMS

ACUTE LEUKAEMIAS OF AMBIGUOUS LINEAGE

- Acute undifferentiated leukaemia
- Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); BCR-ABL1
- Mixed phenotype acute leukaemia with t(v;11q23); MLL rearranged
- Mixed phenotype acute leukaemia, B/myeloid, NOS
- Mixed phenotype acute leukaemia, T/myeloid, NOS
- Natural killer (NK) cell lymphoblastic leukaemia/lymphoma

PRECURSOR LYMPHOID NEOPLASMS

B lymphoblastic leukaemia/lymphoma

- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
- B lymphoblastic leukaemia/lymphoma with t(v;11q23) MLL rearranged
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
- B lymphoblastic leukaemia/lymphoma with hyperdiploidy
- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); IL3-IGH
- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)

T lymphoblastic leukaemia/lymphoma

MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic B-cell marginal zone lymphoma
- Hairy cell leukaemia
    - Splenic B-cell lymphoma/leukaemia, unclassifiable
    - Splenic diffuse red pulp small B-cell lymphoma
    - Hairy cell leukaemia-variant
- Lymphoplasmacytic lymphoma
- Waldenströmmacroglobulinemia
- Heavy chain diseases
    - Alpha heavy chain disease
    - Gamma heavy chain disease
    - Mu heavy chain disease

- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseousplasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
    - Paediatric nodal marginal zone lymphoma

- Follicular lymphoma
    - Paediatric follicular lymphoma

- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma

- Diffuse large B-cell lymphoma (DLBCL),NOS
    - T-cell/histiocyte rich large B-cell lymphoma
    - Primary DLBCL of the CNS
    - Primary cutaneous DLBCL, leg type
    - EBV positive DLBCL of the elderly
    - DLBCL associated with chronic inflammation
- Lymphomatoidgranulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8- associated multicentricCastleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

MATURE T-CELL AND NK-CELL NEOPLASMS

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK-cells
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative disease of childhood
- Hydroavacciniforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lympomatoidpapulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous CD4 positive small/medium T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative

HODGKIN LYMPHOMA

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
    - Nodular sclerosis classical Hodgkin lymphoma
    - Lymphocyte –rich classical Hodgkin lymphoma
    - Mixed cellularity classical Hodgkin lymphoma
    - Lymphocyte-depleted classical Hodgkin lymphoma

9.3 APPENDIX 3:

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131043

NAME: (Principal Investigator)	Dr Nasreen Alli
DEPARTMENT:	Department of Oral Pathology CM Johannesburg Academic Hospital
PROJECT TITLE:	Head and Neck Lymphomas: A 20 Year Retrospective Review of Cases Diagnosed in an Oral Pathology Unit, Johannesburg, South Africa
DATE CONSIDERED:	25/10/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof S Meer
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 07/02/2014

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 M131043Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

9.4 APPENDIX 4: Turnitin Report

turnitin Turnitin Originality Report
SMNasDraft42DEC2015forturnitin1.docx by Null Null

From Head and Neck Lymphomas: A 20 year Retrospective Review of Cases Diagnosed in an Oral Pathology Unit
(DQG777S1VT73YFL8sWnN42b0u524qhbznX9jotxSkoCF8FiWNi0FK9Dy9LN0n2yAhYnxx6U1ULdYCkMk689qXpro4pl93TWG8yK)

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2

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Pei Lin. "Hematopoietic Lesions", Diagnostic Surgical Pathology of the Head and Neck, 2009

3

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4

9.5 APPENDIX 5: Approval of title letter

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172040

Reference: Ms Mpumi Mnqapu
E-mail: mpumi.mnqapu@wits.ac.za

28 October 2013
Person No: 679925
PAG

Dr N Alli
24 Detroit Street
Havenside
Chatsworth
4092
South Africa

Dear Dr Alli

Master of Science in Dentistry: Approval of Title

We have pleasure in advising that your proposal entitled *Head and neck lymphomas: A 20 year retrospective review of cases diagnosed in an oral pathology unit, Johannesburg, South Africa* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

9.6 APPENDIX 6: Raw data

Year	Patient	Age	Gender	Subtype	HL/ NHL	N/ EN	Site	O/ EO
2012	1	12	M	NS CHL	HL	N	cervical LN	EO
2012	2	27	F	NLP HL	HL	N	cervical LN	EO
2012	3	34	M	DLBCL	NHL	EN	palate	O
2012	4	38	F	DLBCL	NHL	N	cervical LN	EO
2012	5	47	F	NS CHL	HL	N	cervical LN	EO
2012	6	32	F	PBL	NHL	EN	buccal mucosa	O
2012	7	32	F	PBL	NHL	EN	maxilla	O
2012	8	42	M	PBL	NHL	EN	Floor of mouth	O
2012	9	28	M	MC CHL	HL	N	cervical LN	EO
2012	10	44	M	DLBCL	NHL	EN	Salivary gland	EO
2012	11	47	F	NS CHL	HL	N	cervical LN	EO
2012	12	40	M	PBL	NHL	EN	buccal mucosa	O
2012	13	75	M	DLBCL	NHL	N	cervical LN	EO
2012	14	46	M	DLBCL	NHL	EN	WR	O
2012	15	38	F	PBL	NHL	EN	buccal mucosa	O
2012	16	59	F	Burkitt-like lymphoma	NHL	EN	orbit	EO
2012	17	30	M	DLBCL	NHL	EN	neck	EO
2012	18	40	F	DLBCL	NHL	EN	WR	O
2012	19	29	F	Peripheral T-cell lymphoma (NOS)	NHL	EN	neck	EO
2012	20	54	M	PBL	NHL	EN	lip	O
2012	21	27	F	NS CHL	HL	N	cervical LN	EO
2012	22	28	F	NS CHL	HL	N	cervical LN	EO
2012	23	43	M	DLBCL	NHL	EN	posterior nasal space	EO
2012	24	42	M	PBL	NHL	EN	mandible	O
2012	25	47	F	NS CHL	HL	N	cervical LN	EO
2012	26	41	M	NK/T-cell lymphoma (nasal type)	NHL	EN	nasal cavity	EO
2012	27	36	M	DLBCL	NHL	EN	gingiva	O
2012	28	46	M	PBL	NHL	EN	buccal mucosa	O
2012	29	38	F	DLBCL	NHL	N	max-facial LN	EO
2012	30	68	M	Plasma cell myeloma	NHL	EN	Paranasal sinuses	EO
2012	31	29	M	NLP HL	HL	N	cervical LN	EO
2012	32	36	M	DLBCL	NHL	EN	neck	EO
2012	33	41	M	PBL	NHL	EN	maxilla	O
2012	34	32	M	PBL	NHL	EN	nasal cavity	EO
2012	35	41	M	PBL	NHL	EN	maxilla	O
2012	36	36	M	FL	NHL	EN	WR	O
2012	37	25	F	NLP HL	HL	N	cervical LN	EO
2012	38	15	F	NS CHL	HL	N	cervical LN	EO
2012	39	48	M	PBL	NHL	EN	Buccal vestibule	O
2012	40	21	F	NS CHL	HL	N	cervical LN	EO
2012	41	37	M	Anaplastic large cell lymphoma	NHL	N	cervical LN	EO
2012	42	25	M	DLBCL	NHL	N	cervical LN	EO
2012	43	30	M	DLBCL	NHL	N	cervical LN	EO
2012	44	42	M	PBL	NHL	EN	Oral cavity (NOS)	O
2012	45	34	F	MC CHL	HL	EN	neck	EO
2012	46	22	F	PBL	NHL	EN	Pharynx	EO
2012	47	33	F	BL	NHL	EN	mandible	O
2012	48	41	M	PBL	NHL	EN	palate	O
2012	49	57	M	DLBCL	NHL	EN	WR	O
2012	50	45	F	PBL	NHL	EN	palate	O

2012	51	76	F	PBL	NHL	EN	Salivary gland	EO
2012	52	28	F	BL	NHL	EN	mandible	O
2012	53	51	F	NLP HL	HL	N	cervical LN	EO
2012	54	64	M	DLBCL	NHL	EN	WR	O
2012	55	37	M	PBL	NHL	EN	mandible	O
2012	56	52	M	DLBCL	NHL	EN	WR	O
2012	57	38	M	DLBCL	NHL	N	cervical LN	EO
2012	58	43	F	FL	NHL	N	max-facial LN	EO
2011	59	32	F	PBL	NHL	EN	maxilla	O
2011	60	39	F	MC CHL	HL	N	cervical LN	EO
2011	61	56	M	PBL	NHL	EN	maxilla	O
2011	62	38	M	PBL	NHL	EN	maxilla	O
2011	63	17	M	MC CHL	HL	N	cervical LN	EO
2011	64	51	M	DLBCL	NHL	N	cervical LN	EO
2011	65	27	F	PBL	NHL	EN	maxilla	O
2011	66	45	F	MC CHL	HL	N	cervical LN	O
2011	67	40	M	PBL	NHL	EN	palate	O
2011	68	40	M	PBL	NHL	EN	mandible	O
2011	69	38	F	PBL	NHL	EN	palate	O
2011	70	31	F	PBL	NHL	EN	Alveolus	O
2011	71	32	M	MC CHL	HL	N	cervical LN	EO
2011	72	29	M	NK/T-cell lymphoma (nasal type)	NHL	EN	Paranasal sinuses	EO
2011	73	62	M	SLL	NHL	N	cervical LN	EO
2011	74	18	M	NS CHL	HL	N	cervical LN	EO
2011	75	31	F	PBL	NHL	EN	palate	O
2011	76	33	F	NK/T-cell lymphoma (nasal type)	NHL	EN	maxilla	O
2011	77	14	F	NS CHL	HL	N	cervical LN	EO
2011	78	34	F	DLBCL	NHL	N	cervical LN	EO
2011	79	27	F	PBL	NHL	EN	palate	O
2011	80	18	M	NLP HL	HL	N	cervical LN	EO
2011	81	39	M	NS CHL	HL	N	cervical LN	EO
2011	82	40	F	PBL	NHL	N	max-facial LN	EO
2011	83	22	F	DLBCL	NHL	N	cervical LN	EO
2011	84	33	F	DLBCL	NHL	N	cervical LN	EO
2011	85	33	M	PBL	NHL	EN	posterior nasal space	EO
2011	86	42	F	DLBCL	NHL	N	max-facial LN	EO
2011	87	45	M	DLBCL	NHL	EN	buccal mucosa	O
2011	88	31	F	DLBCL	NHL	EN	WR	O
2011	89	67	M	Mantle cell lymphoma	NHL	N	cervical LN	EO
2011	90	29	M	DLBCL	NHL	EN	Jaw (NOS)	O
2011	91	40	F	DLBCL	NHL	N	cervical LN	EO
2011	92	32	M	NK/T-cel lymphoma (nasal type)	NHL	EN	palate	O
2011	93	59	M	PBL	NHL	EN	maxilla	O
2011	94	42	M	PBL	NHL	EN	palate	O
2011	95	40	M	DLBCL	NHL	EN	Paranasal sinuses	EO
2011	96	41	F	DLBCL	NHL	EN	Posterior nasal space	EO
2011	97	42	F	PBL	NHL	EN	maxilla	O
2011	98	57	M	DLBCL	NHL	EN	mandible	O
2011	99	30	M	NLP HL	HL	N	cervical LN	EO
2011	100	31	M	DLBCL	NHL	EN	nasal cavity	EO

2011	101	26	F	PBL	NHL	EN	maxilla	O
2011	102	92	M	DLBCL	NHL	EN	WR	O
2011	103	36	F	PBL	NHL	EN	maxilla	O
2011	104	77	F	SLL	NHL	N	max-facial LN	EO
2011	105	34	F	DLBCL	NHL	EN	WR	O
2011	106	38	M	DLBCL	NHL	EN	nasal cavity	EO
2011	107	37	M	PBL	NHL	EN	Floor of mouth	O
2011	108	41	M	PBL	NHL	EN	gingiva	O
2011	109	38	M	FL	NHL	N	cervical LN	EO
2011	110	40	M	PBL	NHL	EN	palate	O
2011	111	60	M	SLL	NHL	N	cervical LN	EO
2011	112	37	F	DLBCL	NHL	EN	Salivary gland	EO
2011	113	24	M	Anaplastic large cell lymphoma	NHL	N	cervical LN	EO
2011	114	28	M	PBL	NHL	EN	palate	O
2011	115	38	M	DLBCL	NHL	N	cervical LN	EO
2011	116	31	F	BL	NHL	N	cervical LN	EO
2011	117	31	F	BL	NHL	EN	Oral cavity (NOS)	O
2011	118	40	F	DLBCL	NHL	N	cervical LN	EO
2011	119	32	M	NS CHL	HL	N	cervical LN	EO
2011	120	61	F	NK/T-cell lymphoma (nasal type)	NHL	EN	nasal cavity	EO
2010	121	46	M	PBL	NHL	EN	maxilla	O
2010	122	50	F	DLBCL	NHL	N	cervical LN	EO
2010	123	42	M	Extraosseous plasmacytoma	NHL	EN	maxilla	O
2010	124	27	M	BL	NHL	N	cervical LN	EO
2010	125	24	M	DLBCL	NHL	N	cervical LN	EO
2010	126	16	F	Anaplastic large cell lymphoma	NHL	EN	neck	EO
2010	127	45	F	DLBCL	NHL	N	cervical LN	EO
2010	128	10	M	Anaplastic large cell lymphoma	NHL	N	cervical LN	EO
2010	129	36	M	MC CHL	HL	N	cervical LN	EO
2010	130	47	M	NS CHL	HL	N	cervical LN	EO
2010	131	49	M	DLBCL	NHL	EN	mandible	O
2010	132	27	F	DLBCL	NHL	N	cervical LN	EO
2010	133	12	F	PBL	NHL	N	cervical LN	EO
2010	134	43	M	PBL	NHL	EN	maxilla	O
2010	135	57	M	Mantle cell lymphoma	NHL	EN	buccal mucosa	O
2010	136	33	F	DLBCL	NHL	EN	WR	O
2010	137	31	M	DLBCL	NHL	N	cervical LN	EO
2010	138	56	F	DLBCL	NHL	EN	Tonsillar fossa area	O
2010	139	56	M	SLL	NHL	N	cervical LN	EO
2010	140	28	F	Peripheral T-cell lymphoma (NOS)	NHL	EN	Submental area	EO
2010	141	36	M	PBL	NHL	EN	maxilla	O
2010	142	35	M	DLBCL	NHL	N	max-facial LN	EO
2010	143	31	M	DLBCL	NHL	N	cervical LN	EO
2010	144	70	M	DLBCL	NHL	EN	WR	O
2010	145	46	M	Solitary plasmacytoma of bone	NHL	EN	maxilla	O
2010	146	56	M	DLBCL	NHL	EN	WR	O
2010	147	43	F	DLBCL	NHL	EN	Buccal vestibule	O
2010	148	37	M	Peripheral T-cell lymphoma (NOS)	NHL	EN	palate	O
2010	149	46	M	PBL	NHL	EN	buccal mucosa	O
2010	150	31	M	PBL	NHL	EN	Buccal vestibule	O

2010	151	48	M	DLBCL	NHL	EN	Buccal vestibule	O
2010	152	40	F	DLBCL	NHL	N	cervical LN	EO
2010	153	47	M	Plasma cell myeloma	NHL	EN	Scalp	EO
2010	154	84	F	DLBCL	NHL	N	max-facial LN	EO
2010	155	22	F	DLBCL	NHL	N	cervical LN	EO
2010	156	57	M	PBL	NHL	EN	nasal cavity	EO
2010	157	55	F	PBL	NHL	EN	mandible	O
2010	158	46	M	PBL	NHL	EN	nasal cavity	EO
2010	159	18	M	NLP HL	HL	N	max-facial LN	EO
2010	160	29	M	PBL	NHL	EN	mandible	O
2010	161	26	F	DLBCL	NHL	EN	gingiva	O
2010	162	42	F	DLBCL	NHL	EN	gingiva	O
2010	163	41	M	PBL	NHL	EN	Salivary gland	EO
2010	164	31	M	PBL	NHL	EN	mandible	O
2010	165	35	M	PBL	NHL	EN	mandible	O
2010	166	48	M	FL	NHL	N	cervical LN	EO
2010	167	9	F	DLBCL	NHL	N	cervical LN	EO
2010	168	26	M	PBL	NHL	EN	palate	O
2010	169	17	M	MC CHL	HL	N	cervical LN	EO
2010	170	26	F	BL	NHL	EN	buccal mucosa	O
2010	171	48	M	PBL	NHL	EN	gingiva	O
2010	172	36	F	DLBCL	NHL	EN	mandible	O
2010	173	50	M	DLBCL	NHL	N	max-facial LN	EO
2010	174	41	M	PBL	NHL	EN	maxilla	O
2010	175	65	M	Plasma cell myeloma	NHL	EN	nasal cavity	EO
2010	176	45	F	DLBCL	NHL	EN	Salivary gland	EO
2009	177	26	F	PBL	NHL	EN	gingiva	O
2009	178	46	F	DLBCL	NHL	EN	WR	O
2009	179	44	M	DLBCL	NHL	EN	Floor of mouth	O
2009	180	48	M	PBL	NHL	EN	maxilla	O
2009	181	30	M	DLBCL	NHL	EN	mandible	O
2009	182	28	F	PBL	NHL	EN	gingiva	O
2009	183	44	M	DLBCL	NHL	EN	Face	EO
2009	184	31	F	PBL	NHL	EN	Posterior nasal space	EO
2009	185	38	M	DLBCL	NHL	N	cervical LN	EO
2009	186	42	M	DLBCL	NHL	N	cervical LN	EO
2009	187	39	M	PBL	NHL	EN	mandible	O
2009	188	29	F	DLBCL	NHL	EN	palate	O
2009	189	33	F	PBL	NHL	EN	palate	O
2009	190	45	M	PBL	NHL	EN	maxilla	O
2009	191	43	F	DLBCL	NHL	N	cervical LN	EO
2009	192	30	F	PBL	NHL	EN	buccal mucosa	O
2009	193	46	F	DLBCL	NHL	EN	Buccal vestibule	O
2009	194	44	M	PBL	NHL	EN	gingiva	O
2009	195	37	F	DLBCL	NHL	N	cervical LN	EO
2009	196	29	M	DLBCL	NHL	EN	WR	O
2009	197	30	F	PBL	NHL	N	cervical LN	EO
2009	198	27	F	DLBCL	NHL	N	cervical LN	EO
2009	199	34	F	DLBCL	NHL	EN	nasal cavity	EO
2009	200	50	M	PBL	NHL	EN	buccal mucosa	O

2009	201	33	F	DLBCL	NHL	EN	neck	EO
2009	202	37	M	PBL	NHL	EN	gingiva	O
2009	203	45	M	DLBCL	NHL	EN	maxilla	O
2009	204	34	F	DLBCL	NHL	EN	WR	O
2009	205	44	M	DLBCL	NHL	EN	neck	EO
2009	206	43	F	PBL	NHL	EN	nasal cavity	EO
2009	207	45	F	DLBCL	NHL	EN	Posterior nasal space	EO
2009	208	59	F	Plasma cell myeloma	NHL	EN	maxilla	O
2009	209	56	F	DLBCL	NHL	EN	Larynx	EO
2009	210	39	F	PBL	NHL	EN	mandible	O
2009	211	50	M	DLBCL	NHL	N	cervical LN	EO
2009	212	57	M	DLBCL	NHL	N	cervical LN	EO
2009	213	30	F	DLBCL	NHL	EN	Oropharynx	O
2009	214	33	F	DLBCL	NHL	N	cervical LN	EO
2009	215	46	M	PBL	NHL	EN	gingiva	O
2009	216	36	M	PBL	NHL	EN	WR	O
2009	217	77	M	Plasma cell myeloma	NHL	EN	maxilla	O
2009	218	84	M	PBL	NHL	EN	nasal cavity	EO
2009	219	43	M	PBL	NHL	EN	gingiva	O
2009	220	48	F	Extraosseous plasmacytoma	NHL	EN	gingiva	O
2009	221	30	F	BL	NHL	EN	mandible	O
2009	222	41	M	Mantle cell lymphoma	NHL	EN	Posterior nasal space	EO
2009	223	88	F	Marginal zone lymphoma	NHL	N	cervical LN	EO
2009	224	31	F	NS CHL	HL	N	cervical LN	EO
2009	225	38	M	NS CHL	HL	N	cervical LN	EO
2009	226	6	M	BL	NHL	EN	Paranasal sinuses	EO
2009	227	33	F	NS CHL	HL	N	cervical LN	EO
2009	228	14	F	T-cell acute lymphoblastic lymphoma	NHL	N	cervical LN	EO
2009	229	4	M	Anaplastic large cell lymphoma	NHL	EN	Floor of mouth	O
2009	230	36	F	BL	NHL	EN	Posterior nasal space	EO
2009	231	11	M	Peripheral T-cell lymphoma (NOS)	NHL	EN	maxilla	O
2009	232	38	M	DLBCL	NHL	N	cervical LN	EO
2009	233	19	M	NLP HL	HL	N	max-facial LN	EO
2009	234	34	M	DLBCL	NHL	N	cervical LN	EO
2009	235	33	F	NS CHL	HL	N	cervical LN	EO
2009	236	34	F	Anaplastic large cell lymphoma	NHL	EN	maxilla	O
2009	237	42	M	Extraosseous plasmacytoma	NHL	EN	nasal cavity	EO
2009	238	60	M	MALT lymphoma	NHL	EN	buccal mucosa	O
2008	239	35	M	PBL	NHL	EN	mandible	O
2008	240	39	M	PBL	NHL	EN	buccal mucosa	O
2008	241	17	F	DLBCL	NHL	EN	Salivary gland	EO
2008	242	41	F	PBL	NHL	EN	palate	O
2008	243	51	M	PBL	NHL	EN	buccal mucosa	O
2008	244	53	F	Plasma cell myeloma	NHL	EN	mandible	O
2008	245	61	F	DLBCL	NHL	EN	neck	EO
2008	246	41	F	PBL	NHL	EN	palate	O
2008	247	35	M	PBL	NHL	EN	palate	O
2008	248	36	M	PBL	NHL	EN	gingiva	O
2008	249	51	M	PBL	NHL	EN	Oral cavity (NOS)	O
2008	250	58	M	PBL	NHL	EN	Face	EO
2008	251	33	F	DLBCL	NHL	EN	Salivary gland	EO

2008	252	37	F	DLBCL	NHL	EN	Submandibular area	EO
2008	253	38	M	PBL	NHL	EN	Posterior nasal space	EO
2008	254	44	M	PBL	NHL	EN	Posterior nasal space	EO
2008	255	43	F	DLBCL	NHL	EN	Pharynx	EO
2008	256	42	F	PBL	NHL	EN	buccal mucosa	O
2008	257	11	F	PBL	NHL	N	cervical LN	EO
2008	258	32	M	PBL	NHL	EN	maxilla	O
2008	259	42	M	PBL	NHL	EN	gingiva	O
2008	260	43	F	Atypical BL	NHL	EN	maxilla	O
2008	261	60	F	MALT lymphoma	NHL	EN	Salivary gland	EO
2008	262	52	F	Plasma cell myeloma	NHL	EN	maxilla	O
2008	263	41	M	NK/T-cell lymphoma (nasal type)	NHL	EN	Face	EO
2008	264	25	F	MC CHL	HL	EN	buccal mucosa	O
2008	265	41	F	NS CHL	HL	N	cervical LN	EO
2008	266	44	M	PBL	NHL	EN	gingiva	O
2008	267	50	F	Plasma cell myeloma	NHL	EN	mandible	O
2008	268	38	F	Plasma cell myeloma	NHL	EN	mandible	O
2008	269	24	F	SLL	NHL	EN	Parapharynx	EO
2008	270	55	F	Peripheral T-cell lymphoma (NOS)	NHL	EN	nasal cavity	EO
2008	271	60	M	PBL	NHL	EN	Larynx	EO
2008	272	44	F	Atypical BL	NHL	EN	buccal mucosa	O
2008	273	36	F	NK/T-cell lymphoma (nasal type)	NHL	EN	nasal cavity	EO
2008	274	19	M	Anaplastic large cell lymphoma	NHL	EN	buccal mucosa	O
2008	275	66	F	Plasma cell myeloma	NHL	EN	gingiva	O
2008	276	50	F	Peripheral T-cell lymphoma (NOS)	NHL	N	cervical LN	EO
2007	277	60	M	PBL	NHL	EN	Paranasal sinuses	EO
2007	278	45	F	DLBCL	NHL	N	max-facial LN	EO
2007	279	35	M	PBL	NHL	EN	gingiva	O
2007	280	50	M	PBL	NHL	EN	Floor of mouth	O
2007	281	32	M	DLBCL	NHL	EN	buccal mucosa	O
2007	282	40	F	DLBCL	NHL	N	cervical LN	EO
2007	283	54	M	PBL	NHL	EN	Buccal vestibule	O
2007	284	42	M	DLBCL	NHL	EN	Salivary gland	EO
2007	285	41	M	DLBCL	NHL	N	max-facial LN	EO
2007	286	20	M	PBL	NHL	EN	Paranasal sinuses	EO
2007	287	38	M	PBL	NHL	EN	gingiva	O
2007	288	63	F	DLBCL	NHL	EN	Tongue	O
2007	289	27	F	PBL	NHL	EN	mandible	O
2007	290	29	M	DLBCL	NHL	EN	gingiva	O
2007	291	46	F	DLBCL	NHL	N	max-facial LN	EO
2007	292	39	F	PBL	NHL	EN	Paranasal sinuses	EO
2007	293	23	F	DLBCL	NHL	EN	palate	O
2007	294	58	M	PBL	NHL	EN	palate	O
2007	295	38	M	PBL	NHL	EN	Paranasal sinuses	EO
2007	296	60	F	Plasma cell myeloma	NHL	EN	maxilla	O
2007	297	32	M	PBL	NHL	EN	maxilla	O
2007	298	39	M	PBL	NHL	EN	mandible	O
2007	299	37	M	PBL	NHL	EN	lip	O
2007	300	50	M	PBL	NHL	EN	gingiva	O
2007	301	16	M	NLP HL	HL	N	cervical LN	EO
2007	302	38	F	Atypical BL	NHL	EN	Submandibular area	EO
2007	303	74	F	DLBCL	NHL	EN	Salivary gland	EO

2007	304	36	M	NLP HL	HL	N	cervical LN	EO
2007	305	31	F	Peripheral T-cell lymphoma (NOS)	NHL	EN	maxilla	O
2007	306	32	M	NS CHL	HL	N	cervical LN	EO
2007	307	34	M	Peripheral T-cell lymphoma (NOS)	NHL	EN	palate	O
2007	308	66	F	FL	NHL	EN	WR	O
2006	309	47	M	PBL	NHL	EN	maxilla	O
2006	310	29	M	DLBCL	NHL	EN	palate	O
2006	311	34	M	PBL	NHL	EN	buccal mucosa	O
2006	312	31	M	PBL	NHL	EN	maxilla	O
2006	313	31	M	DLBCL	NHL	EN	maxilla	O
2006	314	30	F	DLBCL	NHL	EN	gingiva	O
2006	315	37	M	DLBCL	NHL	EN	gingiva	O
2006	316	28	M	PBL	NHL	EN	maxilla	O
2006	317	50	F	DLBCL	NHL	N	max-facial LN	EO
2006	318	37	F	DLBCL	NHL	EN	Salivary gland	EO
2006	319	31	M	DLBCL	NHL	EN	gingiva	O
2006	320	53	M	PBL	NHL	EN	maxilla	O
2006	321	28	F	DLBCL	NHL	EN	Jaw (NOS)	O
2006	322	39	F	PBL	NHL	EN	buccal mucosa	O
2006	323	42	F	PBL	NHL	EN	palate	O
2006	324	33	F	PBL	NHL	N	max-facial LN	EO
2006	325	52	M	PBL	NHL	EN	gingiva	O
2006	326	54	F	PBL	NHL	EN	mandible	O
2006	327	32	M	PBL	NHL	EN	buccal mucosa	O
2006	328	45	F	DLBCL	NHL	EN	mandible	O
2006	329	57	F	Extraosseous plasmacytoma	NHL	EN	nasal cavity	EO
2006	330	44	F	DLBCL	NHL	EN	palate	O
2006	331	29	F	MC CHL	HL	EN	palate	O
2006	332	55	M	Mantle cell lymphoma	NHL	N	cervical LN	EO
2006	333	33	M	Atypical BL	NHL	EN	buccal mucosa	O
2006	334	28	F	Atypical BL	NHL	EN	gingiva	O
2006	335	59	F	Atypical BL	NHL	N	max-facial LN	EO
2006	336	26	F	Burkitt-like lymphoma	NHL	EN	mandible	O
2006	337	42	F	Burkitt-like lymphoma	NHL	EN	Submandibular area	O
2006	338	54	M	FL	NHL	N	cervical LN	EO
2006	339	30	F	NS CHL	HL	N	cervical LN	EO
2006	340	47	M	PBL	NHL	EN	gingiva	O
2005	341	50	F	PBL	NHL	N	cervical LN	EO
2005	342	77	F	MALT lymphoma	NHL	EN	palate	O
2005	343	63	M	SLL	NHL	EN	Jaw (NOS)	O
2005	344	43	M	Peripheral T-cell lymphoma (NOS)	NHL	N	max-facial LN	EO
2005	345	65	F	Extraosseous plasmacytoma	NHL	EN	nasal cavity	EO
2005	346	43	F	Plasma cell myeloma	NHL	EN	Paranasal sinuses	EO
2005	347	37	M	PBL	NHL	EN	maxilla	O
2005	348	56	M	SLL	NHL	EN	Tongue	O
2005	349	31	F	DLBCL	NHL	EN	Oral cavity (NOS)	O
2005	350	42	F	NLP HL	HL	N	cervical LN	EO
2005	351	41	F	DLBCL	NHL	EN	maxilla	O
2005	352	34	F	PBL	NHL	EN	buccal mucosa	O
2005	353	40	M	DLBCL	NHL	EN	buccal mucosa	O
2005	354	28	M	PBL	NHL	EN	maxilla	O
2005	355	39	M	PBL	NHL	EN	palate	O

2005	356	53	F	PBL	NHL	EN	palate	O
2005	357	43	M	BL	NHL	EN	maxilla	O
2005	358	45	M	PBL	NHL	N	cervical LN	EO
2005	359	33	F	PBL	NHL	EN	palate	O
2005	360	82	M	FL	NHL	N	cervical LN	EO
2005	361	39	M	PBL	NHL	EN	maxilla	O
2005	362	48	F	DLBCL	NHL	EN	maxilla	O
2005	363	51	M	BL	NHL	EN	mandible	O
2005	364	32	F	PBL	NHL	EN	maxilla	O
2005	365	48	M	PBL	NHL	EN	maxilla	O
2004	366	34	M	PBL	NHL	EN	mandible	O
2004	367	64	M	Solitary plasmacytoma of bone	NHL	EN	mandible	O
2004	368	unknown	F	DLBCL	NHL	EN	mandible	O
2004	369	29	F	PBL	NHL	EN	palate	O
2004	370	80	M	SLL	NHL	EN	maxilla	O
2004	371	43	M	DLBCL	NHL	EN	Tongue	O
2004	372	42	F	Peripheral T-cell lymphoma (NOS)	NHL	EN	gingiva	O
2004	373	20	F	NS CHL	HL	N	max-facial LN	EO
2004	374	31	M	PBL	NHL	EN	gingiva	O
2004	375	54	F	FL	NHL	N	max-facial LN	EO
2004	376	45	F	DLBCL	NHL	EN	Salivary gland	EO
2004	377	74	M	DLBCL	NHL	EN	maxilla	O
2004	378	40	F	DLBCL	NHL	EN	palate	O
2004	379	31	F	Peripheral T-cell lymphoma (NOS)	NHL	EN	Oropharynx	O
2004	380	32	M	PBL	NHL	EN	palate	O
2004	381	23	M	PBL	NHL	EN	mandible	O
2004	382	59	M	DLBCL	NHL	EN	buccal mucosa	O
2004	383	68	F	FL	NHL	N	cervical LN	EO
2004	384	52	F	DLBCL	NHL	EN	palate	O
2004	385	26	F	PBL	NHL	EN	maxilla	O
2004	386	44	F	B-cell NHL (NOS)	NHL	EN	Floor of mouth	O
2004	387	52	M	PBL	NHL	EN	buccal mucosa	O
2004	388	28	F	MC CHL	HL	N	cervical LN	EO
2004	389	65	F	DLBCL	NHL	EN	Oropharynx	O
2004	390	84	F	SLL	NHL	N	cervical LN	EO
2004	391	31	M	T-cell rich B-cell Lymphoma	NHL	EN	Salivary gland	EO
2004	392	51	M	Plasma cell myeloma	NHL	EN	maxilla	O
2004	393	44	F	PBL	NHL	EN	palate	O
2004	394	30	M	Burkitt-like lymphoma	NHL	N	cervical LN	EO
2003	395	44	M	DLBCL	NHL	EN	Tongue	O
2003	396	34	M	NLP HL	HL	N	cervical LN	EO
2003	397	40	M	PBL	NHL	EN	Submandibular area	EO
2003	398	62	M	DLBCL	NHL	EN	Salivary gland	EO
2003	399	21	M	NLP HL	HL	N	max-facial LN	EO
2003	400	50	M	DLBCL	NHL	EN	Submandibular area	EO
2003	401	36	M	PBL	NHL	EN	buccal mucosa	O
2003	402	34	F	DLBCL	NHL	N	cervical LN	EO
2003	403	34	M	PBL	NHL	EN	gingiva	O
2003	404	61	F	SLL	NHL	EN	Tongue	O
2003	405	29	F	DLBCL	NHL	EN	gingiva	O
2003	406	35	F	PBL	NHL	EN	palate	O

2003	407	52	F	Peripheral T-cell lymphoma (NOS)	NHL	N	cervical LN	EO
2003	408	28	M	Acute undifferentiated leukemia	NHL	EN	Paranasal sinuses	EO
2003	409	78	F	MALT lymphoma	NHL	EN	mandible	O
2003	410	20	F	PBL	NHL	EN	gingiva	O
2003	411	34	F	DLBCL	NHL	EN	gingiva	O
2003	412	32	F	PBL	NHL	EN	maxilla	O
2003	413	unknown	M	NLP HL	HL	N	cervical LN	EO
2003	414	32	M	PBL	NHL	EN	buccal mucosa	O
2003	415	41	M	PBL	NHL	EN	palate	O
2003	416	61	F	MALT lymphoma	NHL	EN	Salivary gland	EO
2003	417	47	M	PBL	NHL	EN	mandible	O
2003	418	39	M	PBL	NHL	EN	maxilla	O
2003	419	41	M	PBL	NHL	EN	Oral cavity (NOS)	O
2003	420	43	M	NK/T-cell lymphoma	NHL	EN	palate	O
2003	421	unknown	M	BL	NHL	EN	mandible	O
2003	422	48	F	DLBCL	NHL	N	cervical LN	EO
2003	423	34	M	PBL	NHL	EN	gingiva	O
2003	424	3	M	BL	NHL	EN	mandible	O
2002	425	37	M	NK/T-cell lymphoma	NHL	EN	Paranasal sinuses	EO
2002	426	33	F	B-cell NHL (NOS)	NHL	EN	mandible	O
2002	427	26	M	Acute undifferentiated leukemia	NHL	EN	buccal mucosa	O
2002	428	32	M	PBL	NHL	EN	palate	O
2002	429	46	M	MALT lymphoma	NHL	EN	palate	O
2002	430	27	F	PBL	NHL	EN	gingiva	O
2002	431	52	M	DLBCL	NHL	N	cervical LN	EO
2002	432	26	F	PBL	NHL	EN	Oral cavity (NOS)	O
2002	433	40	M	DLBCL	NHL	N	max-facial LN	EO
2002	434	unknown	F	DLBCL	NHL	N	cervical LN	EO
2002	435	31	F	PBL	NHL	EN	gingiva	O
2002	436	50	F	PBL	NHL	EN	Oral cavity (NOS)	O
2002	437	33	M	DLBCL	NHL	N	cervical LN	EO
2002	438	44	F	PBL	NHL	EN	Tongue	O
2002	439	10	M	BL	NHL	EN	mandible	O
2002	440	71	M	DLBCL	NHL	EN	palate	O
2002	441	50	F	DLBCL	NHL	N	cervical LN	EO
2002	442	50	F	DLBCL	NHL	EN	Submandibular area	O
2002	443	50	M	DLBCL	NHL	EN	gingiva	O
2001	444	32	M	PBL	NHL	EN	Jaw (NOS)	O
2001	445	58	F	MALT lymphoma	NHL	EN	Salivary gland	EO
2001	446	72	F	MALT lymphoma	NHL	EN	palate	O
2001	447	50	M	DLBCL	NHL	EN	maxilla	O
2001	448	26	M	PBL	NHL	EN	Face	EO
2001	449	52	F	Extraosseous plasmacytoma	NHL	EN	Retromolar mucosa	O
2001	450	10	M	BL	NHL	EN	Jaw (NOS)	O
2001	451	47	F	MC CHL	HL	N	cervical LN	EO
2001	452	50	F	Solitary plasmacytoma of bone	NHL	EN	maxilla	O
2001	453	2	M	BL	NHL	EN	mandible	O
2001	454	3	Unknown	DLBCL	NHL	EN	Salivary gland	EO
2001	455	34	M	Solitary plasmacytoma of bone	NHL	EN	palate	O
2001	456	82	M	DLBCL	NHL	N	cervical LN	EO
2001	457	31	F	DLBCL	NHL	N	cervical LN	EO
2001	458	32	F	DLBCL	NHL	EN	palate	O

2001	459	unknown	F	DLBCL	NHL	EN	gingiva	O
2001	460	60	M	Anaplastic large cell lymphoma	NHL	EN	buccal mucosa	O
2001	461	34	F	Burkitt-like lymphoma	NHL	EN	buccal mucosa	O
2001	462	38	F	PBL	NHL	EN	palate	O
2001	463	47	M	Anaplastic large cell lymphoma	NHL	EN	gingiva	O
2001	464	70	F	MALT lymphoma	NHL	EN	Salivary gland	EO
2000	465	36	F	PBL	NHL	EN	mandible	O
2000	466	26	M	Plasma cell myeloma	NHL	EN	palate	O
2000	467	13	M	BL	NHL	EN	maxilla	O
2000	468	69	F	Solitary plasmacytoma of bone	NHL	EN	mandible	O
2000	469	36	F	PBL	NHL	EN	Tongue	O
2000	470	26	M	DLBCL	NHL	N	cervical LN	EO
2000	471	62	M	DLBCL	NHL	EN	gingiva	O
2000	472	73	F	Mantle cell lymphoma	NHL	EN	lip	O
2000	473	72	F	DLBCL	NHL	N	cervical LN	EO
2000	474	6	F	BL	NHL	EN	Jaw (NOS)	O
2000	475	63	F	DLBCL	NHL	EN	Posterior nasal space	EO
2000	476	34	M	DLBCL	NHL	EN	palate	O
2000	477	5	F	Burkitt-like lymphoma	NHL	EN	Paranasal sinuses	EO
1999	478	22	M	DLBCL	NHL	EN	Jaw (NOS)	O
1999	479	57	M	Extraosseous plasmacytoma	NHL	EN	gingiva	O
1999	480	40	M	DLBCL	NHL	N	max-facial LN	EO
1999	481	16	F	NK/T-cell lymphoma	NHL	EN	maxilla	O
1999	482	32	M	PBL	NHL	EN	mandible	O
1999	483	28	M	DLBCL	NHL	EN	buccal mucosa	O
1999	484	85	F	SLL	NHL	N	cervical LN	EO
1999	485	39	F	DLBCL	NHL	EN	mandible	O
1998	486	21	F	BL	NHL	EN	maxilla	O
1998	487	5	F	BL	NHL	EN	maxilla	O
1997	488	54	M	FL	NHL	N	cervical LN	EO
1997	489	12	F	Solitary plasmacytoma of bone	NHL	EN	palate	O
1997	490	42	F	NLP HL	HL	N	cervical LN	EO
1996	491	58	F	MC CHL	HL	N	cervical LN	EO
1996	492	69	F	T-cell lymphoma (NOS)	NHL	EN	maxilla	O
1996	493	28	M	BL	NHL	EN	maxilla	O
1995	494	25	M	DLBCL	NHL	EN	neck	EO
1995	495	51	M	Plasma cell myeloma	NHL	EN	buccal mucosa	O
1994	496	91	M	DLBCL	NHL	EN	maxilla	O
1994	497	unknown	M	Anaplastic large cell lymphoma	NHL	EN	gingiva	O
1994	498	14	F	NLP HL	HL	N	cervical LN	EO
1993	499	23	F	DLBCL	NHL	N	cervical LN	EO
1993	500	44	M	MC CHL	HL	N	cervical LN	EO
1993	501	12	F	Lymphoblastic lymphoma (NOS)	NHL	EN	palate	O
1993	502	11	M	BL	NHL	EN	mandible	O
1993	503	69	F	DLBCL	NHL	EN	palate	O
1993	504	100	F	Solitary plasmacytoma of bone	NHL	EN	maxilla	O