

**Incidence, Trends of Prevalence and Pathological Spectrum
of Head and Neck Lymphomas at National Health
Laboratory Service-Tygerberg**



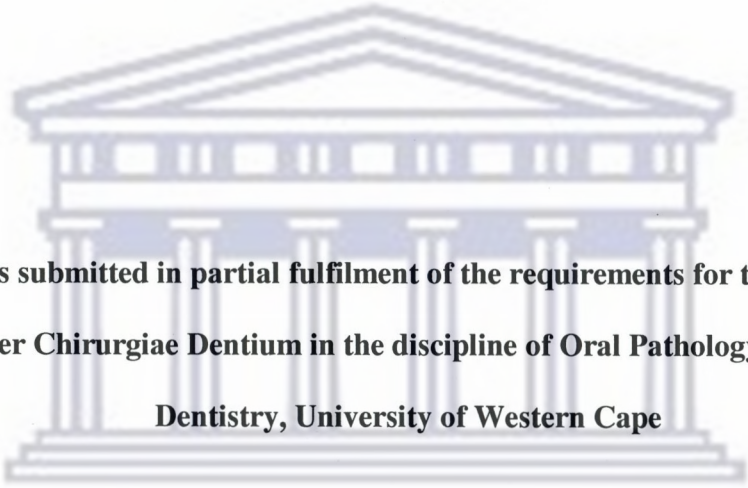
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**Incidence, Trends of Prevalence and Pathological Spectrum of Head
and Neck Lymphomas at National Health Laboratory Services-
Tygerberg**

MANOGARI CHETTY

The logo of the University of the Western Cape, featuring a classical building with a pediment and columns.

**A thesis submitted in partial fulfilment of the requirements for the degree of
Magister Chirurgiae Dentium in the discipline of Oral Pathology, Faculty of
Dentistry, University of Western Cape**

**UNIVERSITY of the
WESTERN CAPE**

Supervisor: Prof JJ Hille

External supervisor: Prof J Bezuidenhout

**Incidence, Trends of Prevalence and Pathological Spectrum of Head
and Neck Lymphomas at National Health Laboratory Services-
Tygerberg**

Manogari Chetty

Keywords

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Head and neck

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NHLS-Tygerberg

Western Cape

Referral centres

Age

Sex

Acquired immunodeficiency syndrome

Human immunodeficiency virus



Abstract

Incidence, Trends of Prevalence and Pathological Spectrum of Head and Neck Lymphomas at National Health Laboratory Services-Tygerberg

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MChD (Oral Pathology) minithesis, Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of Western Cape

Among malignant lesions, lymphoma ranks second only to squamous cell carcinoma in frequency of occurrence in the head and neck. Lymphomas in HIV patients' are second in frequency to Kaposi's sarcoma as AIDS-defining tumours. About 50% of lymphomas in HIV patients are extranodal and more than half of these occur in the head and neck area.

The number, variety and diagnostic complexity of lymphoma cases that have primarily arisen in the head and neck region has steadily increased in the surgical pathology service of the National Health Laboratory Services (NHLS) – Tygerberg. This observation is particularly relevant in the context of increasing HIV infection rates in the population of South Africa as demonstrated by a study in 2006 conducted by the Medical Research Council of South Africa.

This is a retrospective study using the records of cases of head and neck lymphomas diagnosed at NHLS-Tygerberg over the last five years. The aim of this study is to investigate the prevalence of head and neck lymphomas (HNL) at NHLS-Tygerberg from January 2002 to December 2006. The objective of this study is to determine the frequency and types of HNL and to determine, if possible, an association between the incidence of HNL and the HIV status of the patients. Trends of prevalence in terms of

gender, referral centres, HIV status, age of patients and site of presentation are also examined.

The results of this study show an increase in the number of patients with HNL from January 2002 to December 2006. A significant increase is noted in the number of HIV positive patients documented each year, from 17% in 2002 to 33% in 2006. Western Cape- urban (WC-U) remains the largest referral center. A notable increase is seen, each year, in the number of patients referred to Tygerberg-NHLS from the Eastern Cape (EC) and Western Cape- rural (WC-R) areas. A significant number of HIV positive patients are referred from the Eastern Cape and Western Cape rural areas. The average age of disease presentation in the HIV positive group of patients is 35 years with the unknown group being 46 years and the HIV negative group being 54 years.

The main categories of lymphoma that presented in HIV positive patients are plasmablastic lymphoma (PBL) and diffuse large B-cell lymphoma (DLBCL), which together form 56% of cases. 26% of cases are Hodgkin's lymphoma (HL); the second largest group of HNL cases. Burkitt's lymphoma (BL) consists of 8% of cases. 7% of cases are T-cell lymphomas. 3% of cases are Mantle zone lymphomas. No cases of SLL and Follicular lymphomas (FL) are described in this group of patients.

DLBCL and HL form 27% each of the cases in patients with a negative HIV status. A significant number of Follicular lymphomas (15%), small lymphocytic lymphoma (SLL) (9%), MALT (7%), and T-cell lymphomas (8%) are identified. No PBL are seen in this group of patients.

The incidence of HNL at NHLS-Tygerberg has increased over the last five years. This trend parallels that seen in other developing countries such as Tanzania, Nigeria, Thailand and India. This increase is possibly due to an increase in the number of referrals to our center, an increase in the overall population of the Western Cape, an

increase in the number of HIV positive patients and the high incidence of EBV infection in the general population of the Western Cape.

Social issues, such as poverty, lack of adequate education, female dependence on partners, rural communities and the non-availability of anti-retroviral drugs (ARV) and highly active anti-retroviral therapy (HAART) to most of the population that require these drugs, are considered major contributing factors.

A trend is noted in the increased number of female patients diagnosed each year with HNL. A predominance of DLBCL was identified in our series. This is consistent with previous reports and studies on HNL. The number of biologically aggressive lymphomas, such as DLBCL, Plasmablastic and Burkitt's lymphomas diagnosed each year, has also significantly increased. These were prevalent mainly in the HIV positive group of patients who were also younger compared to the HIV negative patients.

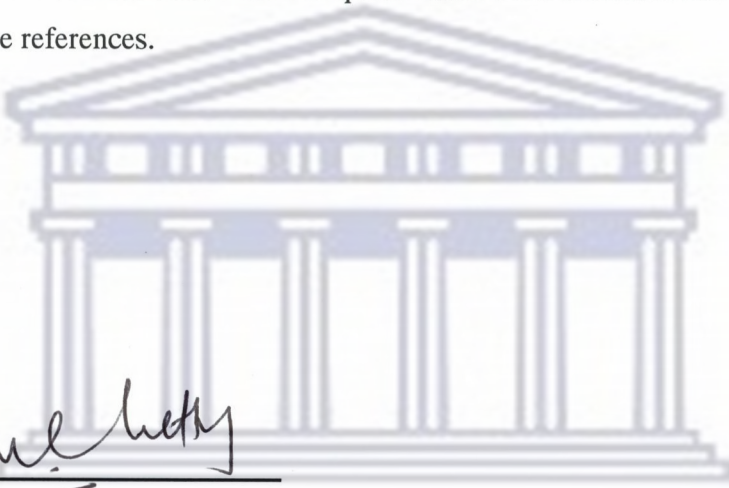
The documented findings of this study will serve as a guideline for the estimation of head & neck lymphoma burden and risk assessment at NHLS- Tygerberg.

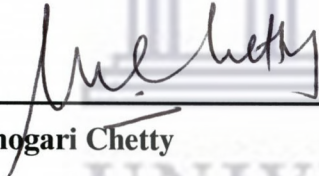
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12 November 2007

Declaration

I, Manogari Chetty, hereby declare that the contents of this mini-thesis titled, *Incidence, Trends of Prevalence and Pathological Spectrum of Head and Neck Lymphomas at National Health Laboratory Services-Tygerberg*, is my own original work, that it has not been submitted for any degree or examination at any university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.





Manogari Chetty

Date: 20 / 08 / 08

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Introduction

Among malignant lesions, lymphoma ranks second only to squamous cell carcinoma in frequency of occurrence in the head and neck.

They may involve nodal and extranodal sites. Hodgkin's lymphoma (HL) often presents as nodal disease, with a predilection for cervical and mediastinal nodes. Frequent involvements of the submental and submandibular nodes are also noted^{1,2,3}.

Non-Hodgkin's lymphoma (NHL) presents up to 40% of the time at an extranodal site. Moreover, 2% to 3% of these extranodal cases may arise primarily in the oral cavity and jaws where they clinically present as a mass that may or may not show ulceration. The lesions are initially symptom free, but may occasionally be painful, and the patients rarely present with fever or weight loss, hence, clinicians frequently miss oral lymphomas. Primary lymphoma in the jaw is a disease that presents with a non-specific radiological appearance, which may mimic osteomyelitis or periodontal pathology⁴. Oral lymphoma often is a component of a disseminated disease process that may involve regional nodes as well. Other times, it may represent a primary extranodal disease confined to the oral cavity or jaws^{3,5}.

Despite the high prevalence of infection by the Human Immunodeficiency Virus (HIV) in South Africa, information on its association with lymphoma is sparse. The number, variety and diagnostic complexity of lymphoma cases that have primarily arisen in the head and neck region has been observed to be steadily increasing in the surgical pathology service at the National Health Laboratory Services (NHLS) – Tygerberg. This observation is particularly relevant in the context of increasing HIV infection rates in the population of the South Africa as demonstrated by a study in 2006 conducted by the Medical Research Council of South Africa⁶.

Lymphomas in HIV patients' are second in frequency to Kaposi's sarcoma as AIDS-defining tumors⁷. About 50% of lymphomas in HIV patients are extranodal and more than half of these occur in the head and neck area. Although HIV-associated lymphomas display a marked propensity to involve extranodal sites such a GIT, CNS and liver, unusual sites such as the oral cavity and jaw are often involved. There is now increased reporting of lymphomas in the orbit, oropharynx, mandible and salivary glands^{2,8}.

Studies have concluded that a high level of suspicion for lymphoma is required in all cases of head and neck lesions in patients with HIV infection to facilitate management as well as avoid risky clinical compromises. Several authors have also observed that oral presentation of NHL may in fact be the first sign of HIV syndrome^{9,10}. Burkitt's lymphoma in the head and neck area, especially the jaws, may be the first manifestation of AIDS in a substantial number of patients, since it can develop in the presence of relatively sustained peripheral counts of CD4 positive cells¹¹.

No data exists on the prevalence of head and neck lymphomas (HNL) in patients from the Western Cape. This is a retrospective study.

The aim of this study is, therefore, to investigate a possible increase in the frequency of HNL and to document the pathological spectrum of HNL at NHLS- Tygerberg for the five-year period, January 2002 to December 2006. We examine trends in as many contexts as the data will support, such as, gender, referral centres, HIV status, age of patients and the site of presentation. We attempt to determine an association between the prevalence of HNL and the HIV status of the investigated patients.

We hypothesize an increase in the number of HNL in head and neck pathology specimens due to HIV infection.

The documented findings of this study will serve as a guideline for the estimation of head & neck lymphoma burden and risk assessment at Tygerberg. This study will

hopefully raise the clinicians' level of awareness, enhance diagnostic accuracy and ultimately improve patient management.



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CHAPTER 1

Literature Review

In developed countries, malignant lymphomas, represent approximately 5% of malignant neoplasms and involves nodal or extranodal sites with the head and neck region being second most frequently involved². In developing countries, the incidence of lymphomas is said to be higher, but exact figures could not be accessed in the literature search.

Lymphomas affect patients over a wide age range, but most patients are in the 6th and 7th decade. Patients with underlying immunodeficiency states, e.g. HIV infection, are also usually younger. Burkitt's lymphoma occurs predominantly in children and young adults. The incidence of lymphoma in children is increasing in the USA and is the third most common childhood cancer, with the frequency in the head and neck being second only to the abdomen¹².

Unusual clinical presentations of HNL have also been described, such as cystic salivary gland masses, diffuse swelling of the parotid gland, in conditions of Sjogren's syndrome, as submandibular masses, and as unexpected findings in patients presenting with squamous cell carcinoma which may significantly complicate post operative management^{13, 14, 15}.

Frequently oral lymphoid neoplasms masquerade as reactive lesions, gingivitis and periodontitis. Several high-grade lymphomas e.g. plasmablastic lymphomas, diffuse large B-cell lymphomas often mimic advanced periodontal disease i.e. their main oral symptoms are pain, swelling, numbness and tooth mobility. Other reported cases are that of mandibular fractures that initially mimicked osteomyelitis. Many also present

as soft tissue masses with or without ulceration involving mainly the palate, gingiva and alveolar mucosa^{7, 10, 16}.

A study that described the geographical distribution of Kaposi's sarcomas and lymphomas in Africa before the AIDS epidemic, reported that the rates of Burkitt's lymphoma were three to four times the rates for leukaemia in children in the Western populations. The general incidence of NHL was no higher than in the West and very low rates were indicated for much of southern Africa¹¹.

Soon after the start of the AIDS epidemic in the early 1980s, AIDS and cancer became the focus of many epidemiological, molecular biological and virological studies, leading to some important discoveries. The natural history of cancers in patients with HIV infection differs from those without. Unusual aspects of tumour location, growth behaviour and therapeutic response distinguish tumours in patients with HIV¹.

Recent findings, suggest that it is readily apparent that, at the end of the second decade of the AIDS epidemic in developing countries, NHL is increasing in incidence and the natural history of Burkitt's lymphoma is evolving. It was noted that since 1990, there is almost a doubling of the NHL incidence with increases in high grade NHL and extranodal disease. A causal link between infectious agents, immunosuppression and lymphomagenesis has been determined¹⁷.

Sub-Saharan Africa is considered home to more than 60% of all human immunodeficiency virus (HIV) infected cases. The pandemic is fuelled by endemic poverty, malnutrition, gender inequality and sexual and cultural practices. It is stated, that this region has contributed to more than 90% of childhood deaths related to HIV infection and about 93% of childhood acquired immunodeficiency syndrome (AIDS)-related deaths. Although no country in Africa is spared the infection, the bulk of the

disease is seen in East and Southern Africa, with the highest recorded rates of 20% to 50% in Zimbabwe^{18, 19, 20}.

Although infections, especially tuberculosis, have emerged as the most important HIV/AIDS-associated killers in recent times, AIDS-associated malignancies are increasingly identified in the later stages of the disease.

As a result of incomplete data from African countries, it is unclear whether the epidemiology and risks of these cancers are the same as observed in the developed countries²⁰.

A case-control study of 913 black cancer patients from Johannesburg and Soweto, South Africa, aged 15 – 50 years, was undertaken to measure the association between human immunodeficiency virus (HIV) infection and cancers believed to have an infective etiology. This study showed a strong association between HIV infection and Kaposi's sarcoma and an elevated association with non-Hodgkin's lymphoma (NHL). According to this study, no other cancers, including cervical and liver cancers, showed significantly elevated odds ratios associated with HIV infection²¹.

Further studies in South Africa, in 2000, also showed significantly increased risks of Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and cancers of the cervix and vulva. It is suggested that under-ascertainment and earlier death from AIDS related illnesses, may explain the relative lack of documentation of HIV-associated lymphomas in South Africa²².

Lymphomas that develop in HIV-positive patients are predominantly aggressive B-cell lymphomas. In a proportion of cases, they are considered AIDS- defining conditions and are the initial manifestation of AIDS. The most common HIV-associated lymphomas include: Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma (PEL), and plasmablastic lymphoma (PL). Hodgkin lymphoma is also increased in the setting of HIV. The WHO divides the HIV-associated lymphomas into three categories; lymphomas

occurring in immunocompetent patients, lymphomas occurring more specifically in HIV positive patients and lymphomas occurring in other immunodeficiency states²³.

Accumulating data suggests that HIV-infected patients are at an increased risk for developing Hodgkin's lymphoma. Hodgkin's lymphoma is now the most common non AIDS-defining malignant disease in HIV and is also increasing in incidence^{23,24,25}.

It is apparent that as the AIDS pandemic proceeds, the burden of neoplastic disease is increasing in developing nations. The introduction of highly active antiretroviral therapy (HAART) has decreased the incidence of AIDS-associated lymphomas in Western countries²⁵, but less than 1% of AIDS patients are receiving HAART in the HIV epicentre of sub-Saharan Africa²⁶. Current therapeutic approaches are not well documented. Pragmatic prevention and therapeutic interventions suitable for the resource-constrained setting are clearly needed and with further therapeutic advances that extend survival of HIV infected individuals by reconstitution of immune competence, may lead to additional alterations in cancer risk^{26,27}.

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CHAPTER 2

Research Design and Methodology

2.1 Aim

The aim of this study is to investigate the frequency of head and neck lymphomas (HNL) at the National Health Laboratory Services – Tygerberg over the last five years.

2.2 Objectives

1. To identify and establish the frequency of HNL diagnosed in the last 5 years from January 2002 up to and including December 2006
2. To examine trends of prevalence in terms of gender, referral centre, HIV status, age of patients and site of presentation.
3. To document the histological types of HNL that have presented.
4. To determine, if possible, an association between the incidence of HNL and the HIV status of the investigated patients.

2.3 Hypothesis

There is an increase in the frequency of HNL in head and neck pathology specimens due to HIV infection.

2.4 Design

This is a retrospective study using records of cases of head and neck lymphomas diagnosed at Tygerberg hospital over the last five years.

2.5 Method

All records of biopsies of head and neck specimens submitted for histopathological and cytopathological diagnoses to the Department of Anatomical Pathology, from the

last 5 years, were reviewed. All head and neck specimens were analysed, with central nervous system and thyroid lesions excluded.

Two hundred and fifty nine head and neck lymphoma (HNL) cases were accessioned and assessed. Patient data, including age, sex, HIV status, referral centre, site and histological type of lymphoma according to the WHO classification, was recorded. In cases where the HIV status of the patient could not be elicited, the status was designated as 'unknown' (UNK).

2.5 Data Capture

For each year data was recorded on an excel spreadsheet and included:

- Year of diagnosis
- Case number e.g. 1, 2, 3 etc.
- Demographic data - Referral centre:
 - Private (P)
 - Eastern Cape (EC)
 - Western Cape rural areas (WC-R) included:
 - Eben Donges
 - Paarl
 - Hottentots Holland Hospital
 - Western Cape urban areas (WC-U) included:
 - Tygerberg hospital
 - Karl Bremmer hospital
- Age of patient
- Gender
 - Male (M)
 - Female (F)
- HIV status of the patient

- Positive (pos)
 - Negative (neg)
 - Unknown (unk)
- Lymphoma type (WHO classification 2001): Diagnoses
- Plasmablastic lymphoma (PBL)
 - Burkitt's lymphoma (BL)
 - Diffuse large B-cell lymphoma (DLBCL)
 - Diffuse large B-cell lymphoma of follicular origin (DLBCL-F)
 - Follicular lymphoma (FL)
 - Small lymphocytic lymphoma (SLL)
 - Mantle cell/zone lymphoma (MZ)
 - Mucosa associated lymphomas (MALT)
 - Hodgkin lymphoma (HL)
 - Hodgkin lymphoma- nodular sclerosis (HL-NS)
 - Hodgkin lymphoma- mixed cellularity (HL-MC)
 - Hodgkin lymphoma- lymphocyte depleted (HL-LD)
 - Hodgkin lymphoma- lymphocyte rich (HL-LP)
 - T-cell lymphomas (T-CELL)
 - T-cell lymphomas - Anaplastic large cell (ANAP)
 - T-cell lymphomas - peripheral (T-PER)
 - T-cell lymphomas - cutaneous (T-CUT)
- Site of biopsy:
- Oral cavity, pharynx and tonsil (OC)
 - Nasal and paranasal sinuses (N)
 - Cervical lymph nodes which included submandibular, sublingual and preauricular nodes (CN)
 - Skin from the head and neck area (SKIN)

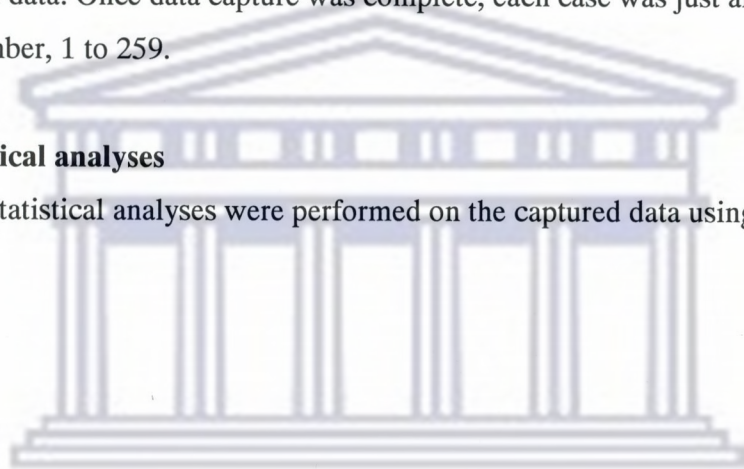
- Nodal or extranodal presentation
 - Nodal (N)
 - Extranodal (EN)

2.6 Ethics Statement

All patient related data was treated as strictly confidential and kept in a secure place. No patient file numbers or names were used; only case numbers were used to access and record data. Once data capture was complete, each case was just allocated a single number, 1 to 259.

2.7 Statistical analyses

Relevant statistical analyses were performed on the captured data using the Statistica program.



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CHAPTER 3

Results

Patient data was analysed using the Statistica programme. Trends in as many contexts as the data would support were assessed.

3.1 Number of HNL per year

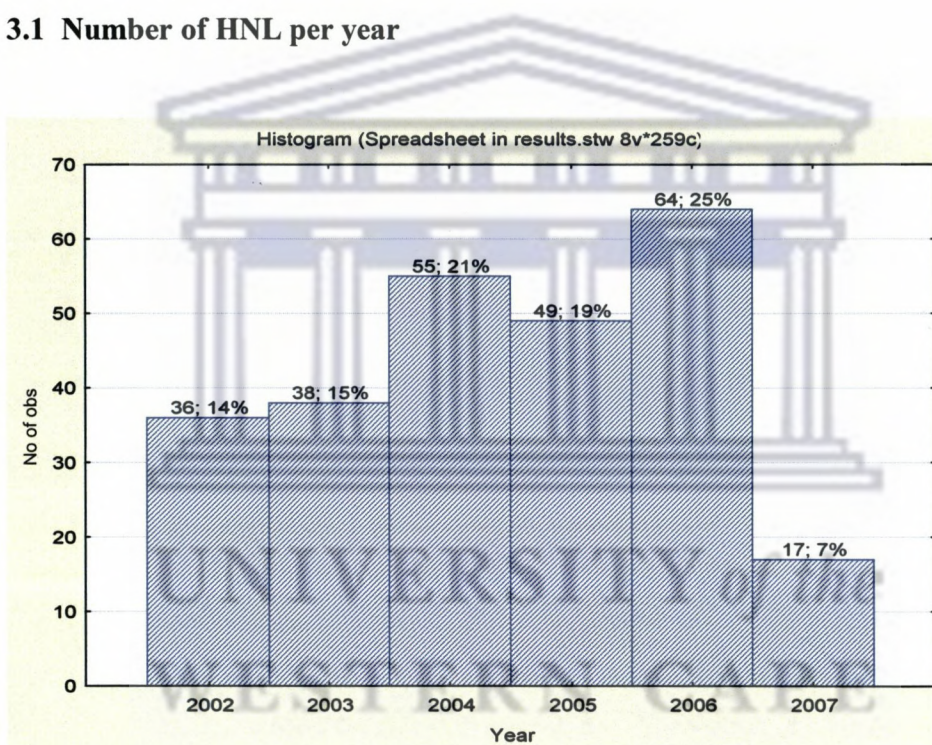


Fig. 1: Documented number of HNL cases per year.

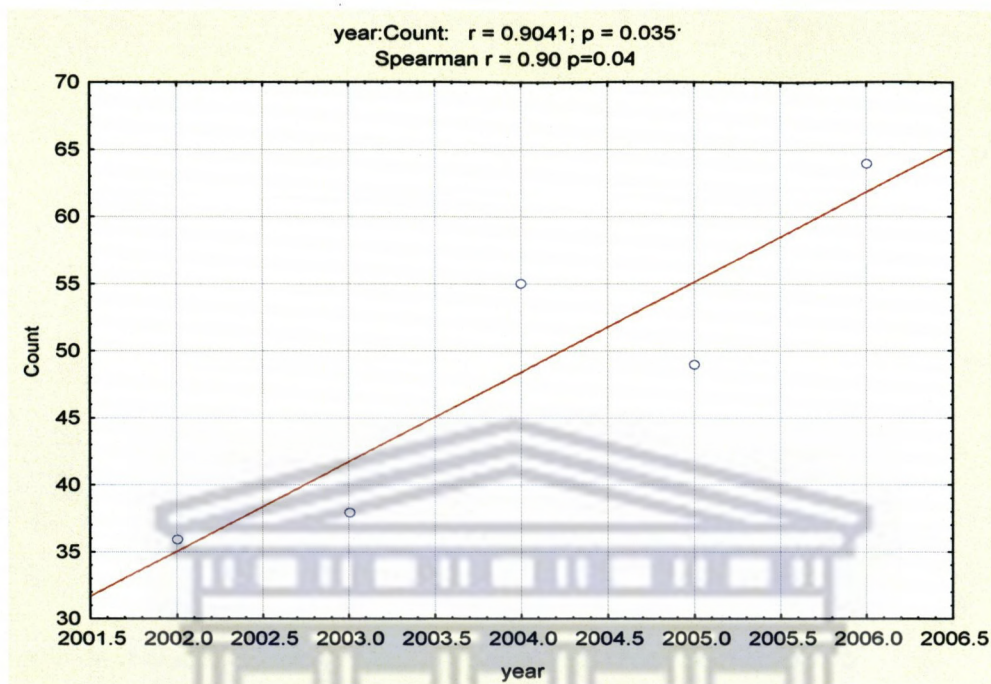


Fig. 2: Graph showing number of cases of HNL per year

A statistically significant increase is noted each year, in the number of patients diagnosed with HNL from January 2002 to December 2006. Cases from 2007, i.e. up to and including April 2007 are also recorded in Fig. 1; representing 7% of the total number of cases.

3.2 HIV status of patients

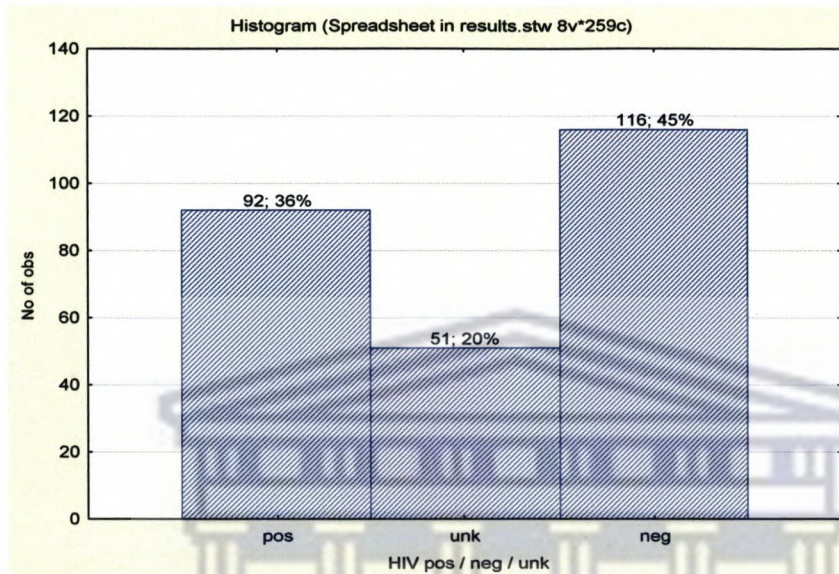


Fig. 3: HIV status of the patients recorded as the number of positive (pos), negative (neg) and unknown (unk) cases

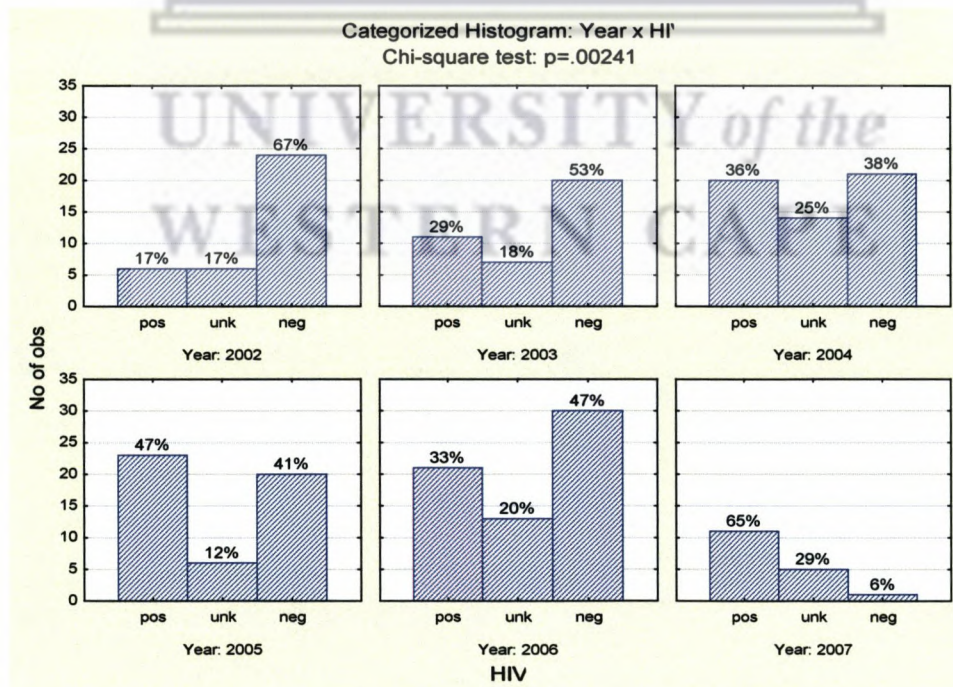


Fig. 4: Categorized record of HIV status of patients for each year

A significant increase is noted in the number of HIV positive patients documented each year from 17% in 2002 to 33% in 2006. A trend is also noted in terms of an increase in the number of cases of patients with an unknown HIV status. A significant decrease in the number of HIV negative cases is noted from 67% in 2002 to 47% in 2006.

3.3 Referral centers

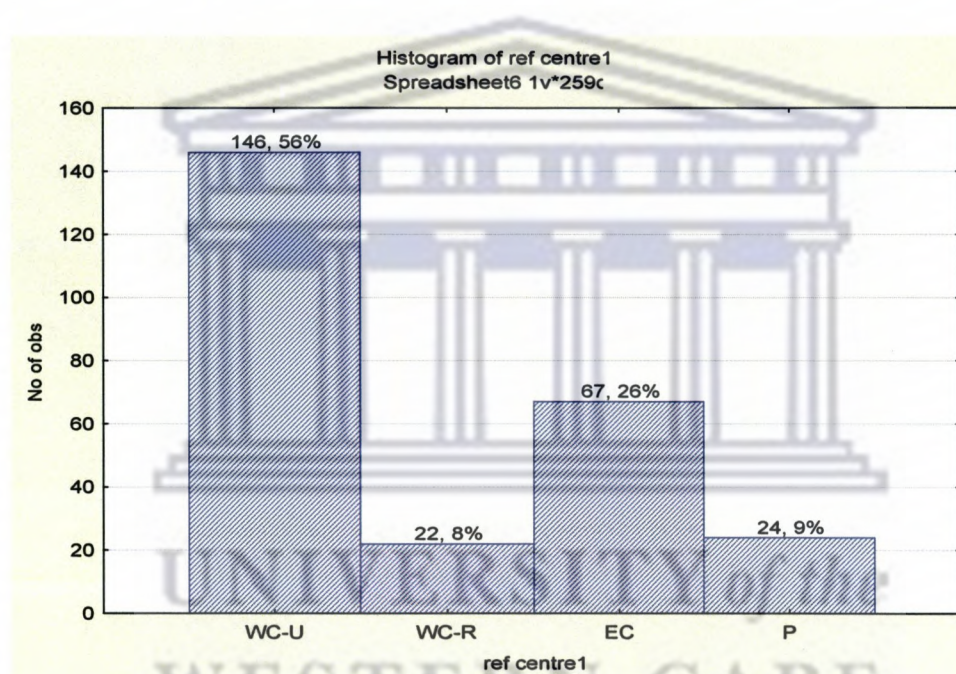


Fig. 5: Details of referral centers from which patients presented at NHLS-Tygerberg

146 of patients were referred from Tygerberg, Carl Bremmer and Groote Schuur hospitals. These referrals were documented as the urban areas of the Western Cape (WC-U).

The second largest referral area was the Eastern Cape (EC) with a pool of 67 patients. Western Cape – rural (WC-R) included patients from Eben Donges hospital, Paarl, Stellenbosch and Hottentot’s Holland hospital. Private patients (P) were referred predominantly from Pathcare. The frequency of referrals from WC-R and P are similar, at 8% and 9% respectively.

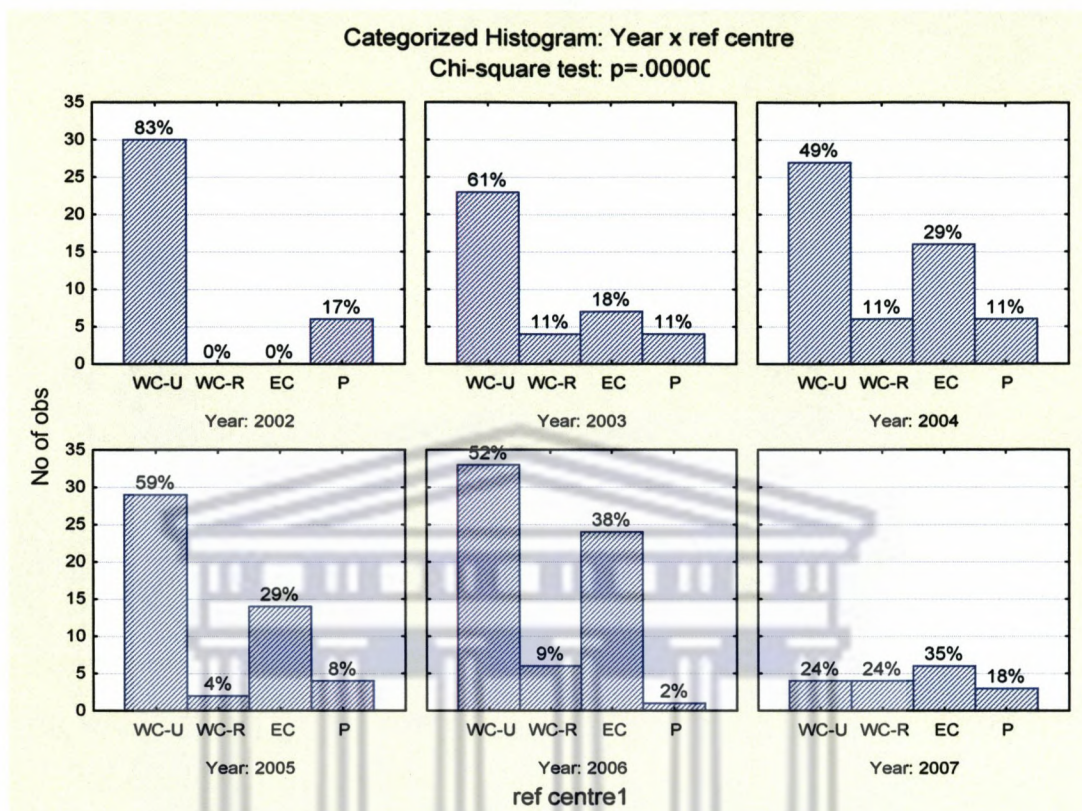


Fig. 6: Histogram showing trends in the number of referrals from various centers each year

Western Cape- urban (WC-U) remains the largest referral center. A notable increase is seen, each year, in the number of patients referred to Tygerberg-NHLS from the Eastern Cape (EC). A significant increase is also evident, for the four months of 2007, in the numbers of referrals from Western Cape- rural (WC-R) and the Eastern Cape.

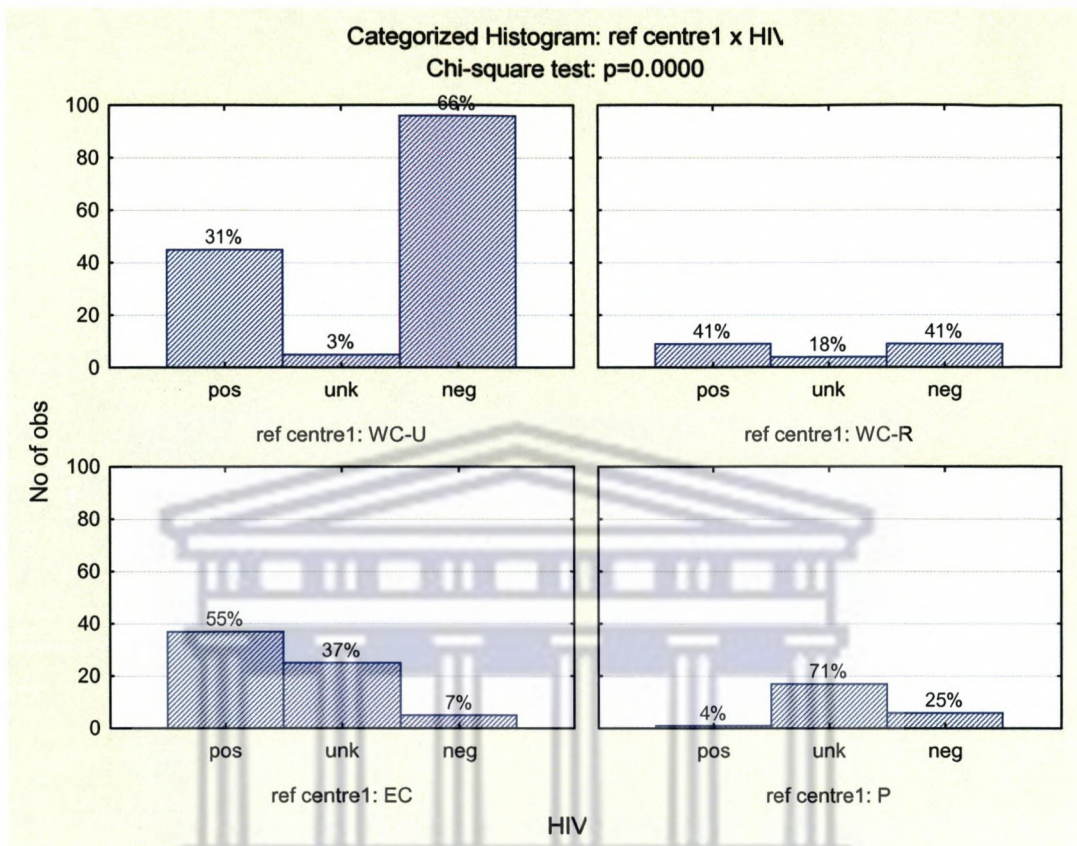


Fig. 7: Description of the HIV status of patients from the various referral centers

A significant number of HIV positive patients are referred from the Eastern Cape and Western Cape rural areas. Although the largest percentage of patients with an unknown HIV status are from private practices, 37% of cases from the Eastern Cape also, are of patients with an unknown status. It is significant to note that the Eastern Cape also has the lowest number of referred patients with a negative HIV status and Western Cape- urban has the highest number of HNL cases where patients are HIV-negative.

3.4 Gender of patients

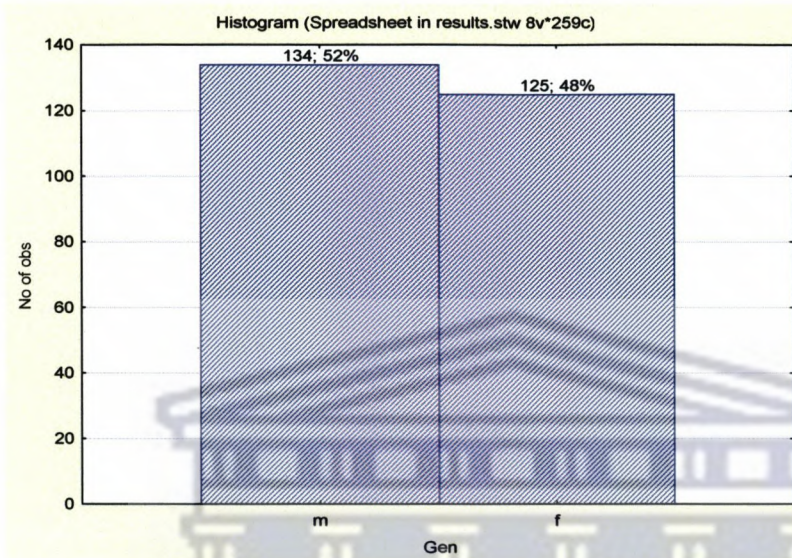


Fig. 8: Frequency of male (m) and female (f) patients

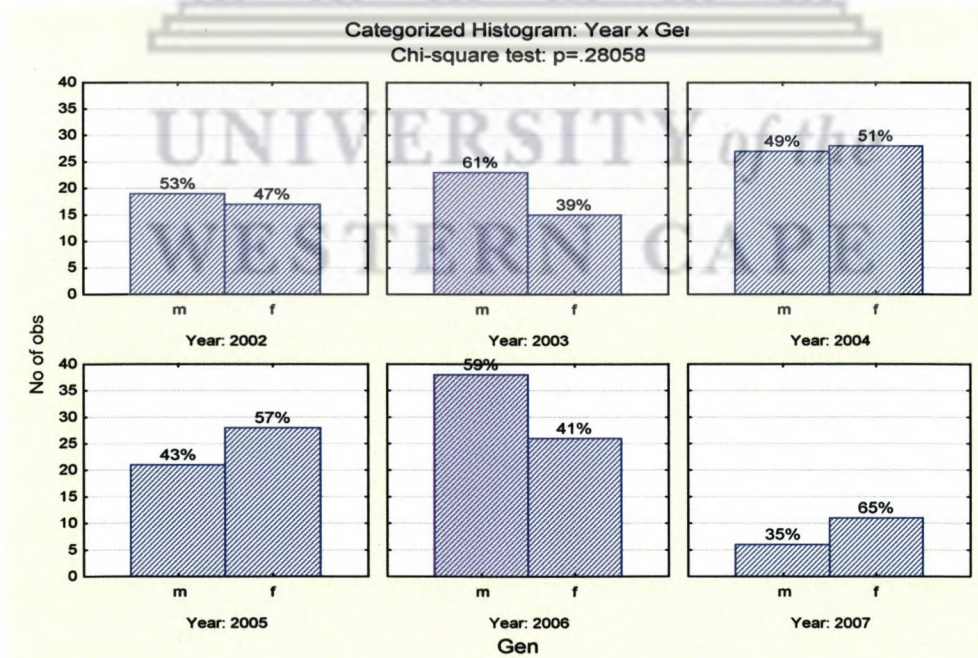


Fig. 9: Frequency of male and female patients each year

A four percent difference is noted in the patient pool in terms of gender, with the number of male patients being slightly more than female patients. Although this difference is statistically insignificant, a trend is noted in terms of an increase in the number of female patients presenting each year with HNL.

3.5 Age at presentation of HNL

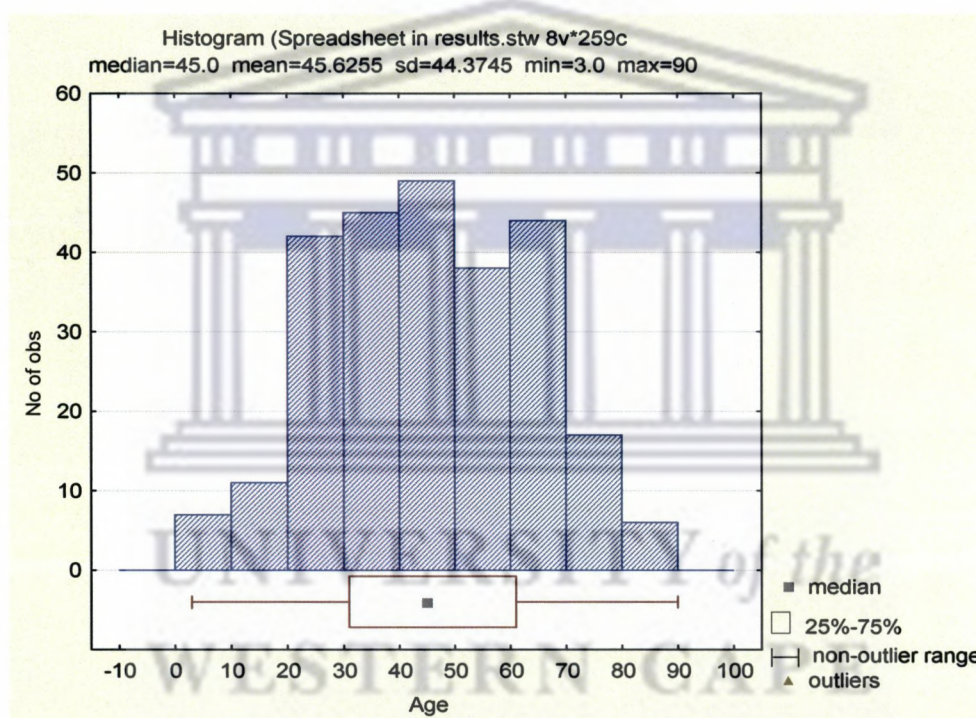


Fig. 10: Age range of patients

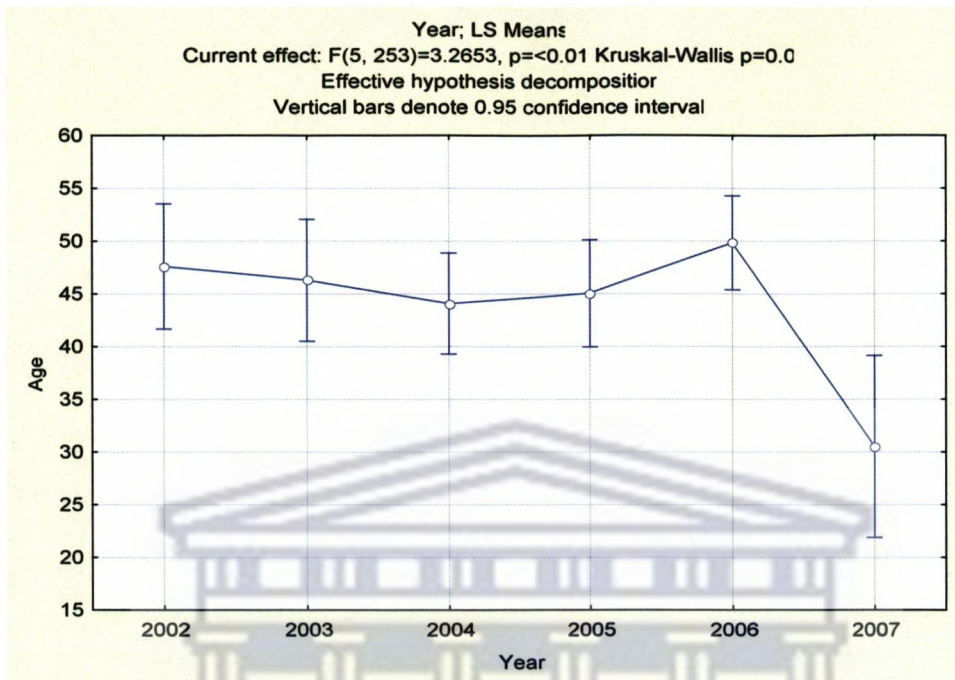


Fig. 11: Average age at presentation of disease per year

The age range of the patients presenting with HNL is between 3 and 90 years with the largest number of cases occurring between 20 and 70 years. Within this group, 145 patients are between 20 and 50 years and 81 patients are between the ages 51 and 70 years. The average age at presentation is 45 years for the time period 2002 to 2006. Although 2007 includes only 4 months of data, a significant drop is noted for the average age at presentation of disease, from 45 to 31 years.

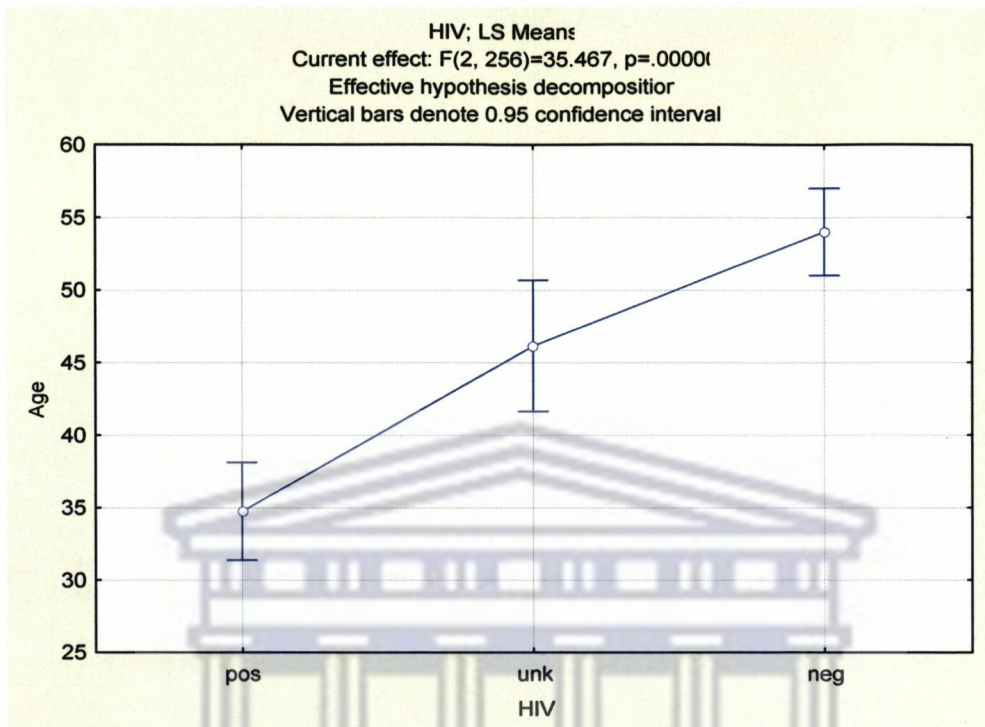


Fig. 12: Graph showing average age of patients in HIV positive, unknown and negative categories

A significant difference is noted in the ages at presentation of disease in the HIV positive patients relative to those patients with an unknown and negative status. The average age of disease presentation in the HIV positive group of patients is 35 years with the unknown group being 46 years and the negative group being 54 years.

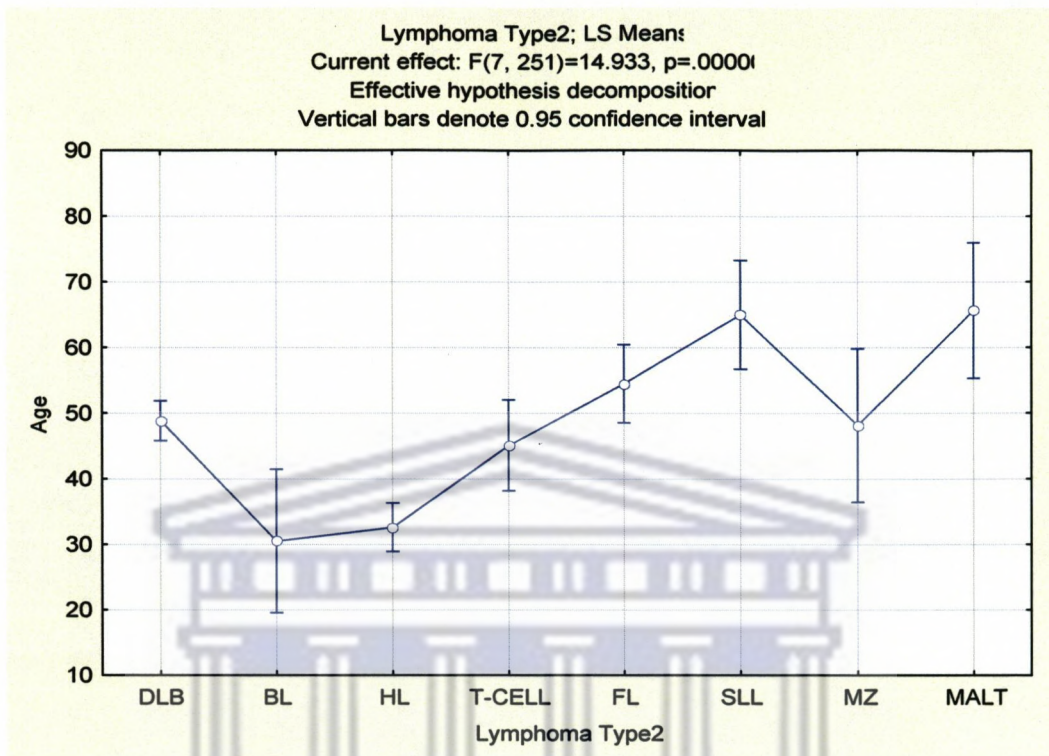


Fig. 13: Average age at presentation of the various categories of HNL

A significant difference exists between the average ages at presentation of the various types of lymphomas that have been documented. Burkitt's lymphoma has the lowest age range at presentation and small lymphocytic lymphoma and mucosa associated lymphomas (MALT) tend to present in patients between 60 and 70 years.

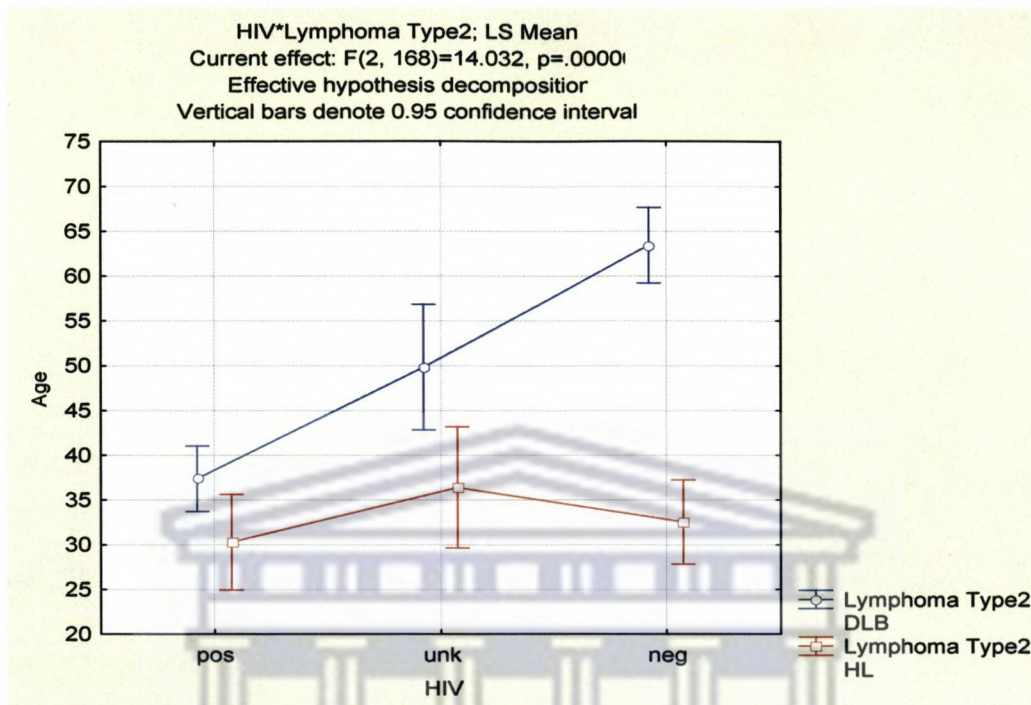


Fig. 14: Average age at presentation of B-cell lymphomas and Hodgkin lymphoma

For this particular statistical analysis DLB represents Plasmablastic lymphoma, Burkitt's lymphoma and DLBCL. The average age at presentation of these B-cell lymphomas are 37 years in HIV positive patients, 50 years and 63 years in the unknown and HIV negative categories respectively. Hodgkin lymphoma presented at an average age of 30 years in HIV positive groups of patients with a slight increase to 35 years in the age at presentation in HIV negative patients.

3.6 Site of HNL presentation

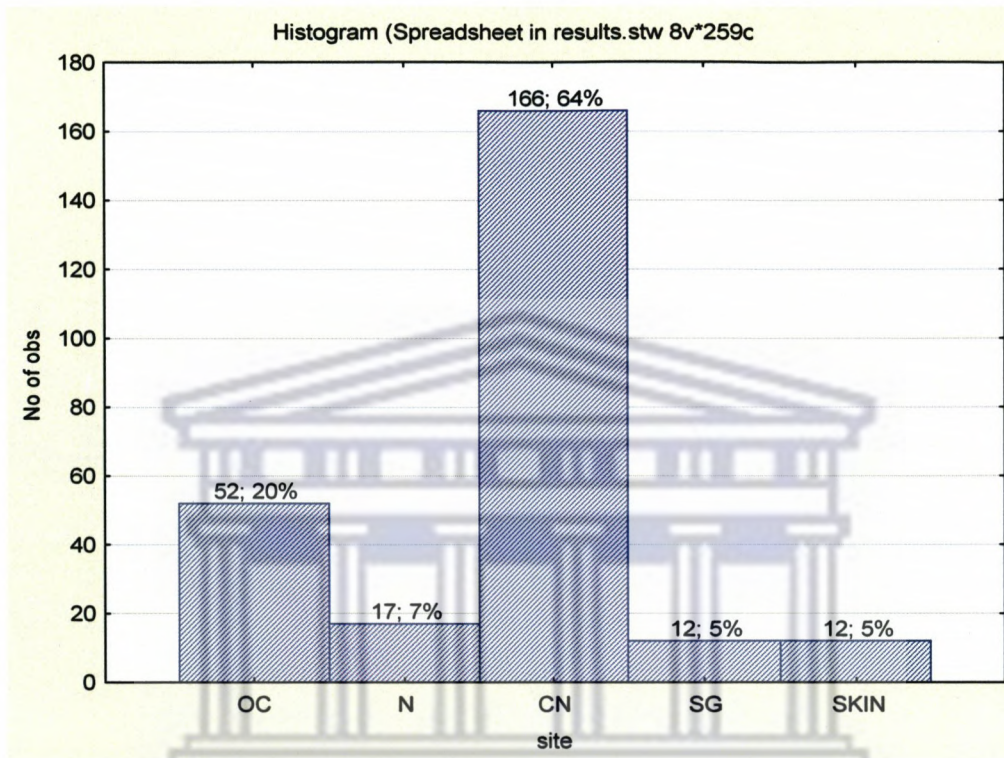


Fig. 15: Site of presentation of the various HNL

The cervical nodes (CN) were affected in 64% of patients. Included in the description of cervical nodes are submental and submandibular lymph nodes. 20% of disease presented in the oral cavity (OC).

The nasopharynx and nasal sinuses (N) were affected in 7% of patients.

Salivary glands (SG) were involved in 5% of cases. Included in the description of salivary glands are the parotid, submandibular and submental glands.

5% of disease presented in the skin (SKIN) region of the head and neck area.

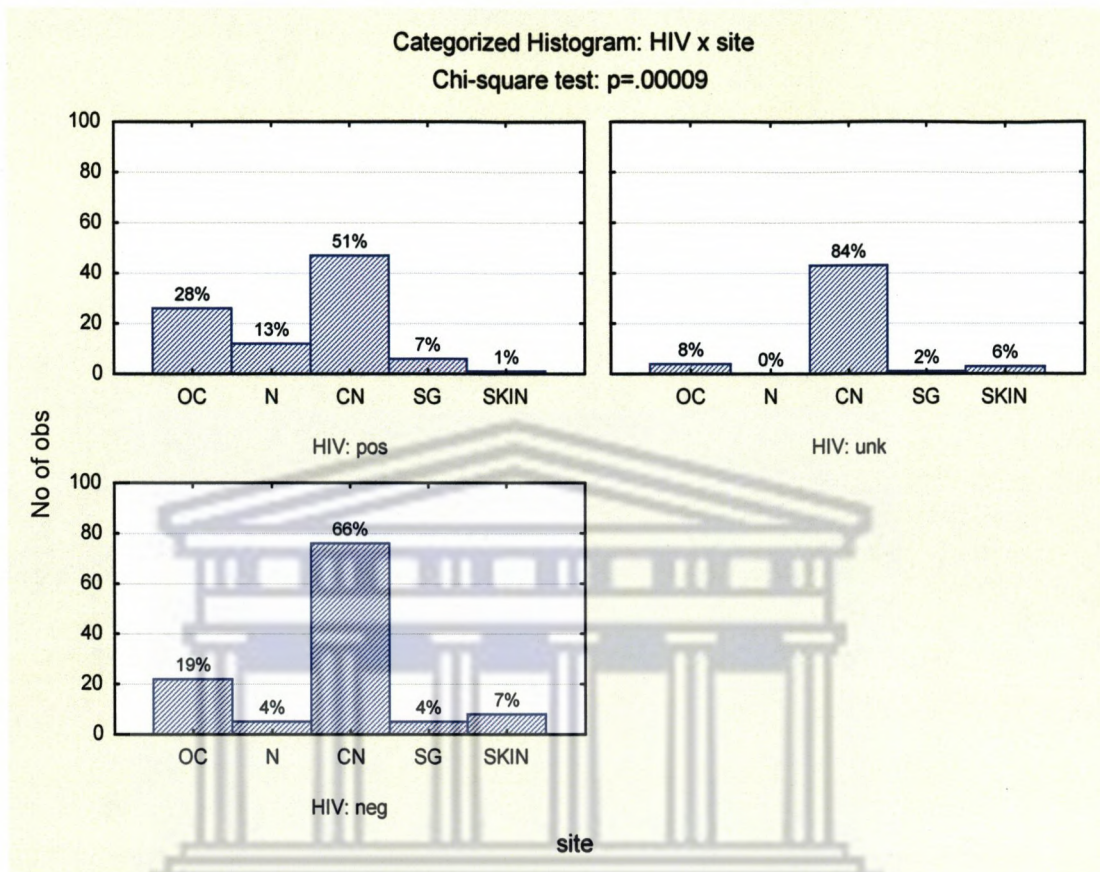


Fig. 16: Site of disease presentation in the HIV positive, HIV negative and 'unknown' group of patients

A significant difference exists between the sites of presentation of disease in each group of patients at our center.

In the HIV positive group, disease presented equally between nodal and extranodal sites. In the unknown and HIV negative group of patients nodal disease predominates with 84% and 66% presenting in the cervical lymph nodes respectively.

The oral cavity is the site of HNL in 28% of the HIV positive patients and 8% and 19% in the unknown and HIV negative categories respectively.

3.7 Frequency and histological types of HNL

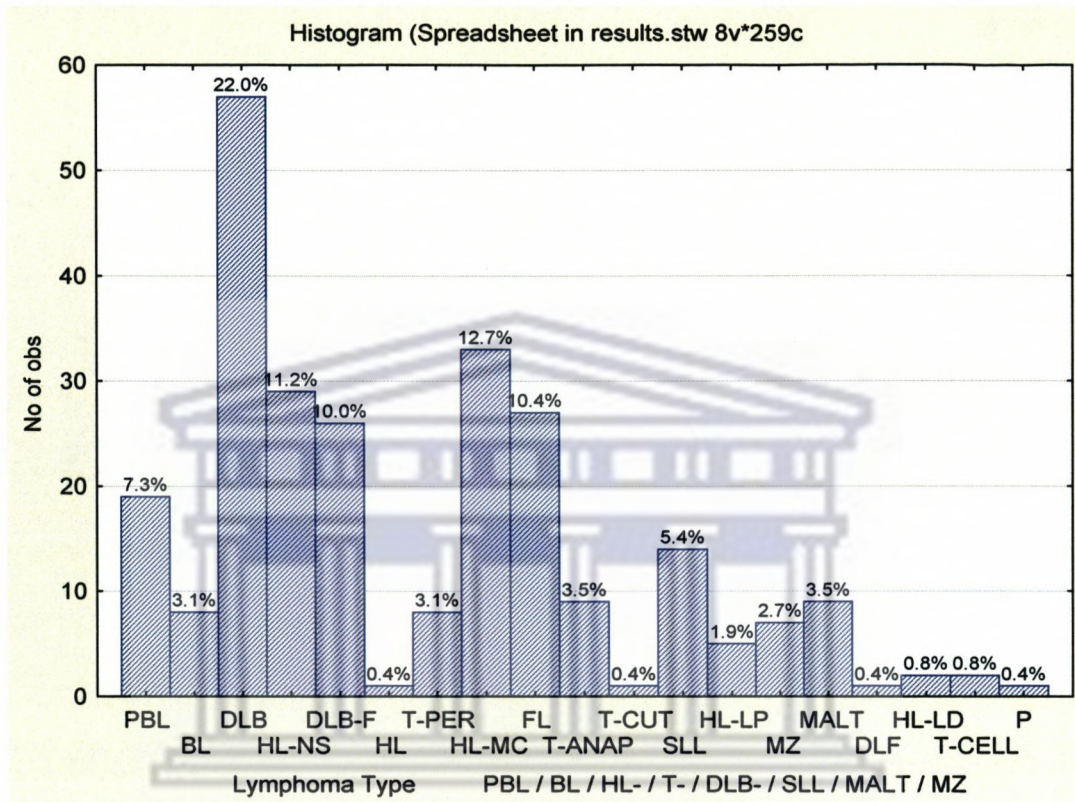


Fig. 17: Outcome details of all documented HNL cases

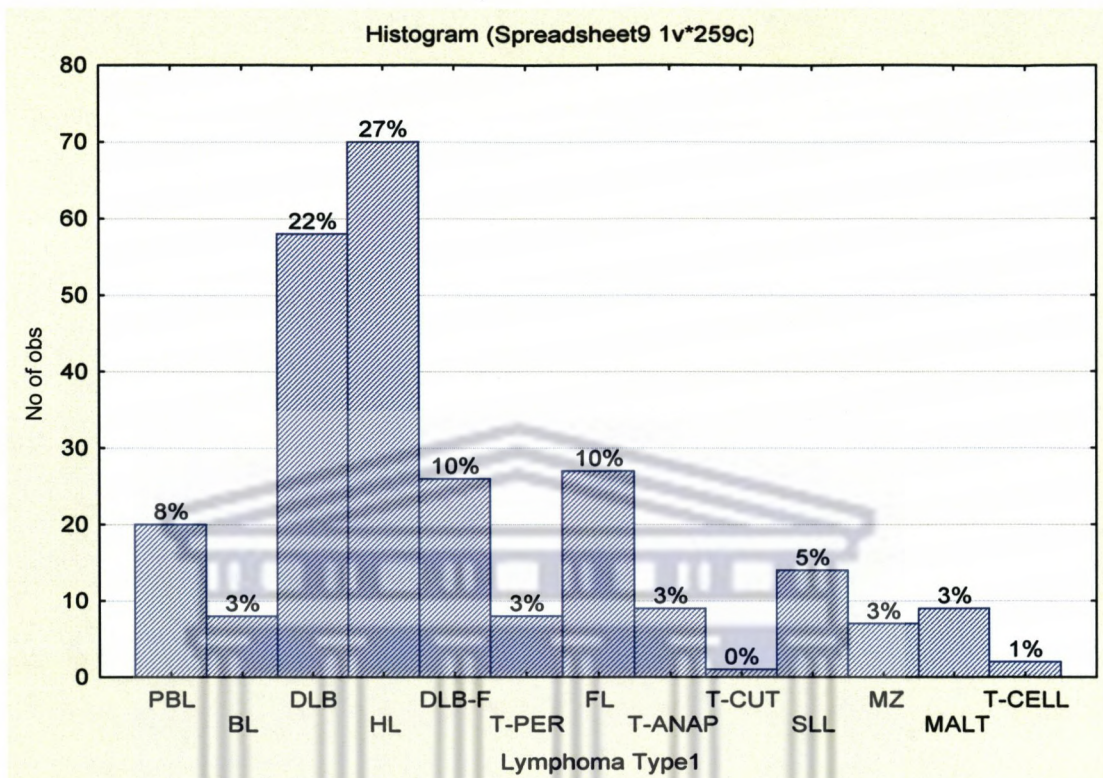


Fig. 18: Outcome details of all documented HNL cases

HL includes HL-MC, HL-NS, HL-NP and HL-LD

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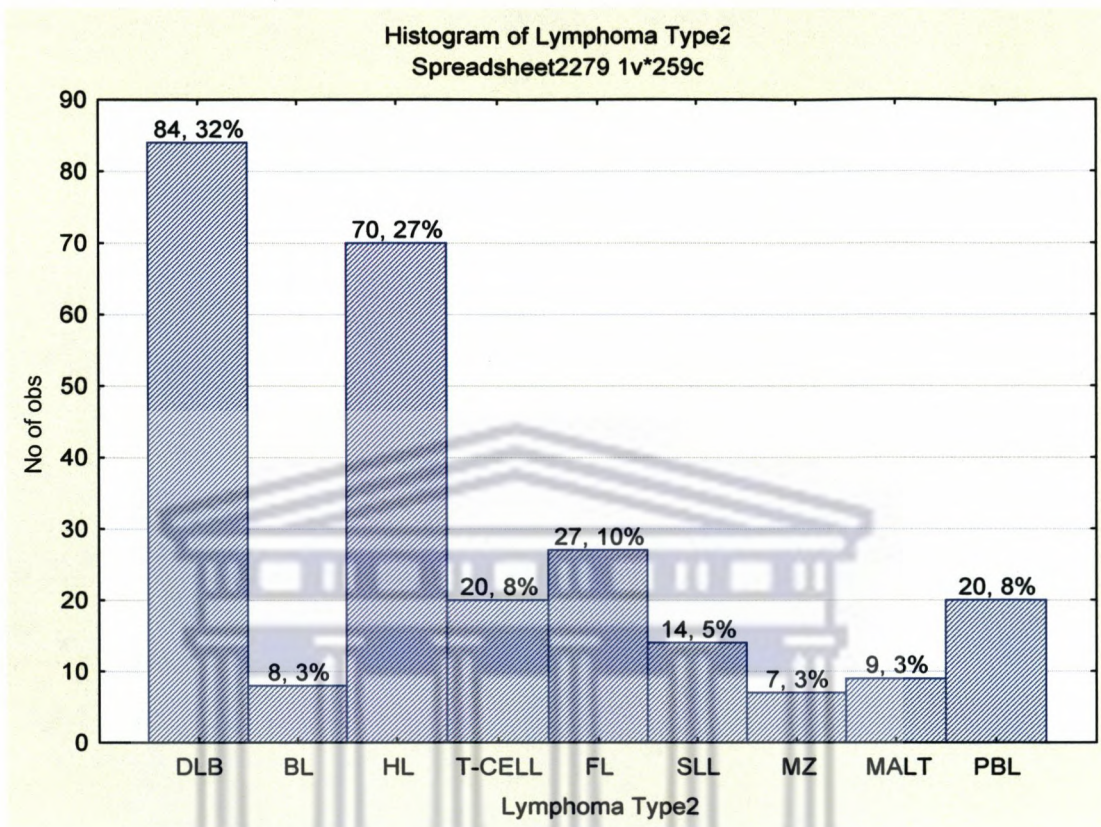


Fig. 19: Outcome details of all documented HNL cases

Group DLB includes DLB and DLB-F

Group T-CELL includes T-ANAP, T-CUT and T-PER

The Diffuse large B-cell (DLB), Hodgkin lymphoma (HL) and T-cell categories have been created in order to make statistical analyses of the data easier. Diffuse large B-cell lymphoma (DLB) is the largest morphological category of HNL that presented in our patient pool, at thirty two percent. This is followed by Hodgkin lymphomas (HL) at 27%, follicular lymphoma (FL) and plasmablastic lymphoma (PBL) at 10% and 8% respectively.

3.8 Frequency of various types of HNL presenting in HIV positive, negative and 'unknown' category

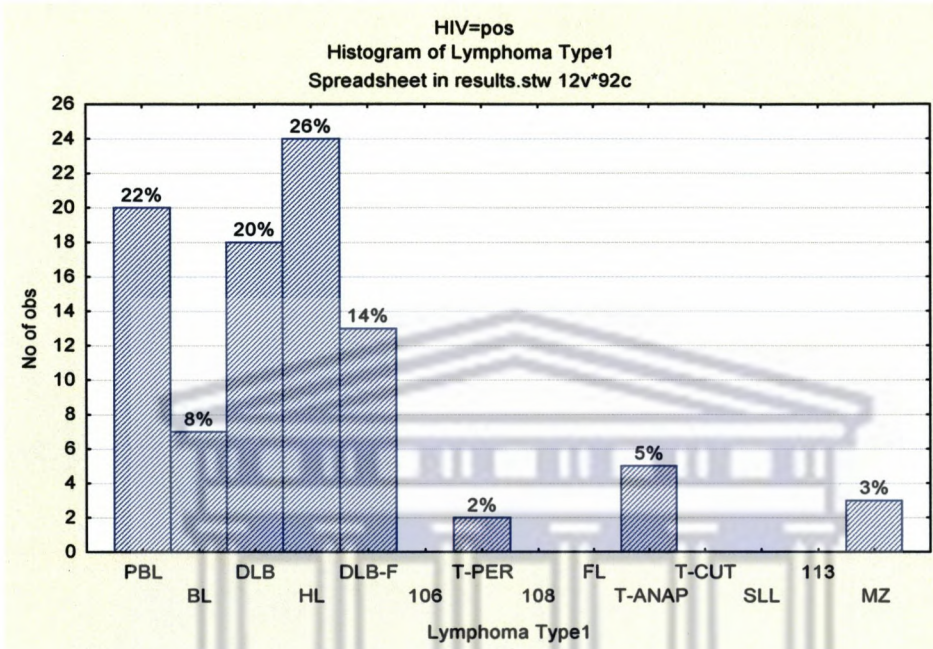


Fig. 20: Morphological categories of lymphoma presenting in HIV positive group

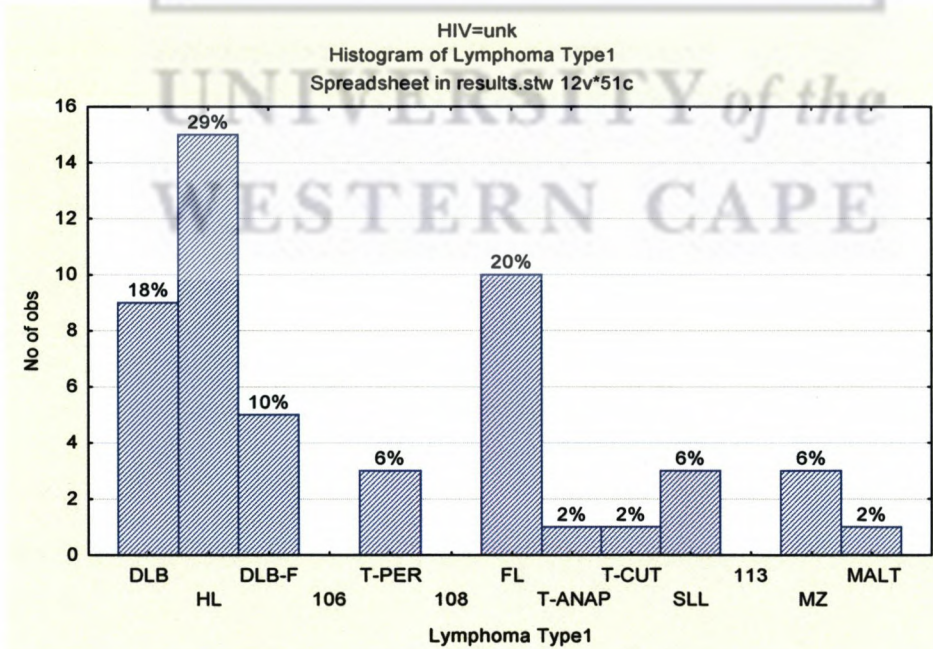


Fig. 21: Morphological categories of lymphoma presenting in 'unknown' group

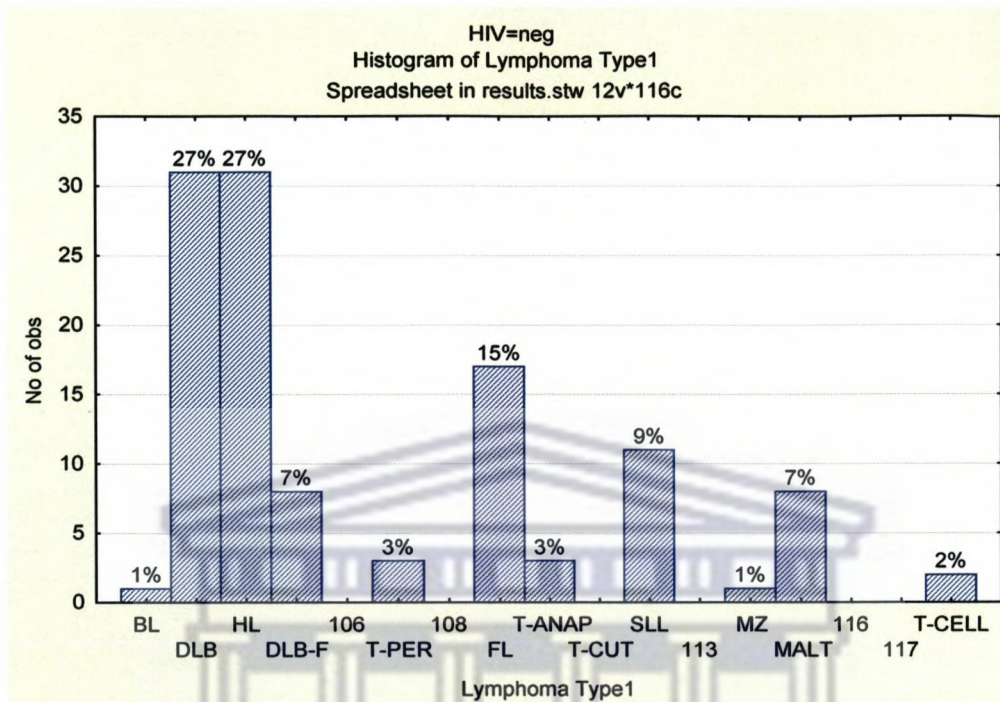


Fig. 22: Morphological categories of lymphoma presenting in HIV negative patients

The main categories of lymphoma that presented in our series in HIV positive patients are PBL and DLB which together form 42% of cases. Hodgkin lymphoma constitutes 26% of cases; the second largest group of HNL cases. This is followed by diffuse large B-cell lymphomas of follicular origin and Burkitt's lymphomas (BL) which form 14% and 8% of cases respectively. Seven percent of cases are T-cell lymphomas. Three percent of cases are Mantle zone lymphomas. No cases of SLL and Follicular lymphomas (FL) are described in this group of patients.

In the group of patients with an unknown HIV status, the largest numbers of cases were in the Hodgkin and Diffuse large B-cell (DLB) category, which includes diffuse large B-cell lymphomas of follicular origin, each presenting with 29% and 28% of cases respectively. Follicular lymphomas formed 20% of cases. 10% of cases are T-cell lymphomas. Six percent of SLL and MZ are described but, no Plasmablastic lymphomas (PBL) and BL are identified in this category of patients.

DLB and HL form 27% each of the cases in patients with a negative HIV status. A significant number of Follicular lymphomas (15%), SLL (9%), MALT (7%) and T-cell lymphomas (8%) are identified. No PBL are seen in this group of patients.

3.9 Hodgkin's lymphoma in HIV positive patients

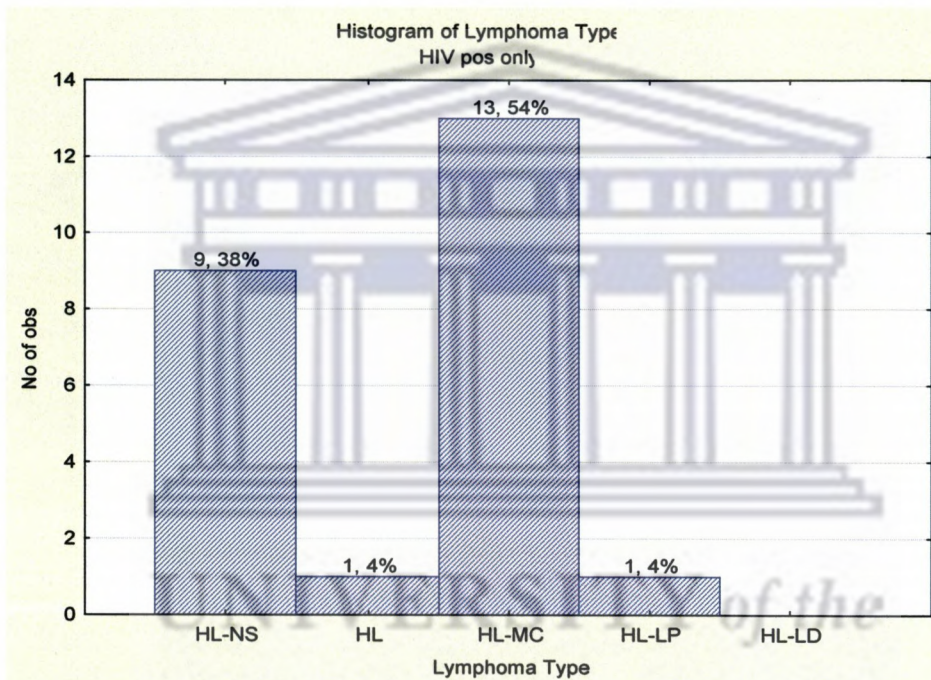


Fig. 23: Morphological subtypes of HL presenting only in the HIV positive patients

In the HIV positive population of patients that presented with Hodgkin lymphoma, 54% of these patients presented with the mixed cellularity subtype followed by 38% that presented with the nodular sclerosing subtype. 98% of HL is Classical HL (CHL).

CHAPTER 4

Discussion

4.1 Increase in the number of HNL cases each year

A statistically significant increase in the number of referred HNL cases is noted from January 2002 to December 2006. This increase could be attributed to a number of different logistical reasons. The total number of specimens referred to the Department of Anatomical pathology increases each year. In addition, the number of referral centers has increased to include the Eastern Cape and rural Western Cape. A growth in the South African population has also been documented and might have contributed to the increase in the number of cases.

Influence of HIV pandemic

The number of patients diagnosed as HIV positive continues to grow in the Western and Eastern Cape⁶. This trend is reflected in the increase in the number of cases of HIV positive patients with HNL that is referred to our center. In our series of cases, although a rise is seen in the number of cases with an 'unknown' HIV status, several of these could represent patients with a positive HIV status. This suggests that the number of absolute cases of HIV positive patients could be under-represented. Some studies describe an increased burden of lymphoma seen against a dramatically progressing AIDS epidemic²⁸. At present, several molecular pathways can be described that identify the role of the human immunodeficiency virus in lymphomagenesis⁵⁴.

Effect of HAART

Some studies report that HAART has had a dramatic effect on the natural history of HIV disease, reducing the associated morbidity and mortality and improving overall survival of patients with lymphomas in developed countries. Further contradictory reports exist in terms of the incidence of NHL since that advent of HAART. Some authors noted that the incidence of NHL has not decreased significantly and an increase in patients diagnosed with lymphoma at CD4+ counts greater or equal to 200cells/microL, is noted²⁹. Other authors report a significant decrease in the incidence of NHL since 1996³⁰. Both these reports, however, suggest that the median survival time increased from 3 months to 13 months and that HAART-era patients were more likely women.

In South Africa, it is predominantly the urban population that receives ARV's and HAART. Their survival time has, therefore, lengthened; indicating that this is another possible reason for the increase in HNL cases each year.

It must still be stated that in 2005, the South African government declared that only 10% of people needing ARV's and HAART are actually on treatment and recent figures presented at the AIDS conference show a decline in patients going on ARV's nationally³¹.

4.2 Rural vs. urban areas

The largest percentage of HIV positive patients are referred from the Eastern Cape followed by the rural areas of the Western Cape. There is a significant increase in the numbers of HNL cases from HIV positive patients being referred each year from these predominantly rural, economically challenged areas of South Africa. This trend of increasing numbers of HIV positive patients and numbers of HNL from rural areas has been noted and documented in studies in India, Tanzania and Nigeria^{32,33,34}. A study on epidemiology of HIV in South Africa showed that rural areas had the

highest HIV prevalence. This study also shows an increasing rural HIV positive female population and a decline in the incidence of HNL in the urban male and female population⁶. We notice a trend in the increase in the number of female patients being referred to our center each year.

4.3 Factors contributing to increasing HIV prevalence and lymphoma burden

Poverty

In a study performed in South Africa in 2006, on the relationship between poverty and AIDS; an increased risk of HIV infection and disease presentation among the poor, due to poverty-related characteristics of low levels of education and inadequate knowledge of the means of avoiding HIV infection, as opposed to the non-poor, is documented³⁵. An increasing HIV incidence and prevalence among young women in rural South Africa, has also been reported. A possible explanation for the trend towards an increase in female patients, each year, is financial dependence on their partners who were more likely not to use condoms. These patients are, therefore, at an increased risk for HIV infection and subsequent increased risk for HNL^{18,35}.

Stigma

According to reports, AIDS stigma and discrimination continue to influence people living with and affected by HIV disease, particularly in rural South Africa where the AIDS burden is so significant. Stigma is perceived as a major limiting factor in primary and secondary HIV/AIDS prevention. It reportedly interferes with accessing early health care, thereby increasing suffering and shortening lives³⁶.

Rural communities

The South African government has outlined detailed plans for free antiretroviral (ARV) rollout, but has not created a plan to address treatment accessibility in rural areas. The results of this study show that many patients in rural areas are unlikely to

have access to ARV's due to several non-drug related costs of obtaining treatment. It is stated that there are great lengths to go before rural patients receive the benefits of ARV's. These policies could explain the increase in the numbers of HIV positive rural patient cases with HNL being referred to our center over the last 5 years^{31,37}.

In many rural communities of South Africa, traditional healers are often the only means of health care delivery available. The level of knowledge and ability to recognize oral lesions of 32 traditional healers, were assessed. It was found that most of these healers recognized lesions, via the use of clinical photographs, such as bleeding gums, oral thrush, hairy leukoplakia, oral ulcerations and parotid enlargement. Hence, it was concluded that traditional healers constitute an untapped resource with enormous potential. It was suggested that a positive bridge be built to link traditional healing with modern medicine in terms of identification and treatment of oral lesions³⁸.

4.4 Age range of patients

In our series, the age range of the patients presenting with HNL is between 3 and 90 years with the largest number of cases occurring between 20 and 70 years. Within this group, 145 patients are between 20 and 50 years. The average age at presentation is 45 years for the time period 2002 to 2006. Although 2007 includes only 4 months of data, a significant drop is noted for the average age at presentation of disease, from 45 to 31 years. A significant difference is noted in the ages at presentation of disease in the HIV positive patients relative to those patients with an unknown and negative status. The average age of disease presentation in the HIV positive group of patients is 35 years with the unknown group being 46 years and the negative group being 54 years.

Only six children below the age of 10 years with HNL were documented in our series. Two of them presented with Burkitt's lymphoma in the oral cavity and jaw

and the other four presented with Hodgkin's lymphoma in the cervical lymph nodes. All 6 children were HIV negative. Children with HNL from the Western Cape and other parts of Southern Africa are referred to Red Cross Hospital. These lesions are then diagnosed at other centers such as Groote Schuur Hospital.

In a study that described the trends in adult medical admissions in rural South African hospitals between 1991 and 2002 showed that between this time, hospital admissions rose by more than a 100% each year. The median age of female patient's fell from 50 to 34 years and the median male patient's age fell from 45 to 39 years. Patients presented with a dual burden of infectious and non-communicable disease, which existed, and still exists against a background of dramatically progressing HIV pandemic³⁹.

In a study in Thailand, in 2003, describing oral NHL in 15 cases, the patients' age ranged from 13 to 70 years with the mean of 42 years. 11 of the 15 patients' were HIV positive⁹.

A further study, in the USA, on oral NHL, reported an age range of 35 to 89 years with a mean of 71 years. Of this group of 40 patients, only two were HIV positive. These HIV positive patients were younger than 50 years³.

A Nigerian study in 2006, on primary head and neck cancers, conclude that there is a rising trend in the occurrence of head and neck cancers in Nigeria, with a considerable proportion of patients being below 30 years³⁴.

Although the average age of disease presentation at Tygerberg is 45 years for patients with HNL, this trend of younger patients being diagnosed each year closely parallels that observed by the authors of the 2003 Thai study and the 2006 Nigerian study. This trend confirms the fact that HNL presents at younger ages in developing countries, especially in HIV positive individuals.

4.5 Nodal vs extranodal presentation of HNL

Limited information is present in the literature regarding head and neck manifestations of NHL. In a study in 2000 at the State University of New York, the authors attempted to describe the head and neck manifestations of NHL in HIV-infected patients and compare it with that seen in non-infected patients. These authors found that extralymphatic disease is significantly more common in HIV-infected patients than non-infected patients¹.

Our data of all patients, showed 64% of disease in lymph nodes and 37% extranodal disease.

A significant difference exists between the sites of presentation of disease in each group of patients at our center.

In the HIV positive group, disease presented equally between nodal and extranodal sites. In the unknown and HIV negative group of patients nodal disease predominates with 84% and 66% respectively.

The oral cavity was the site of 20% of HNL and had the greatest incidence of extranodal disease. It was involved in 28% of the HIV positive patients and 8% and 19% in the unknown and HIV negative categories respectively. These results, in terms of presentation, at our center are consistent with studies done in India and Nigeria^{40,5}. In Nigeria, the oral cavity was the most common site for HNL. In a ten year study, describing the pattern of head and neck malignant tumors, the oral cavity was involved in 37% of HNL cases⁵.

4.6 Histological types of HNL

The vast majority of lymphomas that were documented in our series were B-cell lymphomas. These included diffuse large B-cell lymphomas (DLBCL), which formed 22% of cases, DLBCL of follicular origin that comprised 10%, and Burkitt's lymphoma, 3% of cases. SLL, Mantle cell and Marginal zone lymphomas together

formed 11% of cases. The total frequency of DLBCL was 32%. T-cell lymphomas were 6% of total number of cases.

The International Network on Cancer Treatment and Research (INCTR) recently organized a workshop on NHL in selected developing countries. The WHO classification was used and India, Pakistan, Kuwait and Egypt participated. B-cell lymphomas accounted for 82-88% of all NHL. DLBCL accounted for about 35% of cases in India but for more than 50% in other countries. Mantle cell and marginal zone lymphomas accounted for between 6-10% in India, but there was an apparent paucity of these subtypes in the other countries. Peripheral T-cell lymphomas accounted for 3-5% of NHL in all these countries.

Our results parallel the trend identified by this study in terms of the results obtained from India⁵⁶. The results of a similar study conducted in the USA in 2006³, showed B-cell lymphomas to constitute 98% of their series of which the subtype DLBCL was 58%.

The differences in the relative proportions of subtypes of NHL among and between developing countries and the rest of the world presumably arise from differences in environmental and genetic factors that influence lymphomagenesis and strongly suggest that more research in developing countries would provide valuable insight into the pathogenesis of lymphoid neoplasms.

In our series, lesions described as high-grade lymphomas are Burkitt's lymphoma, DLBCL, and DLBCL that have transformed from a less aggressive Follicular lymphoma and Plasmablastic lymphomas.

These high-grade lymphomas constituted a significant 43% of our cases.

4.7 High grade vs low grade HNL

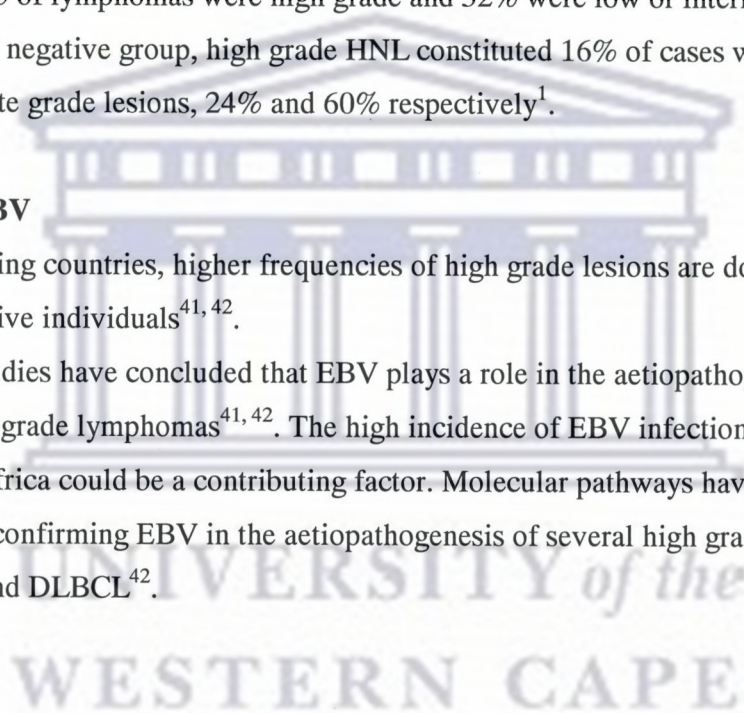
The high-grade lymphomas were found predominantly in the HIV positive group of patients where they formed 64% of cases. In the HIV negative group of patients, these high-grade lymphomas constituted 35% of cases.

A study in the USA of 124 patients in 2000 compared the manifestations of HNL in HIV positive and negative individuals. These authors found that in the HIV positive group, 68% of lymphomas were high grade and 32% were low or intermediate grade. In the HIV negative group, high grade HNL constituted 16% of cases with low and intermediate grade lesions, 24% and 60% respectively¹.

Role of EBV

In developing countries, higher frequencies of high grade lesions are documented in HIV-negative individuals^{41, 42}.

Several studies have concluded that EBV plays a role in the aetiopathogenesis of these high-grade lymphomas^{41, 42}. The high incidence of EBV infection in sub-Saharan Africa could be a contributing factor. Molecular pathways have been identified confirming EBV in the aetiopathogenesis of several high grade lymphomas such as BL and DLBCL⁴².



4.8 HIV associated lymphomas

The WHO divides the HIV-associated lymphomas into three categories; lymphomas also occurring in immunocompetent patients, lymphomas occurring more specifically in HIV positive patients and lymphomas also occurring in other immunodeficiency states²³.

Table 1: Categories of HIV-associated lymphomas as documented by the WHO²³

<p>1. Lymphomas also occurring in immunocompetent patients</p> <p>Burkitt's lymphoma</p> <ul style="list-style-type: none">ClassicalWith plasmacytoid differentiationAtypical <p>Diffuse large B-cell lymphoma</p> <ul style="list-style-type: none">CentroblasticImmunoblastic <p>Extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type (MALT) – rare</p> <p>Peripheral T-cell lymphoma – rare</p> <p>Classical Hodgkin lymphoma</p>
<p>2. Lymphomas occurring more specifically in HIV positive patients</p> <ul style="list-style-type: none">Primary effusion lymphomaPlasmablastic lymphoma
<p>3. Lymphomas also occurring in other immunodeficiency states</p> <ul style="list-style-type: none">Polymorphic B-cell lymphoma

Diffuse large B-cell lymphomas

Existing reports of HNL have shown a similar predominance of DLBCL as was seen in our data (32%). They are usually confined to extranodal sites. DLBCL presented in 34% of HNL cases in HIV positive patients. The cases of DLBCL were not sub-typed into those with or without immunoblastic or centroblastic features.

DLBCL constitutes 30 – 40% of adult NHL in the western countries. In developing countries they constitute an even higher proportion of lymphomas. Over the past few decades the incidence has been increasing, independent of HIV as a risk factor²³.

Infection of the neoplastic cells by EBV may be seen and is more common in cases associated with underlying immunodeficiency^{41, 42}. The findings of the Thai study on oral NHL concluded that EBV may be involved in the pathogenesis of oral NHL particularly in patients with HIV infection⁴².

Plasmablastic lymphoma

Plasmablastic lymphoma (PBL) is a distinctive HIV-associated tumor that is described by the WHO as a lymphoma occurring more specifically in HIV positive patients. It was first described in the jaws and oral cavity. In the oral cavity the most common locations are the gingival and the alveolar mucosa. In a study that aimed to assess the presence of EBV in 11 cases of oral PBL; the EBV genome was detected in all the cases. It was concluded that the virus plays a direct role in the pathogenesis of PBL in the oral cavity⁴³.

PBL has a characteristic immunophenotype. These lesions are negative for LCA and CD20. A small proportion of cells are positive or weakly positive for CD79a, but the majority of cells are positive with PLA (VS38c), CD38 and CD138. The neoplastic cells are positive for EBV and negative for HHV8⁴⁴. The immunophenotype of PBL suggests that it is a bona fide aggressive form of plasma cell neoplasm rather than a B-cell lymphoma, as suggested by the WHO.

Several authors have proved that these lesions do present in extraoral sites such as anorectal area, nasal and paranasal sinuses and cervical lymph nodes⁴⁵.

A few cases have also been described in HIV negative patients⁴⁶. Many authors have subsequently proposed that the term *Plasmablastic lymphoma of the oral cavity* in the WHO classification be revised to simply *Plasmablastic lymphoma*, which would include oral and extra-oral PBL. In our series of HNL cases, the primary site of all PBL was the oral cavity and the lesion was only diagnosed in HIV positive patients.

Burkitt's lymphoma

Burkitt's lymphoma is a highly aggressive, mature B cell non-Hodgkin's lymphoma that is rare outside Africa. Burkitt's lymphoma (BL) was identified in eight cases of all HNL. Six presented in the HIV positive population and two cases were diagnosed in HIV negative children. The age ranges of the patients were between 8 and 38 years.

BL is described as a high-grade HIV-associated lymphoma that can present in non-immunocompromised patients as well. Three histological variants of BL are described, i.e. the classical variant, with plasmacytoid differentiation and atypical BL. The cases of BL at our center were not subtyped and hence were just documented as BL not otherwise specified.

The cases described in this series all presented as extranodal disease in the oral cavity and jaws.

Burkitt's lymphoma is a common co-morbidity of infection with the human immunodeficiency virus. Often it is the atypical variant of BL that is diagnosed in these patients. Although rare, BL has been documented as the initial clinical manifestation of undiagnosed AIDS⁴⁷. A report of a patient that presented with recalcitrant rhino-sinusitis was subsequently diagnosed with sino-nasal Burkitt's lymphoma and HIV. Another case of Burkitt's lymphoma presenting as a rapidly expanding tongue-base mass in a Palestinian man, has also been described⁴⁸.

The EBV genome has been identified in up to 100% of immunodeficiency associated BL in developing countries. EBV genomes can be demonstrated in tumor cells in nearly all endemic cases. It has been noted that low socio-economic status and early EBV infection are associated with a higher prevalence of EBV positive BL in South Africa.

4.9 MALT lymphoma

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a low-grade lymphoma that presents in patients' with a median age of 61 years, and, has a higher incidence of presentation of in the Middle East and the Cape region of South Africa²³. Although described by the WHO, as a HIV-associated lymphoma that presents in other immunocompromised patients as well, it is rare in HIV positive patients.

MALT lymphoma has a predilection for involving extranodal sites and has often, in the pre-immunohistochemical and molecular era, been confused with an inflammatory process especially in the oral cavity^{8, 13, 14}.

Nine cases of MALT lymphoma were diagnosed in our series and presented in patients' with an age range of 55 to 75 years. Five of these cases presented in the parotid gland and four within the oral cavity. No cases were diagnosed in HIV positive individuals. One case was in the category unknown and eight cases were diagnosed in HIV negative individuals.

Salivary gland lymphomas represent approximately 3% of all salivary gland tumors. The parotid gland is most commonly affected in 80% of cases, followed by the submandibular (16%), sublingual glands (2%) and minor salivary glands (2%). Twenty percent of patients with salivary gland lymphomas have clinical or laboratory evidence of Sjogren's syndrome. Myoepithelial sialadenitis, also commonly referred to as benign lymphoepithelial lesion, is also a precursor lesion for non-Hodgkin's lymphoma².

4.10 T-Cell lymphomas

T-cell lymphomas constituted 8% of our total series and 5% of cases in the HIV positive group. The group T-cell lymphomas consisted of Peripheral T-cell and Anaplastic large cell lymphoma.

According to the WHO classification, Peripheral T-cell lymphomas are described as HIV-associated lymphomas that also present in immunocompetent individuals.

Although the WHO describes these lymphomas as rarely presenting in HIV positive individuals, several articles report this lesion in HIV positive individuals. Primary T-cell lymphomas in the esophagus and parotid gland have been described in HIV positive adult patients as well as in several sero-positive children and infants.

Linkage of AIDS and cancer registries has indicated an increase in T-cell lymphomas⁴⁹. A study performed at the National Cancer Institute in the USA on the risk of T-cell lymphomas in persons with AIDS found that of the 6788 cases of NHL assessed, 96 were T-cell lymphomas. The relative risk of T-cell lymphoma, estimated by standardized incidence ratio, was 15.0. Risks were increased for all subtypes, including mycosis fungoides, peripheral lymphomas, cutaneous lymphomas and adult T-cell lymphoma⁵⁰.

In a study performed in Peru, a high proportion of T-cell lymphoma cases were found at an HIV reference center. This study represents the trends seen in developing countries⁵¹.

The literature also reports cases of anaplastic large cell lymphoma (ALCL) arising in HIV positive patients that has presented in the head and neck region. Reports of ALCL primarily involving the jaw and scalp have been published⁵¹.

4.11 Hodgkin's lymphoma

Hodgkin lymphomas (HL) share the following characteristics:

- HL usually arise in lymph nodes, preferentially in the cervical region
- Majority manifest clinically in young adults.

Biological and clinical studies have shown that HL are comprised of two disease entities, nodular lymphocyte predominant HL and classical HL (CHL).

HL has also been described by the WHO as a category of HIV-associated lymphoma that also presents in immunocompetent patients. This fact is represented in this study, where, HL presents as 27% of all HNL with no significant difference in incidence between HIV positive, HIV negative and the unknown group of patients. In our series of cases, HL presented entirely in the cervical lymph nodes and in patients with an age range of 28 to 35 years.

In persons with HIV, HL risk is increased. It still remains unclear whether HIV infection promotes the development of Hodgkin's disease or merely modifies its clinical progression.

Recent studies in developed countries, has shown that HL incidence has unexpectedly increased since HAART was introduced. It was found that for each HL subtype, incidence decreased with declining CD4 counts, but nodular sclerosing decreased more precipitously than mixed cellularity, thereby increasing the proportion of mixed cellularity CHL seen in patients with HIV. This study also concludes that the frequency of HL is lower with severe immunosuppression than with moderate immunosuppression, and HAART related improvements in CD4 counts likely explain the increasing CHL incidence in developed countries^{24,25}.

In the group of HIV positive patients, at our center, mixed cellularity CHL presented in 54% of patients, followed by nodular sclerosing CHL, at 38%. This trend has also

been identified in the USA²⁵. The influence of HAART on our results could not be elicited.

Many studies have suggested that EBV plays a role in the etiology of CHL. It was found that EBV strain type 1 was predominant in Hodgkin's disease in South Africa. The relatively high incidence of CHL and the insignificant difference between the presentation in HIV positive, negative and unknown groups is possibly due to the high incidence of EBV infection in developing countries. This reflects socio-economic conditions leading to malnutrition induced immunological impairment.

4.12 Other B-cell lymphomas

Other B-cell lymphomas that presented in our series of cases were Follicular lymphoma (FL), SLL and Mantle cell lymphomas.

Follicular lymphoma

FL is defined as a neoplasm of follicle centre B-cells, centrocytes and centroblasts, which has at least a partially follicular pattern. The WHO describes FL as a low-grade lymphoma with a median age of 59 years. FL contributed to 10% of our cases and presented only in the lymph nodes of the head and neck region. FL was documented only in the HIV negative and unknown status group of patients and within an age range of 50 to 60 years.

Small lymphocytic lymphoma

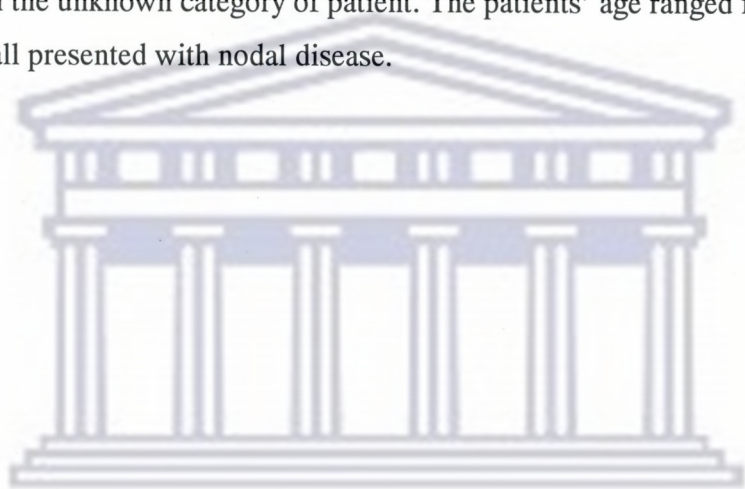
SLL is a low-grade neoplasm of small round monomorphic B-lymphocytes. The disease presents in patients with a mean age of 65 years. In the head and neck region, the disease is predominantly nodal. Fourteen cases (5%) of SLL were diagnosed, and all cases presented in the HIV negative or unknown category. The findings within our series, parallels that of the WHO clinical description in terms of nodal presentation. The age range of patients' was between 55 and 72 years.

Mantle cell lymphoma

Mantle cell lymphoma is a B-cell neoplasm that occurs in older individuals with a median age of 60 years. Lymph nodes and Waldeyer's ring are the most commonly involved head and neck sites²³.

Seven cases (3%) of mantle cell lymphoma were identified in our HNL series.

Although not documented by the WHO as a lymphoma presenting in AIDS patients, three cases were diagnosed in HIV positive individuals, two in HIV negative patients and, two in the unknown category of patient. The patients' age ranged from 40 to 62 years and all presented with nodal disease.



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Conclusion

Several studies have examined incidence trends in HIV-associated lymphomas in developed countries and the effects of antiretroviral therapy on these trends. Significant decreases have been noted in the incidence of these lymphomas, which may, in part be due to the effects of antiretroviral therapy slowing the progression of HIV disease.

The frequency of HNL at NHLS-Tygerberg has increased over the last five years. This trend parallels that seen in other developing countries such as Tanzania, Nigeria, Thailand and India. This increase is possibly due to an increase in the number of referrals to our center, an increase in the overall population of the Western Cape and an increase in the number of HIV positive patients in the general population of the Western Cape.

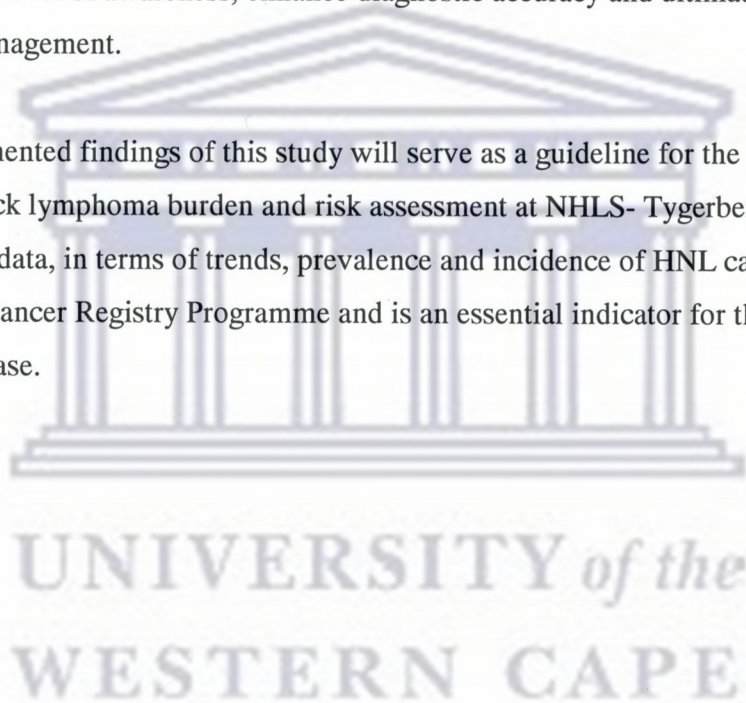
Social issues, such as poverty, lack of adequate education, female dependence on partners, rural communities and the non-availability of ARV's and HAART to most of the population that require these drugs, are considered major contributing factors. The largest number of HIV positive referrals, are from the Eastern Cape and Western Cape rural areas.

A trend is noted in the increased number of female patients diagnosed each year with HNL. A predominance of DLBCL was identified in our series. This is consistent with previous reports and studies on HNL. The number of biologically aggressive lymphomas, such as DLBCL, Plasmablastic and Burkitt's lymphomas diagnosed each year, has also significantly increased. These were prevalent mainly in the HIV positive group of patients who were also younger compared to the HIV negative patients.

A significant increase was also noted in the number of lymphomas with an EBV associated etiology. This is possibly due to the high incidence of EBV infection in developing countries which reflects poor socio-economic conditions leading to malnutrition induced immunological impairment

Many HNL, especially non-Hodgkin's lymphomas present in the oral cavity as tumor masses, ulcers, gingivitis and periodontitis. This study will hopefully raise the clinicians' level of awareness, enhance diagnostic accuracy and ultimately improve patient management.

The documented findings of this study will serve as a guideline for the estimation of head & neck lymphoma burden and risk assessment at NHLS- Tygerberg. Properly structured data, in terms of trends, prevalence and incidence of HNL can augment the National Cancer Registry Programme and is an essential indicator for the magnitude of the disease.

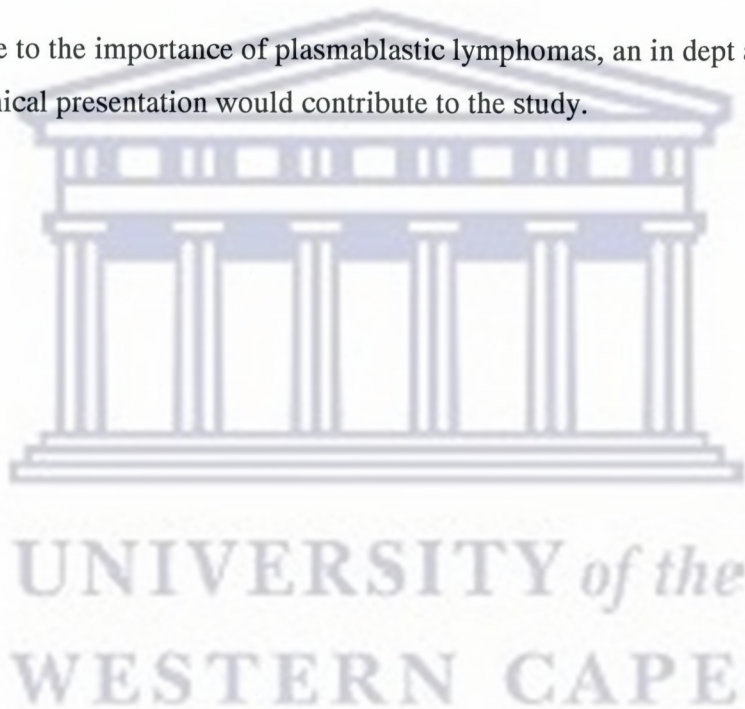


Recommendations

Further recommendation for future research:

1. Difficulty in ascertaining only a HIV positive and HIV negative group of patients was encountered due to lack of sufficient clinical information. Further studies of this nature should include clinicians, hence ensuring more comprehensive clinical input and data.
2. There is, as yet, no significant statistical data in terms of relationship between HIV infection and malignancies in the Western Cape. Larger, preferably multi-centre studies need to be carried out to ascertain the relationship between HIV infection and HNL in the Western Cape.
3. DLBCL cases should be reassessed. Most cases will conform to one of the morphological variants. Several recent studies show that immunophenotyping in patients with DLBCL was associated with particular clinicopathological features^{52, 53}.
4. The WHO describes PBL as a rare variant of DLBCL. Recent studies have described PBL as a distinct large cell lymphoma, with a unique immunoprofile. Cases previously diagnosed as DLBCL can be revisited and the PBL panel of immunohistochemical antibodies applied. This will enable us to separate PBL from cases previously diagnosed as DLBCL. The results would give a more accurate indication of the number of PBL at our center. Recognition of PBL as a distinct clinicopathologic entity will enhance management of patients with this aggressive malignancy.

5. Conflicting reports exist in terms of the role of dual infection of EBV and HHV8 in the pathogenesis of PBL^{33, 43, 54, 55}. A Tanzanian study negates the role of HHV8 in the pathogenesis of PBL³³. A European study shows a definite role of HHV8 in the aetiopathogenesis of solid lymphomas⁵⁴. The application of molecular techniques such as polymerase chain reaction (PCR) and in-situ hybridization (ISH) to cases of PBL at our center might negate or elicit an association with HHV8.
6. Due to the importance of plasmablastic lymphomas, an in dept analysis of clinical presentation would contribute to the study.



References

1. Singh B, Poluri A, Shaha AR. Head and neck manifestations of non-Hodgkin's lymphoma in human immunodeficiency virus-infected patients. *Am J Otolaryngol*. 2000 Jan-Feb;21(!):10-3
2. Francisco V, Pei L, Jeffrey M. Extranodal lymphomas of the head and neck. *Annals of Diagnostic Pathology*. 2005 9:340-350
3. Kemp S, Gallagher G, Kabani S, Noonan V. Oral non-Hodgkin's lymphoma. Review of the literature and World Health Organization classification with reference to 40 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007 Jun 27;(Epub ahead of print)
4. Leiggener CS, Kunz C. HIV-associated lymphoma- an unusual cause of pathological mandibular fracture. Case report and treatment options in immunodeficiency. *Mund Kiefer Gesichtschir*. 2005 9:48-52
5. Amusa YB, Olabanji JK, Akinpelu VO, Olateju SO. Pattern of head and neck malignant tumours in a Nigerian teaching hospital- a ten year review. *West Afr J Med*. 2004 Oct-Dec;23(4):280-5
6. Connolly C, Shisana O, Colvin M. Epidemiology of HIV in South Africa- results of a national, community-based survey. *A Afr Med J*. 2004 Sep;94(9):776-81
7. Mok JS, Pak MW, Chan KF. Oral malignancies in HIV disease: Changes in disease presentation, increasing understanding of molecular pathogenesis, and current management. *Oral surgery, Oral medicine, Oral pathology, Oral radiology and Endodontology*. 2005 Nov;100(5): 571-578
8. Rosenstiel DB, Carroll WR, Listinsky CM. MALT lymphoma presenting as a cystic salivary gland mass. *Head Neck*. 2001. Mar;23(3):254-258
9. Reichart PA, Khongkhunthian P, Bendick C. Oral manifestations in HIV-infected individuals from Thailand and Cambodia. *Med Microbiol Immunol*. 2003 Aug;192(3):157-60

10. Holmes H, Arendorf T. Are the oral manifestations associated with HIV infection really relevant to the practising South African dentist. *SADJ*. 1999 Dec;54(12):631-5
11. Cook MP, Newton R, Beral V, Burkitt's DP. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. *Br J Cancer*. 1998 Dec;78(11):1521-8
12. Adam M, Charles S, Ebert JR, Marc G. Precursor B-cell lymphoblastic lymphoma presenting as an isolated external ear swelling in a two-year old child. *Int J of Pediatric Otorhinolaryngology*. 2005 69:695-699
13. Gluth MB, Orvidas LJ. Bilateral cystic parotid masses and a hypopharyngeal mass: a case report and review of MALT lymphoma in the head and neck. *Am J of Otolaryngology*. 2005 26: 135-137
14. Ando M, Matsuzaki M, Murofushi T. MALT lymphoma presented as diffuse swelling of the parotid gland. *Head and Neck Medicine and Surgery*. 2005. 26:285-288
15. Sheahan P, Hafidh M, Toner M, Timon C. Unexpected findings in neck dissection for Squamous cell carcinoma: Incidence and implications. *Head Neck*. 2005. Jan;27(1):28-35
16. Ranganathan K, Hemalatha R. Oral lesions in HIV infection in developing countries: an overview. *Adv Dent Res*. 2006 Apr 1;19(1):63-8
17. Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of NHL: Trends, geographic distribution, and etiology. *Ann Hematol*. 2005 Jan;84(1):1-12
18. Wilkinson D, Abdool Karim SS, Williams B. High HIV incidence and prevalence among young women in rural South Africa: developing a cohort for intervention trails. *J Acquir Immune Defic Syndr*. 2000 Apr 15;23(5):405-9
19. Naidoo S, Chikte U. HIV/AIDS- the evolving pandemic and its impact on oral health in sub- Saharan Africa. *SADJ*. 1999 Dec;54(12):616-30

20. Asamoah-Odei E, Garcia C, Boerman JT. HIV prevalence and trends in sub-Saharan Africa: no decline and large subregional differences. *Lancet*. 2004 Jul 3-9;364(9428):35-40
21. Sitas F, Bezwoda WR, Levin V, Ruff P. Association between HIV type1 infection and cancer in the black population of South Africa. *Br J Cancer*. 1997;75(11):1704-7
22. Sitas F, Pacella-Norman R, Carrara h, Patel M. The spectrum of HIV-1 related cancers in South Africa. *Int J Cancer*. 2000 Nov 1;88(3):489-92
23. Tumors of Haematopoietic and Lymphoid Tissues. Pathology and Genetics. World health Organization Classification of Tumours. Edited by Elaine S. Jaffe, Nancy Lee Harris, Harald Stein, James W. Vardiman
24. Biggar RJ, Jaffe ES, Goedert JJ. Hodgkin's lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood*. 2006 Dec 1;108(12):3786-91
25. Tanaka PY, Pessoa VP, Pracchia LF. Hodgkin's lymphoma among patients infected with HIV in post-HAART era. *Clin Lymphoma Myeloma*. 2007 Mar;7(5):364-8
26. Lau C, Muula AS. HIV/AIDS in Sub-Saharan Africa. *Croat Med J*. 2004 Aug;45(4):402-14
27. De Clercq E. AIDS in the Third World: how to stop the HIV infection rates? *Verh K Acad Geneesk Belg*. 2007;69(2):65-80
28. Nov A. Update in HIV lymphoma. *Curr Opin Oncol*. 2006 Sep;18(5):449-55
29. Palmieri C, Treibel T, Large O, Bower M. AIDS-related non-Hodgkin's lymphoma in the first decade of highly active antiretroviral therapy. *QJM*. 2006 Dec;99(12):811-26
30. Barclay LR, Buskin SE, Kahle EM, Aboulaflia DM. Clinical and immunologic profile of AIDS-related lymphoma in the era of highly active antiretroviral therapy. *Clin Lymphoma Myeloma*. 2007 Jan;7(4):272-9
31. Wilson DP, Blower S. How far will we need to go to reach HIV-infected people in rural South Africa? *BMC Med*. 2007 Jun 19;5:16

32. Elango JK, Gangadharan P, Sumithra S, Kuriakose MA. Trends of head and neck cancers in urban and rural India. *Asian Pac J Cancer Prev*. 2006 Jan-Mar;7(1):108-12
33. Kaaya EE, Castanos-Velez E, Ekman M. AIDS and non AIDS-related malignant lymphoma in Tanzania. *African Health Sciences* 2006;6(2):69-75
34. Otoh EC, Johnson NW, Mandong BM, Danfillo IS. Primary head and neck cancers in Jos, Nigeria: a revisit. *West Afr J Med*. 2006 Apr-Jun;25(2):92-100
35. Tladi LS. Poverty and HIV/AIDS in South Africa: an empirical contribution. *SAHARA J*. 2006 May;3(1):369-81
36. Skinner D, Mfecane S. Stigma, discrimination and the implications for people living with HIV/AIDS in South Africa. *SAHARA J*. 2004 Nov;1(3):157-64
37. Kahn K, Tollman SM, Collinson MA, Clark SJ. Research into health, population and social transitions in rural South Africa: data and methods of the Agincourt Health and Demographic Surveillance System. *Scand J Public Health Suppl*. 2007 Aug;69:8-20
38. Rudolph MJ, Ogunbodede EO, Mistry M. Management of the oral manifestations of HIV/AIDS by traditional healers and caregivers. *Curationis*. 2007 Mar;30(1):56-61
39. Reid A, Dediccoat M, Lalloo D, Gilks CF. Trends in adult medical admissions in a rural South African hospital between 1991 and 2002. *J Acquir Immune Defic Syndr*. 2005 Sep 1;40(1):53-6
40. Mehrotra R, Singh M, Gupta RK, Singh M, Kapoor AK. Trends of prevalence and pathological spectrum of head and neck cancers in North India. *Indian J Cancer*. 2005 Apr-Jun;42(2):89-93
41. Carbone A. Emerging pathways in the development of AIDS-related lymphomas. *The Lancet Oncology*. 2003 Jan;4(1): 22–29
42. Iamaroon A, Pongsiriwet S, Mahanupab P. Oral non-Hodgkin's lymphomas: studies of EBV and p53 expression. *Oral Dis*. 2003 Jan;9(1):14-8
43. Ferrazzo KL, Mesquita RA, Aburad AT, Nunes FD. EBV detection in HIV-related oral plasmablastic lymphoma. *Oral Dis*. 2007 Nov; 13(6):564-9

44. Folk GS, Abbondanzo SL, Childers EL. Plasmablastic lymphoma: a clinicopathologic correlation. *Annals of Diagnostic Pathology*. 2006;10:8-12
45. Tavora F, Gonzalez-Cuyler LF, Sun CJ. Extra-oral plasmablastic lymphoma: report of a case and review of literature. *Human Pathology*. 2006 Apr;37:1233-1236
46. Lin F, Zhang K, Quiery AT, Prichard J. *Arch Pathol Lab Med*. 2004 May;128:581-84
47. Liang CW, Li HY, Chang KP, Chen CK, Chen YL. HIV infection initially presenting as sinonasal Burkitt's lymphoma. *Am J Otolaryngol*. 2006 Nov-Dec;27(6):433-5
48. Feinberg SM, Ou SH, Gu M, Shibuya TY. Burkitt's lymphoma of the base of the tongue: a case report and review of the literature. *Ear Nose Throat J*. 2007 Jun;86(6):356-60
49. Arzoo KK, Bu X, Espina BM, Seneviratne L, Nathwani B, Levine AM. T-cell lymphoma in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004 Aug 15;36(5) :1020-7
50. Biggar RJ, Engels EA, Frisch M, Goedert JJ. Risk of T-cell lymphomas in persons with AIDS. *J Acquir Immune Defic Syndr*. 2001 Apr 1;26(4) :371-6
51. Piira TA, Ries K, Kjeldsberg CR, Perkins SL. Anaplastic large-cell lymphoma presenting primarily in bone in a patient with AIDS. *Hematol Pathol*. 1994;8(3):111-6
52. Colomo L, Perales M, Rives S, Martinez A, Bosch F. Clinical impact of the differentiation profile assessed by immunophenotyping in patients with DLBCL. *Blood*. 2003 Jan 1;101(1):78-84
53. Hoffmann C, Tiemann M, Schrader C, Janssen D, Wolf E. AIDS-related B-cell lymphoma (ARL): correlation of prognosis with differentiation profiles assessed by immunophenotyping. *Blood*. 2005 Sep 1;106(5):1762-9
54. Carbone A, Gloghini A. AIDS-related lymphomas: from pathogenesis to pathology. *Br J Haematol*. 2005 Sep 5;130:662-670

55. Dong HY, Scadden DT, deLeval L, Tang Z. Plasmablastic lymphoma in HIV-Positive patients- An aggressive EBV associated Extramedullary Plasmacytic Neoplasm. *Am J Surg Pathol*. 2005 Dec 12;29: 1633-40
56. Naresh KN, Advani S, Adde M, Aziz z, Banavali S, Bhatia K. Belgaumi A, Ezzat A, Norton A. Report of an International Network of Cancer Treatment and Research workshop on NHL in developing countries. *Blood Cells Mol Dis*. 2004 N-v-Dec;33(3):330-7



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APPENDIX I

Format of Data capture table

Year of Diagnosis	Case no.	Referral centre	Age	Gender	HIV status	Diagnoses	Site	Nodal or Extranodal



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