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THE CHANGING PATTERN OF HODGKIN LYMPHOMA IN ADULTS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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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 Medicine (Internal Medicine)

Johannesburg, 2017

DECLARATION

I, David Turatsinze, declare that this research report is my own work. It is being submitted for the degree of MMed (Internal Medicine) to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Johannesburg, November 2017

……

David Turatsinze

ETHICS COMMITTEE APPROVAL

This research was approved by the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (clearance certificate number: **M130826**).

DEDICATION

To my wife, children, parents, relatives and friends.

ACKNOWLEDGEMENTS

I would like to thank Professor Moosa Patel, for all his support, encouragement, advice and assistance in the planning of this study, and for his excellent supervision throughout this study despite his busy daily activities.

Dr. Fatima Bibi Fazel, for her perfect and continuous assistance in this study.

My family, especially my wife Sandra and Children for their patience and taking over my share of domestic work and for their understanding during the many hours spent while working on this research report; and to anyone else that I may have forgotten.

The staff of the Clinical Haematology Unit, Department of Medicine at CHBAH and the patients whose records I reviewed in order to make this study possible.

ABSTRACT

Introduction

Hodgkin lymphoma (HL) is a malignancy of lymphoid cells that was first described by Thomas Hodgkin in 1832. It is recognized histologically by the presence of the characteristic Reed-Sternberg cells, bathed in a reactive cellular background of inflammatory cells. Hodgkin lymphoma is less common than Non-Hodgkin Lymphoma (NHL) and accounts for approximately 10-20 % of all the lymphomas encountered. It is most often seen in young adults, with a peak frequency in the third decade of life.

Hodgkin lymphoma is characterized by the orderly spread of disease from one lymph node group to another (contiguous spread and centripetal distribution) and by the development of systemic symptoms, particularly with advanced stage disease. True extra nodal disease is uncommon.

Pathologically, Hodgkin lymphoma is categorized into two groups: Nodular lymphocyte predominant Hodgkin lymphoma which accounts for about 5% and Classical Hodgkin lymphoma which accounts for 95%. Classical Hodgkin lymphoma is further subdivided into four subtypes: Nodular sclerosis classical Hodgkin lymphoma, Mixed cellularity classical Hodgkin lymphoma, Lymphocyte rich classical Hodgkin lymphoma and Lymphocyte depleted classical Hodgkin lymphoma.

Once the diagnosis is confirmed on a lymph node or tissue biopsy, a complete work up is done, which includes blood investigations, a bone marrow aspirate and biopsy and appropriate radiological investigations. Following on this, the treatment is individualized and includes both supportive care and specific therapy. The specific initial treatment of Hodgkin lymphoma involves combination chemotherapy and where necessary involved field radiotherapy. Cure is a realistic goal in more than 90% of patients with early stage disease. A delicate balance exists

between optimal initial treatment and the development of late complications of the disease, mainly related to treatment.

The last decade has witnessed the emergence of Hodgkin lymphoma occurring with increasing frequency in association with the Human Immunodeficiency virus (HIV) infection. The relative risk is 10-20 fold higher with HIV seropositivity, compared to the general population. HIV associated Hodgkin lymphoma is generally more aggressive, presents with advanced stage disease, frequent 'B' symptoms, less favorable histology, more frequent bone marrow involvement and overall a poorer prognosis compared to Hodgkin lymphoma in HIV seronegative individuals.

This study was aimed at exploring and defining the changing pattern of Hodgkin lymphoma at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2005 to December 2012. Other objectives were to review: (i) the impact of HIV on the clinical pattern of disease and (ii) the different treatment options and the outcome of the patients.

Patients and Methods

This was a retrospective review of all adult patients with Hodgkin lymphoma seen at the Clinical Hematology Unit, Department of Medicine from January 2005 to December 2012 at CHBAH. Descriptive analysis was conducted through the computation of frequency tables for categorical variables and appropriate measures of central tendency i.e. mean ± SD/median (IQR) for continuous variables. Kaplan Meier survival curves were plotted to determine the survival probability of the patients based on demographic and clinical characteristics.

Results

A total of 150 patients with a confirmed diagnosis were included in the study. Ninety three percent of the patients were of black ethnicity. There were 84 males (56%) and 66 females (44%), with a male to female ratio of 1.27:1. The median age of the patients was 37 years, with a peak frequency in the third and fourth decades of life. HIV seropositivity was noted in 90 patients (60%), with the remaining 60 patients (40%) being seronegative. For the whole group of 150 patients, lymphadenopathy was the most common presenting feature (92.7%). 'B' symptoms were present in 74.7% of the patients. Advanced stage disease was noted in 74% of the patients and a performance status of ≥2 was evident in 66.7% of the patients.

A comparison of the HIV seropositive and HIV seronegative patients shows that there is a statistically significant difference between the histological subtypes (mixed cellularity with HIV seropositivity and nodular sclerosis with HIV seronegativity), TB association (higher with HIV seropositivity) and more bone marrow involvement with HIV seropositivity. However, the median survival was shorter in HIV seropositive compared to HIV seronegative individuals.

Conclusion

As compared to the current literature on Hodgkin lymphoma (particularly from the developed world), our study showed a high prevalence of HIV and TB, in association with Hodgkin lymphoma. There is a paradigm shift at our institution, from an early period in the 1980's with no HIV seropositivity in association with HL, to <50% in the 1990's and early 2000's, to > 50% in the last decade. The association between HIV and HL has an impact on the clinical presentation and outcome of the patients. Therefore, health care workers need to be aware of this emerging and increasing association between HIV and Hodgkin lymphoma.

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LIST OF ABBREVIATIONS

ABVD	Doxorubicin (Adriamycin), Bleomycin, Vinblastine, Dacarbazine
AIDS	Acquired immune deficiency syndrome
AIHA	Auto immune haemolytic anaemia
ALT	Alanine transaminase
ASCT	Autologous stem cell transplantation
AST	Aspartate transaminase
BCL-2	B-cell lymphoma 2
BCNU	Bis-chloroethylnitrosourea
BEACOPP	Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin /Vincristine, Procarbazine, prednisolone
CCF	Congestive Cardiac Failure
CD	Cluster of differentiation
CHBAH	Chris Hani Baragwanath Academic Hospital
CHL	Classical Hodgkin lymphoma
CR	Complete Remission
CT scan	Computed tomography scan
CTD	Connective tissue disease
CXR	Chest X-ray
DFS	Disease Free survival
DLBCL	Diffuse large B-cell lymphoma
DXT	Deep X-ray Therapy (Radiotherapy)

EBV	Epstein - Barr virus
ECOG	Eastern Cooperative Oncology Group
EFRT	Extended- field Radiation Therapy
EORTC	European Organisation for Research and Treatment of Cancer
ESHARP	Etoposide, Solumedrol, High dose Ara-cytarabine, Rituximab, Platinol
ESMO	European Society for Medical Oncology
ESR	Erythrocyte Sedimentation rate
ETC	And so on
FGD	Fluorodeoxyglucose
FNA	Fine Needle Aspiration
GBS	Guillain-Barre Syndrome
GSHG	German Hodgkin Lymphoma Study Group
HAART	Highly Active Antiretroviral Therapy
HDCT	High- Dose Chemotherapy
HIV	Human Immunodeficiency Syndrome
HL	Hodgkin Lymphoma
HLA	Human Leukocyte Antigen
H-RS	Hodgkin Reed-Sternberg cell
HRT	Hormone Replacement Therapy
IFRT	Involved-field Radiation therapy
IkB	Inhibitor of kappa kinase B
IPS	International Prognostic Score
ISRT	Involved Site Radiation Therapy
L&H	Lymphocytic and Histiocytic cells

LDcHL	Lymphocyte -depleted classical Hodgkin lymphoma
LMP-1	Latent Membrane Potential 1
LRcHL	Lymphocyte- rich classical Hodgkin lymphoma
LVD	Left Ventricular Dysfunction
MCcHL	Mixed cellularity classical Hodgkin lymphoma
MMR	Mediastinal Mass Ratio
MOPP	Mustargen/mechlorethamine, Oncovin, Procarbazine, Prednisone
NCCN	National Comprehensive Cancer Network
NF-k	Nuclear transcription factor-k
NF-kB	Nuclear factor kappa B
NHL	Non-Hodgkin lymphoma
NLPHL	Nodular lymphocyte- predominant Hodgkin Lymphoma
NS-1	Nodular sclerosis 1
NS-2	Nodular sclerosis 2
NScHL	Nodular sclerosis classical Hodgkin Lymphoma
OCT-2	Octamer Transcription Factor-2
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
RA	Rheumatoid Arthritis
RSC	Reed-Sternberg cell
REAL	Revised European American Lymphoma
RIC	Reduced Intensity Conditioning
RT	Radiotherapy
SCT	Stem Cell Transplant

SLE	Systematic Lupus Erythematous
TB	Tuberculosis
USA	United States of America
WHO	World Health Organisation

1.0 CHAPTER ONE: LITERATURE REVIEW

1.1 INTRODUCTION

Hodgkin Lymphoma (HL) is a malignancy of lymphoid cells that was first described by Thomas Hodgkin and Samuel Wilks in 1832 (1). Three autopsy specimens from the initial suspected seven cases of Hodgkin Lymphoma (HL) were preserved in alcohol until 1998, when Poston proved that two of the three preserved cases were confirmed cases of Hodgkin Lymphoma (HL) as evidenced by the presence of the classic Reed-Sternberg (RS) cells and its associated marker, CD15 (2, 3). Hodgkin Lymphoma (HL) was referred to as lymphogranulomatosis and Hodgkin's disease. However, with the presence of Reed-Sternberg (RS) cells which are of lymphoid origin and are now known to be clonal, the preferred term is Hodgkin Lymphoma (1).

1.1.1 PATHOGENESIS OF HODGKIN LYMPHOMA

Hodgkin Lymphoma (HL) was first described in 1832. However, it was not until recently that its pathogenesis has become better understood. Diagnostic techniques such as immunophenotyping, cytogenetic and molecular profiling have provided new insights into the pathogenesis of Hodgkin Lymphoma (HL). Hodgkin-Reed-Sternberg (H-RS) cells are the diagnostic tumour cells in classic Hodgkin Lymphoma (cHL) and are of B-cell origin (4, 5). Hodgkin-Reed-Sternberg (H-RS) cells are derived from the germinal centre and have clonally rearranged but "crippled" immunoglobulin genes. The cells have lost their capacity to express a high-affinity B-cell receptor and escape negative selection (4, 5).

Several aberrantly activated signalling pathways and transcription factors have been identified that contribute to the rescue of Hodgkin-Reed-Sternberg (HR-S) cells from natural apoptosis. It is

believed that execution of apoptosis is prevented in germinal centre B cells by up-regulation of an inhibitor called c-FLIP (an inhibitor of FAS-mediated apoptosis). Also, high levels of the nuclear transcription factor-k– (NF-k) have been found in H-RS cells; these high NF-k levels may play a role in the pathogenesis by interfering with apoptosis. Epstein Barr virus (EBV) is linked to the development of HL because it is believed that EBV possesses a transforming ability that leads to NF-k activation in antigen-activated B cells (4, 5) .

1.1.2 CLASSIFICATION OF HODGKIN LYMPHOMA

The first histological classification of Lymphoma (including Hodgkin lymphoma) was described by Jackson and Parker in 1944. This was used until 1964 when it was replaced by the Lukes and Butler classification. The Lukes and Butler classification was later simplified at the Rye conference in 1965, and has been used for over 30 years due to its good clinical and pathological correlation. The Rye classification was based on histology and consists of four subtypes: mixed cellularity, nodular sclerosis, lymphocyte rich and lymphocyte depleted subtypes. However, the Rye classification was reviewed in the Revised European-American Lymphoma (REAL) classification in 1994. Hodgkin Lymphoma (HL) was then classified into two entities: 1) nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL), and 2) classical Hodgkin Lymphoma (cHL) which comprises four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte- depleted. Currently the REAL classification still applies and has been accepted and adopted by the World Health Organisation (WHO). Two additional sub- groups have been included in the WHO classification, (i) 'Unclassifiable HL' that is used to describe cases where biopsy material is insufficient, or when the diagnosis of HL is made from an extra nodal site only and (ii) 'Lymphomas with intermediate features between cHL and Diffuse Large B cell Lymphoma

(DLBCL)' - previously known as grey zone lymphomas. These lymphomas have morphologic and phenotypic features of both cHL and DLBCL (5-7).

Tab **Table 1.1: WHO classification of Hodgkin lymphoma**

-Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma 1. Nodular sclerosis classical Hodgkin lymphoma 2. Lymphocyte-rich classical Hodgkin lymphoma 3. Mixed cellularity classical Hodgkin lymphoma 4. Lymphocyte-depleted classical Hodgkin lymphoma

1.1.2.1 Nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) comprises about five percent of all HL's, however; there are variable estimates for the relative frequency of nodular lymphocyte-predominant Hodgkin lymphoma in the pediatric population, ranging from 5-10%. The relative frequency is higher for children younger than 10 years compared with children aged 10 to 19 years. Patients with nodular lymphocyte-predominant Hodgkin lymphoma generally present with localized, non-bulky disease that infrequently involves the mediastinum (8). A proportion of patients may also be asymptomatic.

Nodular lymphocyte-predominant Hodgkin lymphoma is characterized by molecular and immunophenotypic evidence of B-lineage differentiation with the following distinctive features:

- Nodular lymphocyte-predominant Hodgkin lymphoma is characterized by large cells with multilobed nuclei, referred to as “popcorn” cells. These cells express B-cell antigens, such as CD19, CD20, CD22, and CD79A, and are negative for CD15 and may or may not express CD30 (8).
- The OCT-2 and BOB.1 oncogenes are both expressed in nodular lymphocyte-predominant Hodgkin lymphoma; they are not expressed in the cells of patients with classical Hodgkin lymphoma (8).
- Reliable discrimination from non-Hodgkin lymphoma is problematic in diffuse subtypes with lymphocytic and histiocytic cells set against a diffuse background of reactive T-cells
- Nodular lymphocyte-predominant Hodgkin lymphoma can be difficult to distinguish from progressive transformation of germinal centers and/or T-cell-rich B-cell lymphoma (8).

Chemotherapy and/or radiation therapy produce excellent long-term progression-free survival and overall survival in patients with nodular lymphocyte-predominant Hodgkin lymphoma; however, late recurrences have been reported up to 10 years after initial therapy (8).

Deaths observed among individuals with nodular lymphocyte-predominant Hodgkin lymphoma are more frequently related to treatment complications and/or the development of subsequent neoplasms (including non-Hodgkin lymphoma), underscoring the importance of judicious use of chemotherapy and radiation therapy at initial presentation and after recurrent disease (8).

For patients with localised disease that has been fully excised, a "watch and wait" approach may be reasonable. Patients with localised disease also benefit from 20-30Gy of Involved field radiation therapy (IFRT), with the 10-year progression free survival (PFS) for stage I being 85% and 65% for stage II disease. Patients with more advanced disease are usually treated with combination chemotherapy similar to cHL. Rituximab is often added to Doxorubicin (Adriamycin), Bleomycin, Vinblastine, Dacarbazine (ABVD). A study of single agent Rituximab in patients with relapsed disease has shown an overall response rate of 94%. Trials to optimize chemotherapy (with Rituximab) are in progress (8).

1.1.2.2 Classical Hodgkin Lymphoma (cHL)

1.1.2.2.i Pathology of Classical Hodgkin Lymphoma

The characteristic Hodgkin and Reed-Sternberg (HRS) cells in cHL, and the lymphocytic and histiocytic (L and H) cells in NLPHL, account for only 1% to 5% of the entire tumour mass and grow in a unique tumour microenvironment composed of many different cell types, including T cells, B cells, macrophages, neutrophils, eosinophils, plasma cells, mast cells, and fibroblasts (3). RS cells contain at least two nuclei, with their nucleoli occupying more than 50% of the nuclear area. Mononuclear variants of the RS cell also make up the neoplastic cell population. These cells, known as Hodgkin cells, have the same phenotype as the RS cell. The HRS cells are usually of germinal centre B cell origin, but have lost their B cell programming by multiple mechanisms. Hence, their phenotypic expression is not that of a typical B cell. More than 98% of HRS cells express CD30. CD15 expression has been found in approximately 80% of patients with cHL. CD20 is less frequently expressed (9). HRS cells do not produce immunoglobulin.

Although the RS cell is said to be diagnostic of cHL, its presence is not exclusive to HL. Similar cells may be seen in reactive lesions like infectious mononucleosis, in some non-Hodgkin's lymphomas (B and T cell), carcinomas, sarcomas and melanomas (9). Hence the diagnosis of cHL has to be made on finding the neoplastic cells within an appropriate cellular background.

Classical Hodgkin lymphoma is divided into the following four subtypes:

- Lymphocyte-rich classical Hodgkin lymphoma.
- Nodular sclerosis classical Hodgkin lymphoma.
- Mixed-cellularity classical Hodgkin lymphoma.
- Lymphocyte-depleted classical Hodgkin lymphoma.

These subtypes are defined according to the number of Reed-Sternberg cells, characteristics of the inflammatory milieu, and the presence or absence of fibrosis.

Although this classification is mainly based on histopathology, taking into account differences in the composition of the reactive infiltrate and stroma, recent studies have demonstrated that these disease entities are biologically different, with different genomic alterations, gene-expression patterns, cytokine milieu, and clinical behaviour (10).

The epidemiology, clinical presentation, and prognosis of these subtypes are also different (10, 11), but these differences have not yet been translated into changes in the treatment approach, since the Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy regimen remains the mainstay for the treatment of all cHL subtypes.

1.1.2.2.ii Lymphocyte-rich classical Hodgkin lymphoma

Lymphocyte-rich classical Hodgkin lymphoma (LRcHL) may have a nodular appearance, but immunophenotypic analysis allows distinction between this form of Hodgkin lymphoma and

nodular lymphocyte-predominant Hodgkin lymphoma (12). Lymphocyte-rich classical Hodgkin lymphoma cells express CD15 and CD30, while nodular lymphocyte-predominant Hodgkin lymphoma almost never expresses CD15.

1.1.2.2.iii Nodular sclerosis classical Hodgkin lymphoma

Nodular sclerosis classical Hodgkin lymphoma (NScHL) affects young adults and is more common in females. It frequently involves the mediastinum, which comprises the tissues and organs of the chest excluding the lungs. It is less frequently associated with Epstein-Barr virus (EBV) infection and probably requires an intact immune system to develop. The incidence in HIV-positive patients appears to be less as the number of CD4+ lymphocytes declines (13). Several studies using gene-expression profiling and expression of surface markers have suggested a link between mediastinal NScHL and primary mediastinal B-cell lymphoma. In contrast, MCcHL and LDcHL have epidemiological and clinical features that are distinct from NScHL: they are more frequent in males, have a bimodal age distribution, are frequently associated with EBV and HIV infection, and normally spare the mediastinum. The prognosis for MCcHL and LDcHL is worse than for NScHL (2). LRcHL is characterized by older age at presentation, infrequent mediastinal involvement, and excellent prognosis (12) . NScHL is distinguished by the presence of fibrous or collagenous bands that divide the lymph node into nodules. In addition, a Reed-Sternberg cell variant called the lacunar cell may be present (clear area around the RS cell, due to a retraction staining artefact).

Some pathologists subdivide nodular sclerosis into two subgroups (NS-1 and NS-2) on the basis of the number of Reed-Sternberg cells present. Transforming growth factor-beta may be responsible for the fibrosis in the nodular sclerosis Hodgkin lymphoma subtype.

A study of over 600 patients with nodular sclerosis Hodgkin lymphoma from three different university hospitals in the United States showed that two haplotypes in the HLA class II region were identified (HLA-DQA1 and DQB1) , which correlated with 70% increased risk of developing nodular sclerosis Hodgkin lymphoma (8). Another haplotype (DRB1) was associated with a 60% decreased risk. It is hypothesized that these haplotypes result in atypical immune responses that lead to Hodgkin lymphoma (8).

1.1.2.2.iv Mixed-cellularity classical Hodgkin lymphoma

Mixed-cellularity classical Hodgkin lymphoma (MCcHL) is more common in young children than in adolescents and adults. MCcHL accounts for approximately 20% of cases in children younger than 10 years, but only 9% of older children and adolescents aged 10 to 19 years in the United States (12). It is however, the most common subtype in patients with HL in developing countries. Reed-Sternberg cells are frequent in a background of abundant normal reactive cells (lymphocytes, plasma cells, eosinophils, and histiocytes). Interleukin-5 may be responsible for the eosinophilia in mixed-cellularity Hodgkin lymphoma. This subtype can be confused with non-Hodgkin lymphoma. Mixed-cellularity Hodgkin lymphoma is more common in patients with Human immunodeficiency virus (HIV) infection (10, 14).

1.1.2.2.v Lymphocyte-depleted classical Hodgkin lymphoma

Lymphocyte-depleted classical Hodgkin lymphoma (LDcHL) is rare in children but appears to be common in adults with HIV (although much less common than MCcHL and NScHL). This subtype is the rarest variant and is characterized by the presence of numerous large, bizarre malignant cells, many Reed-Sternberg cells, and few lymphocytes. Diffuse fibrosis and necrosis are common.

Many cases previously diagnosed as lymphocyte-depleted Hodgkin lymphoma are now recognized as diffuse large B-cell lymphoma, anaplastic large-cell lymphoma, or nodular sclerosis classical Hodgkin lymphoma with lymphocyte depletion It has the worst prognosis (8).

1.1.3 The Reed – Sternberg Cell

These are large cells (30 to 50 microns in diameter), and are either multinucleated or have a bilobed nucleus with prominent eosinophilic inclusion like nuclei. Reed Sternberg cells (HRS) are CD15 and CD30 positive, and are usually CD20 and CD 45 negative. HRS is capable of survival and unrestricted tumour growth. There are two factors which help the HRS neoplastic capacity: Apoptosis deregulation and constitutive NFkB activity. HRS also expresses C-FLIP which helps down regulate Fas and evades apoptosis. NFkB activity is enhanced by CD40 ligand and latent membrane potential (LMP-1) inhibitor of kappa kinase B (IkB). There may also be defects in IkB. The end result is activation of transcription factors that prevent apoptosis of HRS (14, 15).

1.1.4 The role of Epstein Barr Virus (EBV)

Epstein Barr Virus **(**EBV) has been implicated in the pathogenesis of HL with a frequency of 15 to 50% in the immunocompetent host. An association of EBV with HL is significant in immunocompetent patients with cHL and in HIV patients with HL. EBV has an integration rate of 20-80% into the HRS genome. The exact role of EBV in the pathogenesis of HL is unknown. However, LMP-1 has oncogenic potential by enhancing bcl 2 expression and by acting via the CD40 signalling pathway to evade apoptosis of HRS cells (16-18).

1.2 Epidemiology of Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a rare malignancy of the lymphatic system that affects the B-lymphocytes. Estimates suggest that around 1 in 25,000 people are affected by this malignancy every year and the condition accounts for less than 1% of all malignancies that occur worldwide.

Although HL can affect people of any age, it generally develops among two age groups: in particular, those aged between 15 and 35 years and those aged over 55 years. In the younger age group and in females, the nodular sclerosis subtype is more common, while people in the older age group are more commonly affected by the mixed cellularity subtype (19).

Hodgkin lymphoma (HL) is also more common among people with HIV infection, compared to the general population. In contrast to what is observed for the other forms of lymphoma associated with HIV, HL tends to develop among patients with HIV who have a higher CD4 T-cell count (19).

According to the American Cancer Society, estimates for the United States suggest that in 2014, around 9,190 new cases of HL were diagnosed, involving 4,120 females and 5,070 males.

Hodgkin lymphoma is one of the most curable malignancies, with the 1-year survival rate being in the range of 90% to 95% (19).

Hodgkin Lymphoma (HL) accounts for approximately 10% of all lymphomas. The pattern of age-specific incidence differs by geographic location and appears to parallel the level of industrial development:

- In economically advantaged countries, there is one peak in young adults (approximate age - 20 years) and one in adults of older age (approximate age - 65 years). However, the majority of patients are young adults.
- In economically disadvantaged areas; there is an initial peak in childhood for boys, relatively low rates in young adults, and a late peak in older adults (20, 21).

The predominant histologic subtype also differs by geographic location and economic advancement. In developed countries such as the US, nodular sclerosis classical HL (NScHL) is the predominant histologic subtype and accounts for most disease in young adults. In economically disadvantaged areas, mixed cellularity classical HL (MCcHL) is more frequent in children and older adults. Early industrialized or transitional economies tend to have roughly equal frequencies of the MCcHL and NScHL subtypes (20, 21).

In the US and Europe, the approximate percentage of classic HL cases from each subgroup are as follows (20).

- Nodular sclerosis classical HL (70 percent)
- Mixed cellularity classical HL (20 to 25 percent)
- Lymphocyte rich classical HL (5 percent)
- Lymphocyte depleted classical HL (less than 1 percent)

In a local study done at CHBAH, the proportions of histological subtypes found were as follows:

- Nodular sclerosis classical HL 37%
- Mixed cellularity classical HL 45%
- Lymphocyte rich classical HL 0%
- Lymphocyte depleted classical HL 0% (21).

Risk factors as shown by the above study include: Socioeconomic status and the environment, immunosuppression, autoimmune disorders and risk in family members (21).

1.3 Clinical features of Hodgkin Lymphoma

Hodgkin lymphoma (HL) can present in various ways with slight differences depending on the immune status, age, histological subtypes and geographical area (20-21).

Hodgkin lymphoma (HL) commonly presents with painless enlarging lymph nodes which may wax and wane. Approximately 90% of the lymph nodes are supradiaphragmatic lymph nodes, mostly in the cervical region (22-23).

Less commonly lymphadenopathy may present in sub diaphragmatic sites only (mostly in older patients). The pattern of disease spread is highly predictable, with contiguous spread to the centriaxial lymph nodes being typical. Therefore, mediastinal lymph nodes are commonly affected (23). There may also be infiltration of organs such as the liver, spleen, bone marrow and lungs. However, a patient may also present with local organ specific symptoms such as cough and bone pain as well as deranged laboratory tests or non-specific constitutional symptoms (23) .

In Hodgkin lymphoma (HL), up to one third of patients experience at least one constitutional symptom or 'B' symptom (22). Constitutional symptoms correlate with more advanced stage disease, bulky disease and poor prognosis. Constitutional symptoms include: weight loss of >10% body weight in the preceding six months, unexplained fever and drenching night sweats. The diagnosis of HL may be challenging due to the fact that some patients may present with constitutional symptoms only, for which there is a broad differential diagnosis. Non-specific symptoms include pruritis and alcohol induced lymph node pain. Pruritis has been described in up to 30% of patients with HL (3).

There are two types of extra nodal involvement by HL. These include: 1) Direct local extension from involved lymph nodes or via adjacent lymphatics, which is common e.g. involvement of adjacent pleura, pericardium, skin etc. and 2) Distant extra nodal spread, usually to four main organs: the bone marrow, liver, lung and bone. Distant involvement of extra nodal sites such as the brain and gastrointestinal tract is extremely unusual and the diagnosis should be confirmed with tissue biopsy in such cases. Even in HIV positive individuals with HL, true extra nodal disease (excluding liver, spleen and bone marrow) is most uncommon.

Autoimmune cytopaenias and paraneoplastic manifestations are infrequently associated with HL (24). Autoimmune haemolytic anaemia and autoimmune thrombocytopenia, if found to be associated with HL, usually resolve on treatment of HL (25). Paraneoplastic neurological manifestations include cerebellar disease, sub-acute myelopathy, motor neuropathies, Guillain-Barre syndrome and limbic encephalitis. Treatment of HL usually arrests progression of, and occasionally improves the neurology (24). Paraneoplastic renal involvement usually manifests as glomerulonephritis, which can be of many types, such as minimal change, membranous or membranoproliferative glomerulonephritis (26). It may manifest clinically as nephrotic syndrome, and may precede the onset of HL by months to years (26).

Skin manifestations of HL may be seen in 13-50% of patients (27-29). Most eruptions are non-specific and can resemble conditions such as dermatomyositis and ichthyosis. Actual skin involvement by HL has been reported to in 0.5-7.5% of patients (27). Spread is usually retrograde from involved lymph nodes, and can be described as papules, infiltrations/plaques, nodules/tumours; ulcerative lesions and erythroderma. It may mimic infections like scrofuloderma and herpes zoster. Direct skin involvement by HL is usually a feature of advanced disease and may imply a poorer prognosis (27) .

Other abnormalities associated with HL include: hepatitis, cholangitis, vasculitis, hypercalcaemia, hypoglycaemia, coagulopathies and haemophagocytosis (30).

1.4 Diagnosis of Hodgkin Lymphoma

Hodgkin lymphoma (HL) requires histology for the identification of characteristic tumour cells (HRS or LP cells) within an appropriate reactive cellular background. Thus a complete excision biopsy of a lymph node is necessary so that the sparce tumour cells are not missed and the lymph node architecture can be appreciated (3). However, if the biopsy is from an extranodal site, the diagnosis may be challenging.

There have been diagnostic errors in pathological classifications reported in some studies where NHL may be incorrectly diagnosed as HL in about 3-13% of cases. There has also been inter-observer variation of up to 8% in the classification of HL by an expert panel (3).

The use of cytology and fine needle aspiration (FNA) to diagnose HL has been shown to have a high false negative rate of 15-40% (3). Hence, FNA is not reliable for the diagnosis of HL. However, occasionally a tissue biopsy sample is not technically possible or may be invasive, and then the clinician may diagnose HL, based on the FNA. More recently, there are improvements in flow cytometry methods, specific for the detection of HRS cells, such as nine colour essays and gating methods to include HRS cells, as reported by Fromm, et al (31). NLPHL will still not be able to be detected in this manner (31).

1.5 Staging and investigation of Hodgkin Lymphoma

The Ann Arbor classification and the Cotswolds modification of the Ann Arbor staging for describing the stage of HL at the initial presentation has formed the basis upon which treatment

and prognosis is selected and has allowed comparison of results achieved by different investigators for almost 2 decades (32-35). This classification including the Cotswolds modification of the Ann Arbor staging system is still maintained as the standard classification for HL.Computed tomography scan (CT) is the usual technique for evaluating intrathoracic and infradiagramatic lymph nodes and importantly also the involvement of the spleen and liver with evidence of focal defects (35). Computed tomography scan (CT) also allows for the assessment of bulk disease, which is defined as mediastinal adenopathy/mass which occupies more than one third of the transthoracic diameter or a peripheral mass of more than or equal to 10cm in diameter. It also differentiates extranodal disease that is due to contiguous spread from distant extranodal involvement (35).

A thorough history is necessary to determine the presence or absence of 'B' symptoms, performance status (PS) of the patient assessed using the Eastern Cooperative Oncology Group (ECOG) grading system (See Appendix C), pruritis and other presenting characteristics.

A chest x-ray is also useful, but the mandatory test is the CT scan of the neck, thorax, abdomen and pelvis. A bone marrow trephine biopsy may indicate bone marrow involvement but opinions from different authors indicate that where a PET-CT scan is performed, the bone marrow biopsy may not be necessary in early stages of HL (stage 1A or 2A) with no adverse risk factors as the probability of a positive bone marrow biopsy in these stages is very low (less than 15%) (33-36).

With the increasing use of the PET scan with fluro-deoxyglucose (FDG-PET), with CT as part of the initial staging to serve as a baseline for comparison to assess treatment response, one would ask if PET/CT scan has now replaced a bone marrow biopsy (35). A meta-analysis by Pako et al. showed a sensitivity of 70% for FDG-PET, while the combination (i.e. PET/CT scan) showed a

sensitivity of 85.7% and indicated that only 1.1% of bone marrow involvement would be missed if bone marrow biopsy was omitted (33-36).

A study by Schaefer et al. which included patients with HL and NHL showed that 42% of patients were upstaged with PET/CT compared to conventional staging when bone marrow was assessed. However, only in 14% of these (seven patients) did the stage change from limited stage to advanced disease, thus potentially warranting a change of therapy (37). Other helpful tests would be the Full blood count with a differential count, blood urea and electrolytes, liver function tests, serum calcium, uric acid, lactate dehydrogenase levels, T cell subsets, immunoglobulin levels and in the appropriate setting HIV serology.

1.5.1 The role of PET/CT scanning in the staging of Hodgkin Lymphoma

The use of FDG-PET in the initial staging of HL is gaining importance and favour in many parts of the world. PET/CT is more sensitive than conventional CT scanning; picking up 25-30% more disease than CT (38,39). However, this may upstage a patient and lead to overtreatment and additional related toxicity. With early stage disease on conventional CT scan only, cure rates are > 95%. Patients with advanced stage disease on conventional CT imaging will get more intensive systemic chemotherapy anyway. Thus the role of PET/CT in initial staging is particularly useful where treatment can be modified by doing an interim scan at 2- 4 months post treatment (38-41).

1.6 Management of Hodgkin Lymphoma

The current advanced and modern treatment of HL has resulted in very good outcomes and cure rates, making long term complications of chemo-radiotherapy a reality and an important consideration as part of disease management. However, there is a still a small proportion of patients

who have primary refractory disease (5-10%) or relapse after a complete response (10-30%), despite the overall high cure rates of 70-85% (38).

Treatment of HL should aim at minimizing long term toxicities and achieving optimal cure rates and survival.

1.6.1 Risk stratification of Hodgkin Lymphoma

Based on the clinical scenario, staging, and degree of end-organ damage, patients with HL are categorised into the following three groups, according to the National Comprehensive Cancer Network (NCCN):

- Early- stage favourable
- Early - stage unfavourable
- Advanced stage (8, 39)

The National Comprehensive Cancer Network (NCCN) defines unfavourable factors for stage I-II as follows:

- Bulky mediastinal disease (mediastinal mass ratio [MMR; maximum width of mass/maximum intrathoracic diameter] greater than 0.33 or bulky disease greater than 10 cm.
- “ B symptoms ‘’
- Erythrocyte sedimentation rate (ESR) > 50mm/hr
- More than two- three nodal sites of disease (8).

Table 2: Unfavourable Risk Factors for stages I and II HL

Risk Factor	GSHG	EORTC/LSA
Age	-	Plus or equal 50yrs
Histology	-	MC or LD
ESR or B symptoms	< 50 mm/hr if A or >30 if B	<50mm/hr if A or >30 if B
Mediastinal mass	MMR > 0.33	MMR>0.35
Number of nodal sites	>2	>3
Extranodal lesions	Any	-

GSHG = German Hodgkin Lymphoma Study Group

EORTC= European Organization for Research and Treatment of Cancer

LD= Lymphocyte depletion

MD= Mixed cellularity

A= Absence of 'B' symptoms

B= Presence of 'B' symptoms

Patients with advanced disease are further risk stratified using the International Prognostic score (IPS), which includes the following risk factors (for scoring, each factor receives 1 point):

- Albumin < 40g/l
- Hemoglobin <10.5g/l
- Male gender
- Age ≥ 45 years
- Stage IV disease
- Leucocytosis: white blood cell count (WBC) > 15×10^9/l).
- Lymphopenia: lymphocyte count < 8% of WBC and or absolute lymphocyte count < 0.6×10^9/l) (8, 39, 40).

Based on the IPS score, patients with advanced disease can be categorized as follows:

- Good risk (IPS 0-1)
- Fair risk (IPS 2-3)
- Poor risk (IPS 4-7)

1.6.2 Management of classical Hodgkin lymphoma

Recommendations for primary treatment of classical Hodgkin lymphoma (cHL) vary by stage and risk stratification. Chemotherapy is followed by restaging with PET-CT (40-42).

1.6.2.1 Early-stage Favorable Disease (stage 1a and stage 11a)

Combined modality is the treatment of choice in patients with early-stage cHL. The National Comprehensive Cancer Network (NCCN) guidelines give the ABVD (doxorubicin [Adriamycin/bleomycin/vinblastine/dacarbazine) regimen a category 1 rating (i.e., the recommendation is based on high-level evidence and uniform NCCN consensus that the intervention is appropriate), but also list an 8-week Stanford V regimen (doxorubicin, vinblastine, mechlorethamine [or cyclophosphamide], etoposide, vincristine, bleomycin, and prednisone) as an alternative (8).

For early stage, favorable disease 2-4 cycles of ABVD is administered. Two cycles are suggested in highly selected patients with very favorable disease characterized by the following.

- No bulky disease
- No extra lymphatic involvement
- Fewer than three sites of disease
- Erythrocyte sedimentation rate (ESR) <30 mm/hr., or <50 mm/hr. in patients without B symptoms

- The European Society for Medical Oncology (ESMO) guidelines recommend two to three cycles of ABVD followed by involved-field radiation therapy (IFRT). ESMO recommends against interim PET-guided treatment outside of clinical trials (8).

1.6.2.2 Early-stage Unfavorable Disease

The NCCN supports the following treatments for stage I-II unfavorable (non-bulky) cHL (8).

- ABVD regimen for two cycles and additional ABVD cycles or ABVD with involved-field radiation therapy (ISRT), as warranted **or**
- Stanford V regimen for three cycles (12 weeks) (the regimen includes ISRT) **or**
- Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) regimen for two cycles with HRT.

NCCN recommendations for treatment of early-stage unfavorable (bulky) disease are as follows:

- ABVD for four cycles (category 1 recommendation) followed by HRT **or**
- Stanford V regimen for three cycles (12 weeks) **or**
- Escalated BEACOPP regimen for two cycles plus ABVD for two cycles plus ISRT

The ESMO guidelines recommend four cycles of ABVD with IFRT. In younger patients (≤60 years) a more intensive treatment can be considered, consisting of two cycles of escalated (8) BEACOPP followed by two cycles of ABVD with IFRT.

1.6.2.3 Advanced-stage Disease (1B, 2B, 3, 4 and bulky disease)

The NCCN supports the following treatments for stage III-IV, (non-bulky) cHL (8).

- ABVD for six cycles **or**
- In patients with an IPS <3, Stanford V regimen for three cycles (12 weeks) **or**

- In patients with an IPS ≥4, escalated BEACOPP regimen for six cycles
- For stage III-IV (bulky) cHL, the NCCN recommendations are the same as above, with the addition of ISRT to original sites of bulky disease

The ESMO guidelines recommend the following (9, 41)

- ABVD for six to eight cycles, followed by localized radiotherapy of residual lymphoma larger than 1.5 cm
- Escalated BEACOPP for six cycles, followed by localized radiotherapy of residual lymphoma larger than 2.5 cm

1.6.2.4 Refractory or Relapsed Disease

Both the NCCN and ESMO guidelines recommend high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) for refractory or relapsed disease. The selection of second-line chemotherapy is determined by comparison with the agents previously used. Brentuximab vedotin is recommended for patients who have a failure of autologous stem cell transplantation or failure of at least two prior multi-agent chemotherapy regimens (9, 41).

1.6.3 Management of the elderly patient with HL

With a second peak in the incidence of HL noted in patients over 60 years of age in developed countries, special consideration needs to be given to the management of HL in this sub-group. Elderly patients with HL tend to do worse than younger patients. Disease free survival (DFS) and Overall survival (OS) rates are about 20% lower than for young patients with HL. There are a few reasons for this. Older people have more co-morbid disease, such as cardiovascular and respiratory diseases. They tolerate cytotoxic chemotherapy less well, posing a challenge to administering

chemotherapy with a curative intent. Older patients present with more unfavorable risk factors as compared to young patients. It is hoped that new agents such as monoclonal antibodies, which are better tolerated, will provide a new ray of hope for the optimal management of the elderly patient with HL (42).

1.6.4 PET and CT scans after treatment

Position emission tomography/ Computerized tomography scans (PET/CT) (are very useful in assessing residual masses at the end of chemotherapy. Normally, patients with negative scans after treatment are assumed to be in complete remission (CR). Therefore, treatment can be stopped in this type of patient in CR, as more chemotherapy /radiotherapy has no benefit. However, about 25% of patients with residual disease / masses at the end of chemotherapy will have positive PET scans and they are treated with radiotherapy if localized or chemotherapy if generalized, followed by autologous stem cell transplantation in chemosensitive patients. False positive PET scans may occur in some patients. Results of current trials addressing this issue will hopefully clarify further management (32).

1.6.5 The role of stem cell transplantation in the management of Hodgkin lymphoma

High dose chemotherapy (HDCT) and Autologous Stem cell transplant (ASCT) is the standard treatment for patients in first relapse, although patients with localized disease at relapse may still benefit from radiotherapy. For patients with primary refractory disease, the outcome is not as promising after HDCT and ASCT as compared to patients with relapsed disease. However, these patients with primary refractory disease still have a 20-30% chance of cure with ASCT, after failing first and second line chemotherapy (43).

Position emission tomography/ Computerized tomography scans (PET/CT) do play a significant role prior to highly toxic therapy in patients considered for transplant. PET/CT scan can be used to assess the response to second line chemotherapy prior to HDCT and ASCT. A positive PET/CT scan before transplant is usually associated with higher relapse rates and poorer outcomes post ASCT. However, not all patients with a positive PET/CT scan will relapse post-transplant (7-56% of patients in studies do not relapse), and thus a positive scan should not be the reason for denying a patient HDCT and ASCT, which may be their only chance of cure (9).

For patients who relapse after ASCT, the possibility of an allogeneic stem cell transplant (allo - SCT) does exist. Myeloablative regimens are highly toxic and result in increased morbidity and high transplant-related mortality of 20%. According to transplant registry data, allo-SCT has not been superior to ASCT in terms of PFS and DFS, despite lower relapse rates (43). The increasing practice of reduced intensity conditioning (RIC) allo-SCT in the United Kingdom has been promising. When RIC allo-SCT was compared to myeloablative allo-SCT, RIC regimens were associated with lower transplant related mortality. The increased incidence of chronic graft versus host disease (GVHD) in RIC allo-SCT resulted in lower relapse rates, and was associated with an improved PFS and OS (43). The possibility of graft-versus Hodgkin effect in patients treated with RIC regimens also provides potential for donor lymphocyte infusions as a therapeutic option. The use of monoclonal antibodies and histone deacetylase inhibitors is being tested in clinical trials to assess their utility as maintenance therapy post ASCT to decrease relapse rates. If successful, these agents could potentially be used in allo-SCT as well (43).

1.6.6 New therapies in the management of Hodgkin Lymphoma

The development of novel, targeted therapies offers some hope in the management of HL in patients who are resistant to chemotherapy and who do not tolerate the toxicity of conventional regimens (44, 45).

1.6.6.1 Monoclonal Antibodies

Monoclonal antibodies to CD30 were previously disappointing due to low response rates and high toxicity. Current preparations are much more promising and better tolerated. Brentuximab vedotin is an antibody-drug conjugate, comprising of anti-CD30 chimeric monoclonal antibody, conjugated to an anti-tubulin, auristatin. In a phase II trial of 102 patients who failed ASCT, the overall response rate was 75% with 34% of patients achieving a CR. The response was durable, with a median duration of 47 weeks (46-47).

1.6.6.2 Rituximab

Rituximab is a chimeric monoclonal antibody to CD20 and has shown favorable responses in patients with relapsed and refractory NLPHL. Patients with cHL who had multiple relapses may also respond to rituximab. Patients with NLPHL who are treated with rituximab may relapse with a CD20 negative T cell-rich B cell NHL (48).

1.6.6.3 Histone deacetylase (HDAC) inhibitors

In a study in which Panobinostat was used, an overall response rate of 27% was seen in 129 patients who failed ASCT and the median Progression free survival (PFS) was 5.7 months (45).

1.6.6.4 Mammalian target of rapamycin (mTOR) inhibitors

Everolimus is an (mTOR) inhibitor. An overall response rate of 47% was seen in patients who had relapsed disease. Eight patients had a partial remission (PR), while one patient had a complete remission (CR), with four of these patients being free from progression at 12 months (49, 50).

1.6.7 Side effects of Hodgkin lymphoma treatment

Hodgkin lymphoma (HL) treatment toxicity is similar to other cancer treatments. This includes myelosuppression and other related side effects like neurotoxicity and direct organ toxicities from either chemotherapy and or radiotherapy.

Kaplan developed a concept of extended field radiotherapy (EFRT) in 1962 for the treatment of HL. This resulted in a five year survival improvement to 70% in patients with localized disease (49-51). In the 1970's, MOPP chemotherapy (mechlorethamine, oncovin, procarbazine, and prednisone) was used. In the 1980's, ABVD was introduced in patients that were resistant and refractory to MOPP, while stem cell transplantation remained another option (50).

Since most of the HL patients are young, improvements in therapy increased the cure rate to > 70-85% with early favorable disease. With higher cure rates and increased longevity, the late effects of treatment have become more apparent. These late side effects vary between individuals in relation to the time period post treatment, and modality of treatment received by the patients. Most importantly, patients must be informed of these side effects prior to treatment so that adequate follow up and screening post therapy is facilitated. These late effects include:

1.6.7.1 Second malignancies

Second malignancies are responsible for most of the morbidity and mortality of HL survivors. Most of these malignancies are caused by radiotherapy (RT). RT has a cumulative incidence of development of a second malignancy of 11% at 20 years and 26% at 30 years respectively (52,53). Solid organ tumors like lung cancer, non-melanoma skin cancer, breast cancer and colo-rectal cancer are the most common second malignancies. Less commonly, sarcomas and NHL may occur. Adolescent females are at greater risk for the development of breast cancer, especially those who have received mantle radiotherapy at doses greater than 30Gy (54). The above mentioned cancers have a median time of 14.3 years after treatment and the risk keeps rising with time (55). MOPP (mechlorethamine, oncovin, procarbazine, and prednisone) and BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, oncovin, procarbazine and prednisone) are combination therapies that contain alkylating agents and may be responsible for myelodysplasia and acute leukemia. These complications present at 10 years post therapy with a median latency of three years (54-55).

With the introduction of involved field radiotherapy (IFRT) and involved node radiotherapy (INRT), there has been a substantial reduction of radiation volumes to the organs like the lungs, breast tissue and the heart compared to patients who previously received mantle RT. The new standard of care for early stage disease is 20Gy of IFRT. This may result in reduced doses of radiation and consequently 80% of reduction of radiation dose to breast tissue compared with the previous mantle RT (53). Therefore, in patients who have been exposed to more than 30Gy to the abdomen, pelvis or spine, colo-rectal screening is very important and should start at the age of 35 or 15 years post treatment (54). Monthly breast examination and annual mammography are

recommended for patients at risk of breast cancer from the age of 25 years and eight years post therapy (54).

1.6.7.2 Thyroid disease

Radiotherapy (RT) damages the thyroid vasculature, and up to one third of patients may develop thyroid abnormalities, with hypothyroidism being the most common, although it may be subclinical. Other reported thyroid diseases are Grave's disease, multinodular goiter, thyroiditis, adenoma and carcinoma. Subclinical hypothyroidism must be treated with eltroxin in order to avoid over- stimulation of a gland that is at risk of malignancy. Patients should have annual thyroid function tests done and a palpable nodule needs to be investigated (52-55).

1.6.7.3 Cardiovascular disease

Hodgkin lymphoma (HL) associated cardiovascular disease may be due to the accelerated coronary effects normally caused by mediastinal RT, at doses of more than 35Gy and or anthracycline use with a cumulative risk of 5-10% at 15 years, 16% at 20 years and 34% at 30 years respectively (56, 57). Though the use of IFRT has reduced the risk of cardiovascular disease, it still carries a risk because it involves the superior one third of the heart and the coronary arteries are still in the radiation field.

Mantle RT causes atherosclerosis and left ventricular (LV) dysfunction. However, LV dysfunction with congestive cardiac failure (CCF) can be caused by anthracycline therapy where doses above the toxic limit have been administered (> 550mg/m2 of Adriamycin) and this is normally 1 year after treatment. Other cardiovascular effects include subclinical cardiomyopathy which usually

occurs in patients receiving less than toxic doses with a median follow up of eight years after therapy (56).

Mediastinal RT may cause cardiac valve dysfunction with a risk of 5% in 20 years. Accelerated atherosclerosis may occur in the carotid and subclavian arteries post RT, leading to an increased risk of stroke and transient ischemic attacks.

Risk factors like smoking and existing cardiovascular diseases have to be addressed prior to therapy and management initiated for existing cardiovascular diseases.

Therefore, screening is vital before and after treatment and includes an ECG, Echo sonography (echocardiography) and careful examination for cardiovascular abnormalities.

There is evidence that anti-failure treatment such as the angiotensin converting enzyme inhibitors and beta blockers like carvedilol may play an important role in asymptomatic left ventricular dysfunction, thus preventing progression to/of cardiomyopathy (58).

1.6.7.4 Infertility

The risk of developing premature ovarian failure and azoospermia is a major concern in long-term survivors treated for Hodgkin lymphoma. Alkylating agents such as cyclophosphamide and procarbazine cause prolonged azoospermia in 90–100% of men and premature ovarian failure in 5– 25% of women under the age of 30. The risk of infertility increases with the cumulative dose of alkylating agents and the risk is high after salvage therapy, including conditioning chemotherapy prior to autologous or allogeneic transplantation (57,58). The doxorubicin-bleomycin-vinblastine-dacarbazine regimen is associated with a lower risk of gonadal damage and the rate of infertility is less than 10%. The risk of premature ovarian failure is limited after the doxorubicin-bleomycin-vinblastine-dacarbazine regimen. However, age is an important factor;

women over 30 years of age are at much higher risk of ovarian failure (59). Semen cryopreservation should be routinely offered, especially before initial treatment with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone or salvage therapy with high-dose chemotherapy and autologous transplantation.

Pelvic RT and total body radiation is associated with gonadal damage. This results in ovarian failure leading to premature menopause. Therefore, screening with a thorough physical examination is very important, as is patient education and information on infertility, prior to therapy (59-61).

1.6.7.5 Other associated effects of HL treatment

Mediastinal RT and or use of bleomycin may cause pulmonary effects (such as pulmonary fibrosis, acute respiratory distress syndrome and interstitial pneumonitis). Pulmonary effects have also been reported in elderly patients on bleomycin, even with lower doses (62).

Other associated effects include fatigue, psychosocial problems such as anxiety, depression and post- traumatic stress disorder.

An increased infection risk exists in patients who have had prior splenectomy or splenic irradiation. These patients should receive the influenza vaccine yearly and patients who have had a splenectomy must receive additionally, booster pneumococcal and haemophilus influenza vaccination at appropriate time intervals.

1.7 Human immunodeficiency virus (HIV) and Hodgkin lymphoma

The above two mentioned pathologies present with a peak incidence in the 4th decade (14). With the current introduction of anti-retroviral drugs, HIV sero-positive patients have an improved

survival. HIV associated HL (HIV-HL) differs somewhat from HL in HIV negative patients in terms of incidence, pathology, clinical features, response to treatment and prognosis.

1.7.1 Epidemiology of HIV-HL

1.7.1.1 Incidence and epidemiology

Hodgkin lymphoma (HL) is a non AIDS defining cancer with an increased incidence in HIV positive patients compared to HIV negative patients. The relative risk is 10-20 fold increased with HIV seropositivity (14).

While AIDS- defining cancers like Non-Hodgkin's Lymphoma and Kaposi Sarcoma are decreasing in incidence with the advent of highly active anti-retroviral therapy (HAART), the incidence of non-AIDS defining cancers like HL is on the rise (63).

EBV is associated in almost all cases of HIV-HL due to the impaired immunity in HIV seropositive patients. The EBV latent membrane protein 1 (LMP-1) is found in tissue samples of HIV-HL. LMP1 is responsible for the constitutive NFκB expression that results in activation of signalling pathways for cell growth and decreased apoptosis (17).

1.7.1.2 Clinical Features of HIV-HL

Patients with HIV-HL commonly present with 'B' symptoms, advanced stage disease and more aggressive disease. Involvement of the bone marrow, liver and spleen are more common than in HIV seronegative HL (14).

A study from the Italian cooperative group on AIDS and Tumours (GICAT) showed that patients who were on antiretroviral drugs at the time of HL diagnosis, had B symptoms, were older, had a

higher hemoglobin level and had higher neutrophil counts indicating that antiretroviral drug exposure prior to the diagnosis of HL may somehow modify the clinical picture (64).

1.7.1.3 Pathology of HIV-HL

Patients Pre- HAART with HIV-HL were commonly of the mixed cellularity and lymphocyte depleted subtypes of classical HL. In the post- HAART era, this trend has continued but additionally with the nodular sclerosis subtype. However, mixed cellularity is still the most common histological subtype in HIV-HL (14, 64).

1.7.1.4 Management of HIV-HL

Management of HIV-HL is subdivided into supportive and specific treatment.

Supportive measures: This involves general supportive measures and antiretroviral therapy (analgesics, blood products, antibiotics, allopurinol, growth factors etc.).

Specific treatment: This includes combination chemotherapy regimens such as ABVD, EBVP, MOPP/ABVD hybrid and Stanford V. Remission rates and overall survival are generally lower than in patients with HIV seronegativity (14).

1.7.1.4.1 The benefits of antiretroviral drugs

Patients on antiretroviral therapy have shown less morbidity and higher remission rates associated with improved survival compared to patients not on antiretroviral therapy. Antiretroviral therapy allows for the delivery of standard doses of chemotherapy on time and the option of salvage therapy by autologous stem cell transplantation in relapsed patients with HIV-HL (63,64).

1.8 Tuberculosis and Hodgkin Lymphoma

Tuberculosis and HL have similar clinical features such as the presence of constitutional symptoms, lymphadenopathy, bone marrow infiltration and splenomegaly. Both conditions can coexist in the same patient. Lymph node and bone marrow samples may show evidence of both. Therefore, pathologists need to look carefully for HRS cells with characteristic staining properties and perform stains for Acid-fast bacilli, cultures of mycobacterium TB and in difficult cases, polymerase chain reaction (PCR) to identify TB organisms (65-67).

Tuberculosis in association with HL is common. A study by Kaplan et al. of 201 patients showed an increased incidence of TB in HL. The increased association is due to impaired cellular immunity that predisposes patients with HL to infections (65). Depressed immunity can also be due to chemotherapy, and may facilitate a reactivation of dormant TB bacilli and dissemination of infection. It is therefore imperative that clinicians and pathologists be aware of the close association between TB and HL, especially in areas where TB is endemic, thus ensuring prompt diagnosis of both conditions and timeous institution of appropriate therapy. More work needs to be done regarding interpretation of PET scans in patients with TB and malignancy as false positive results may occur in the presence of infections such as TB (66,67).

2.0 CHAPTER TWO: PATIENTS AND METHODS.

2.1 Study design

This is a retrospective review of all patients with a confirmed histological diagnosis of Hodgkin lymphoma seen at the adult Clinical Hematology Unit, Department of Medicine, CHBAH, from January 2005 to December 2012.

2.2 Study Population

Adult patients with a confirmed diagnosis of HL were admitted to the study with a cut-off age of 14 years and above as per the hospital admission criteria. Patients without histological confirmation of HL were excluded from the study.

2.3 Methods and Procedures

The data were collected using the data collection sheet as shown in Appendix A. Patients were identified using a study number with the name and hospital number being kept on a separate list/sheet. Demographic, clinical, laboratory – including histology, radiological and treatment parameters were recorded on all patients. Response to treatment, and prognostic factors influencing survival and outcome, were also documented. Data was collected on a data collection sheet, after each of the patient files were reviewed. Outcomes to be used for the Kaplan Meier curves were defined as patients who died or were lost to follow up. For the survival analysis, time to event (death/lost to follow up) was recorded using the data collection sheet.

2.4 Data entry and statistical analysis

Information from the patient's files was captured in a Microsoft Excel spread sheet database. The data was analysed by a Statistician. Frequencies of categorical variables were compared using a chi square test. Continuous variables were reported as mean ± standard deviation and differences between groups were compared using a student t-test or non-parametric test (Mann-Whitney) if not normally distributed.

Kaplan-Meier curves were used to determine whether prognostic variables were affecting survival and whether co-variates affected survival. The data was censored for patients lost to follow up. Kaplan Meier curves were used over cox regression as the main aim was to describe the survival rates of patients based on their prognostic variables. Age distribution between HIV positive and negative patients was compared using the non-parametric Wilcoxon rank-sum test. Frequencies of categorical variables such as gender, performance status, site of lymphadenopathy and B symptoms were compared using the Pearson chi square test. All statistical analysis was computed to a significance level of 5% (i.e. $p<0.05$).

3.0 CHAPTER THREE: RESULTS

A total of 167 patients with a confirmed diagnosis of HL were seen during the period 01/01/2005 to 31/12/2012. Seventeen patients were excluded due to incomplete or inadequate information. The remaining 150 patients were evaluable and formed the current study population.

3.2 Descriptive statistics: Frequencies

Table 1: Gender distribution

	Frequency	Percent	Valid Percent	Cumulative Percent
Female	66	44.0	44.0	44.0
Male	84	56.0	56.0	100.0
Total	150	100.0	100.0	

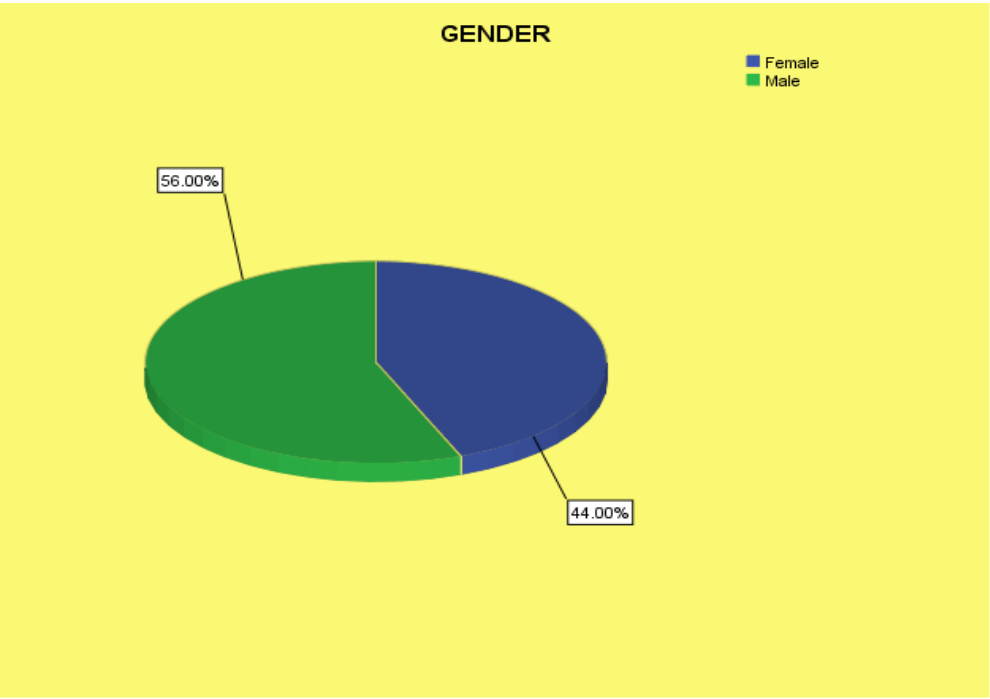

Figure 1: Gender distribution

Table 3 and figure 2 show the percentage breakdown of the distribution of the 150 patients who participated in the survey according to gender. There were 84 males (56%) and 66 females (44%). The male to female ratio was 1.27:1.

Table 2: Current occupation

	Frequency	**Percentage**	**Valid Percentage**	**Cumulative Percentage**
Unemployed	71	47.3	47.3	47.3
Factory workers	22	14.7	14.7	62.0
Scholars	16	10.7	10.7	72.7
Own Business	8	5.3	5.3	78.0
Security guard	6	4.0	4.0	82.0
Merchandiser	5	3.3	3.3	85.3
Hospitality industry	5	3.3	3.3	88.6
Prisoner	4	2.7	2.7	91.3
Pensioner	4	2.7	2.7	94.0
Not documented	4	2.7	2.7	96.7
Finance industry	3	2.0	2.0	98.7
Priest	1	0.7	0.7	99.3
Motor mechanic	1	0.7	0.7	100.0
Total	150	100	100	

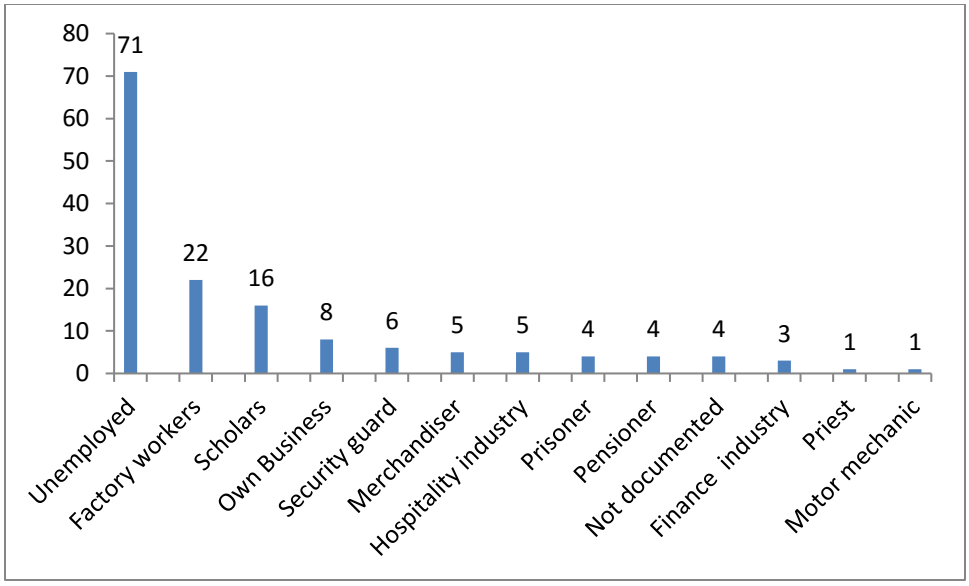

Figure 2: Current occupation

Table 4 and figure 2 above show the breakdown of the distribution of the 150 patients who participated in the survey according to current occupation. A significant number of patients were unemployed at the time of diagnosis of the Hodgkin lymphoma. The three most common occupations were: Factory workers 14.7%, Scholars 10.7% and Business owners (own business) 5.3%.

Table 3: Age distribution

	Frequency	Percentage	Valid Percentage	Cum (%)
10-20	27	18.0	18.0	18.0
21-30	43	28.7	28.7	46.7
31-40	47	31.3	31.3	78.0
> 40	33	22.0	22.0	100.0
Total	150	100.0	100.0	

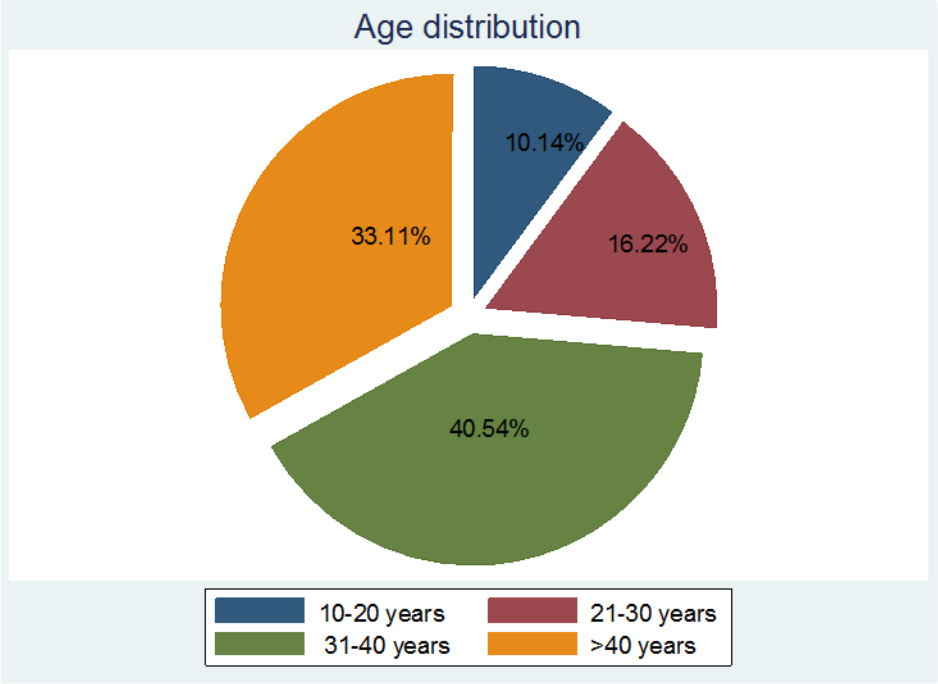

Figure 3: Age distribution

The above table and figure show the breakdown of the distribution of the 150 patients who were studied in the survey according to age. The peak frequency was in the fourth decade of life (31.33%). Mean, median and range are shown below in table 3.4 as being 36 years, 37 years and 15-78 years respectively.

Table 4: Descriptive age analysis

			Statistic	**Std. Error**
AGE	Mean		36.99	1.025
	95% Confidence Interval for	Lower Bound	34.97	
		Upper Bound	39.02	
	5% Trimmed Mean		36.38	
	Median		37.00	
	Variance		155.59	
	Std. Deviation		12.47	
	Minimum		15	
	Maximum		78	
	Range		15-78	
	Interquartile Range		14	
	Skewness		.653	.199
	Kurtosis		.975	.396

The table above gives the descriptive analysis of age as a continuous variable. The mean age of the patients was 36.99±12.47 years. The age range for the study participants was 15-78 years.

Table 5: Ethnic group distribution

	Frequency	Percent	Valid Percent	Cumulative Percent
Black	140	93.3	93.3	93.3
Coloured	6	4.0	4.0	97.3
Asian	3	2.0	2.0	99.3
White	1	0.7	0.7	100
Total	150	100	100	100

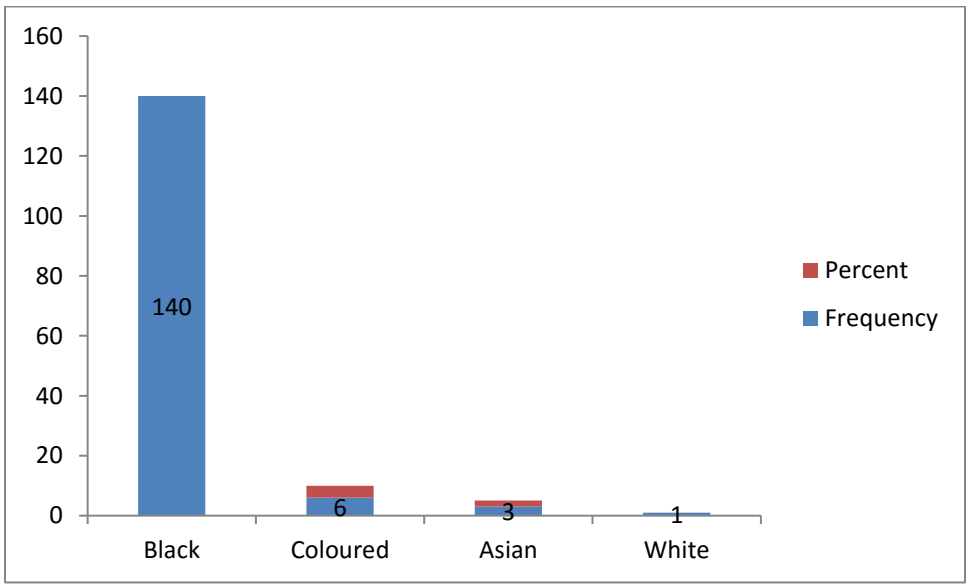

Figure 4: Ethnic group distribution

Table 7 and figure 4 show the breakdown of the distribution of the 150 patients who participated in the survey according to ethnic group. The vast majority of the patients were black (non-Caucasians), accounting for 93.3% of the total

Table 6: Performance status

	Frequency	Percent	Valid Percent	Cumulative Percent
0	26	17.3	17.3	17.3
1	24	16.0	16.0	33.3
2	22	14.7	14.7	48.0
3	48	32.0	32.0	80.0
4	30	20.0	20.0	100.0
Total	150	100.0	100.0	

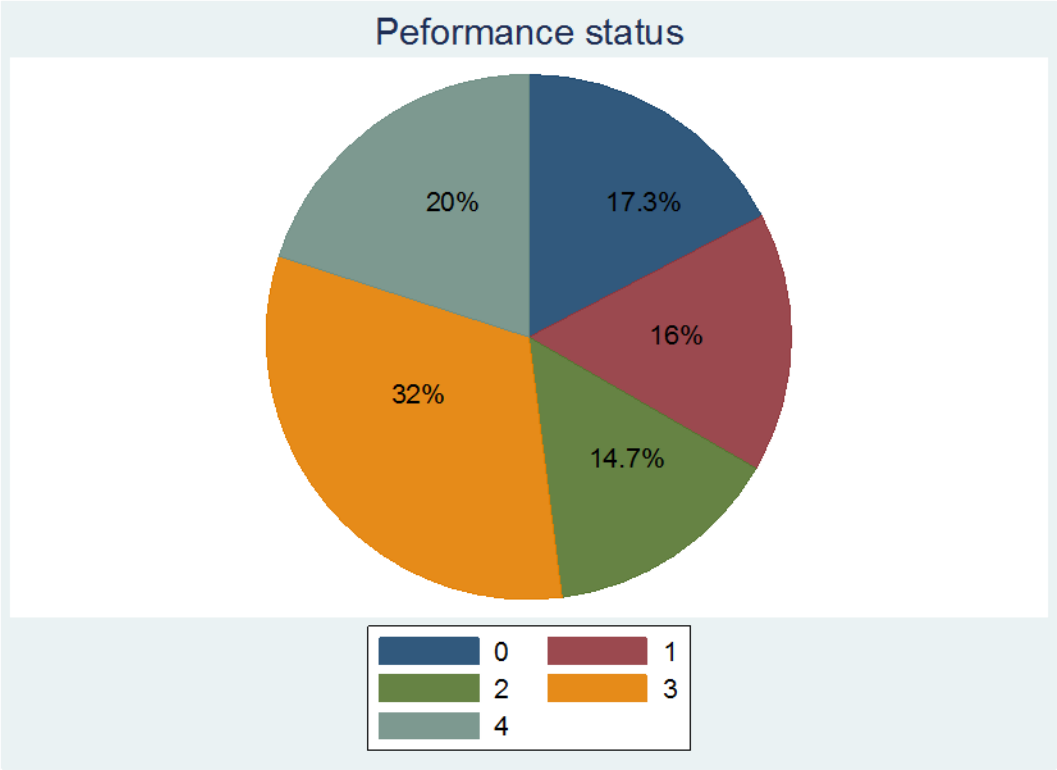

Figure 5: Performance status

Performance status (PS) was assessed using the Eastern Cooperative Oncology Group (ECOG) grading system (See Appendix C). Table 8 and figure 5 show that 48% of the patients had a performance status of ≤ 2, while 52% had a performance status of 3 or 4.

Table 7: 'B' symptoms

	Frequency	Percent	Valid Percent	Cumulative Percent
No	38	25.3	25.3	25.3
Yes	112	74.7	74.7	100.0
Total	150	100.0	100.0	

'B symptoms' include fever, night sweats and weight loss. One hundred and twelve patients (74.7%) had 'B' symptoms at presentation, while 41.3% of the patients did not present with 'B' symptoms.

Table 8: HIV status

	Frequency	Percent	Valid Percent	Cumulative Percent
Negative	60	40.0	40.0	40.0
Positive	90	60.0	60.0	100.0
Total	150	100.0	100.0	

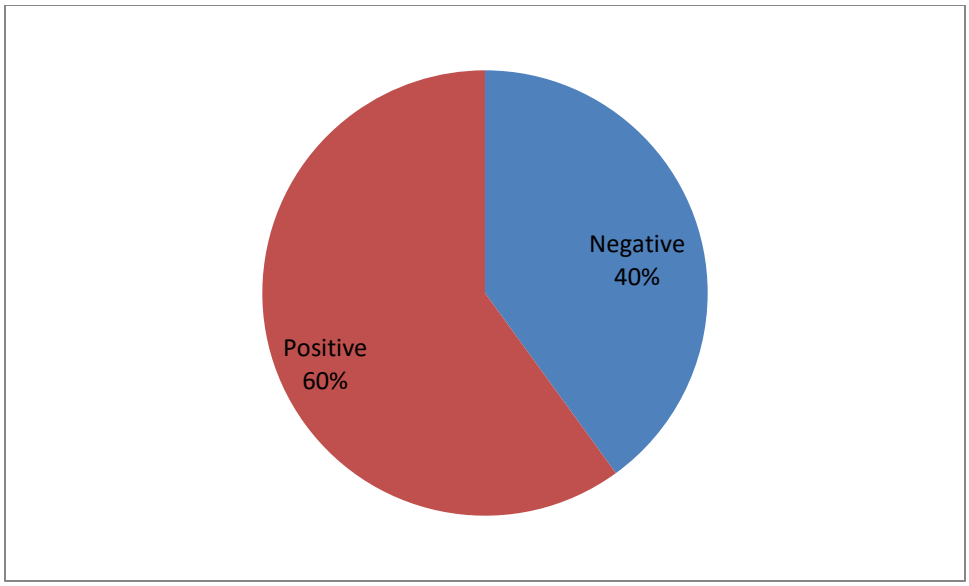

Figure 6: HIV status

The above diagram shows the distribution of the 150 patients with regard to HIV status. HIV positive patients accounted for 60.0% in comparison to 40% who were HIV negative.

Table 9: Comorbid disease excluding HIV and TB

	Frequency	Percent	Valid Percent	Cumulative Percent
No	102	68.0	68.0	68.0
Yes	48	32.0	32.0	100.0
Total	150	100.0	100.0	

Comorbid diseases included hypertension, diabetes, stroke and connective tissue diseases, such as SLE, and RA. As shown above, 32.0% had an underlying comorbid disease.

Table 10: Lymphadenopathy

	Frequency	Percent	Valid Percent	Cumulative Percent
No	11	7.3	7.3	7.3
Yes	139	92.7	92.7	100.0
Total	150	100.0	100.0	

The above table shows the breakdown of the distribution of the 150 patients who participated in the survey. Lymphadenopathy was present in 92.7% of the patients at presentation.

Table 11: Site of lymphadenopathy

	Frequency	Percent	Valid Percent	Cumulative Percent
Cervical only	30	21.5	21.5	21.5
Non-cervical	24	17.3	17.3	38.8
Cervical and Non cervical	85	61.2	61.2	100
Total	139	100	100	

The above table shows the site of lymphadenopathy at presentation. Cervical lymphadenopathy was present in 82.7% of the patients, while non-cervical sites only were involved 17.3% of the patients.

Table 12: Tuberculosis in association with HL

	Frequency	Percent	Valid Percent	Cumulative Percent
No	91	60.7	60.7	60.7
Yes	59	39.3	39.3	100.0
Total	150	100.0	100.0	

The above table shows the breakdown of the distribution of the 150 patients in regard to the association of Tuberculosis. Fifty-nine patients (39.3%) had an association of TB, compared to 60.7% with no association of TB.

Table 13: Diagnosis of Tuberculosis

	Frequency	Percent	Valid Percent	Cumulative Percent
Prior to lymphoma diagnosis	47	79.7	79.9	79.7
During lymphoma treatment	12	20.3	20.3	100
Total	59	100.0	100.0	

The above table shows the distribution of the 150 patients who had an association of Tuberculosis in relation to the time of the diagnosis of HL. Forty-seven patients (79.7%) had a diagnosis of TB made prior to lymphoma diagnosis whereas 20.3% were diagnosed after the lymphoma diagnosis while on treatment for lymphoma.

Table 14: Hepatomegaly and splenomegaly in HL

	Frequency	Percent	Valid Percent	Cumulative Percent
Liver only	32	46.4	46.4	46.4
Spleen only	07	10.1	10.1	56.5
Both Liver and Spleen	30	43.5	43.5	100
Total	69	100	100	

Both the liver and spleen were involved in 43.5% patients. Hepatomegaly only was present in 46.4% while splenomegaly only was evident in 10.1% of the patients.

Table 15: Bone marrow involvement

	Frequency	Percent	Valid Percent	Cumulative Percent
No	122	81.3	81.3	81.3
Yes	28	18.7	18.7	100.0
Total	150	100.0	100.0	

Bone marrow infiltration was present in 18.7% of the patients at presentation.

Table 16: Ann Arbor stage

	Frequency	Percent	Valid Percent	Cumulative Percent
1a	5	3.3	3.3	3.3
1b	6	4.0	4.0	7.3
2a	12	8.0	8.0	15.3
2b	16	10.7	10.7	26.0
3a	13	8.7	8.7	34.7
3b	18	12.0	12.0	46.7
4a	8	5.3	5.3	52.0
4b	72	48.0	48.0	100.0
Total	150	100.0	100.0	

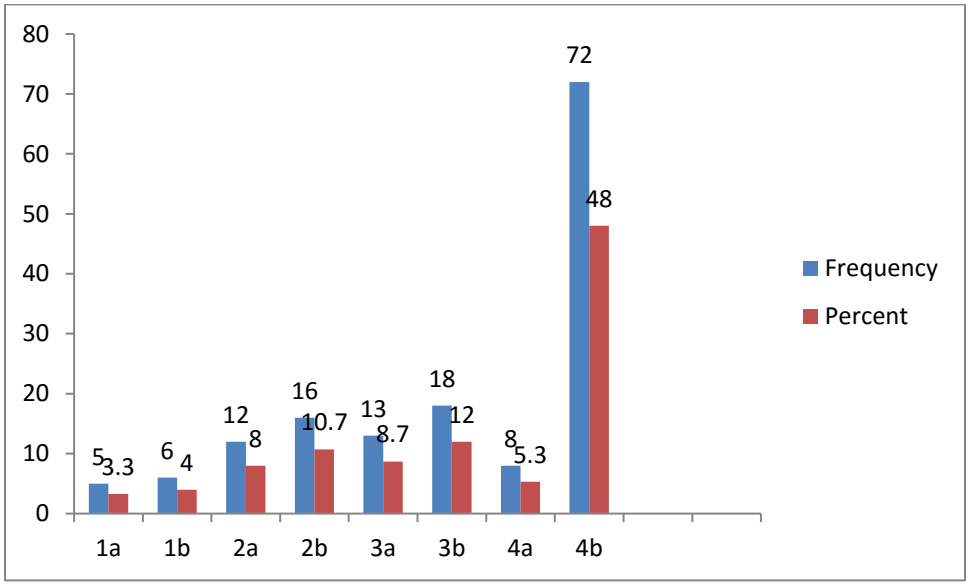

Figure 7: Ann Arbor stage

Table 18 and figure 7 shows the Ann Arbor stage of the patients at diagnosis. Over half of the patients had stage 4 disease (53.3%), while 20.7% of the patients presented with stage 3 disease. Stage 1 and 2 disease accounted for 7.3% and 18.7% of the patients respectively. 'B' symptoms were present in 74.7% of the patients.

Table 17: Chemotherapy

	Frequency	Percent	Valid Percent	Cumulative Percent
No	19	12.7	12.7	12.7
Yes	131	87.3	87.3	100.0
Total	150	100.0	100.0	

Of the 150 patients in the study, 87.3% received chemotherapy and 12.7% did not receive chemotherapy. All the patients who received chemotherapy received initial combination chemotherapy, most commonly with ABVD (Adriamycin, bleomycin, vinblastine, decarbazine) and prednisone.

Table 20: Treatment response after first line chemotherapy

Total number of patients who received > 2 cycles of chemotherapy	Achieved PR	Achieved CR	Defaulted/lost to follow up/unknown	Died
109	35	10	29	35

Table 21: Treatment response after ASCT

Total number of patients who received ASCT	Alive	Relapsed	Defaulted/lost to follow up	Died
10	**04**	**03**	**02**	**01**

Table 19 shows that 87.3% received chemotherapy and 12.7% died prior to receiving chemotherapy. The median number of cycles received was 7.5. Of the patients that received initial chemotherapy, 22 patients received less than 2 cycles of chemotherapy, 48 patients received 2 or more but less than 8 cycles of chemotherapy, and 61 patients received 8 or more cycles of chemotherapy.

Table 18: Disease outcome

	Frequency	Percent	Valid Percent	Cumulative Percent
Alive	48	32	32	32
Died	44	29.3	29.3	61.3
Defaulted	58	38.7	38.7	100.0
Total	150	100.0	100.0	

The above table shows the breakdown of the 150 patients with regard to outcome. Currently 48 patients (32%) are alive, 44 patients (29.3%), have died and 58 patients (38.7%) are lost to follow up /defaulted/could not be traced.

Table 19: Comparison of HIV negative with HIV positive patients

Characteristics	HIV positive N=90	HIV negative N=60	p-value
	N (%)	N (%)	
Age			
Mean (years)	37.8	35.8	0.0569
Age group			
<40 years	62 (70.45)	37 (61.67)	0.2647
>40 years	26 (29.55)	23 (38.33)	0.2647
Gender			
female	38 (42.22)	28 (46.67)	0.2849
male	52 (57.78)	32 (53.33)	0.2849
B symptoms			
present	70 (77.78)	42 (70.00)	0.3103
absent	20 (22.22)	18 (30.00)	0.3103
Histological subtypes			
Mixed cellularity	36 (40.00)	13 (21.67)	0.0190
Nodular sclerosis	21 (23.33)	28 (46.67)	0.0028
Lymphocyte rich	2 (2.22)	2 (3.33)	0.6790
Lymphocyte depleted	6 (6.67)	1 (1.67)	0.1549
Unclassified	25 (27.78)	16 (26.67)	0.8811
Bone marrow involvement			
disease present	24 (26.67)	4 (6.67)	0.0007
disease absent	66 (73.33)	56 (93.33)	0.0007
True extra nodal disease			
yes	4 (4.44)	1 (1.67)	0.3533
no	86 (95.56)	59 (98.33)	0.3533
Association with TB			
yes	44 (48.89)	14 (23.33)	0.0016
no	46 (51.11)	46 (23.33)	0.0016
Liver involvement only	23 (25.36)	8 (13.33)	0.0701
Spleen involvement only	4 (4.44)	2 (3.33)	0.7337
Both liver and spleen involvement	20 (33.3)	10 (16.7)	0.3708
Stage 3 and 4 disease	60 (66.67)	34 (56.67)	0.2148
Bulk disease			
yes	9 (10.00)	6 (10.00)	1.0000
no	81 (90.00)	54 (90.00)	1.0000
Performance status			
0	15 (16.67)	11 (18.33)	0.7916
1	12 (13.33)	12 (20.00)	0.2752
2	10 (11.11)	12 (20.00)	0.1317
3	31 (34.44)	17 (28.33)	0.4318
4	22 (24.44)	8 (13.33)	0.0956

The above table shows a comparison of the demographic and clinical characteristics between HIV seropositive and HIV seronegative patients. There were more HIV positive patients (60%) than HIV negative patients (40%). A review of the different parameters indicate only a statistically significant difference in relation to histology (p=0.019), TB association (p=0.002), and bone marrow involvement by disease (p=0.0007), between HIV seropositive and HIV seronegative patients. However, as per the protocol questionnaire no data was collected regarding CD4 count and viral load for HIV positive patients and patients who were on ARVs.

Table 20: Laboratory results

Number of Patients	Blood Parameters	Mean	Range	Percentage
Females = 66	Hemoglobin (g/dl)	09	1.8-16.5	< 12 in females =36/66 (54.5%)
Males = 84				< 13 in males = 48/ 84 (57.1%)
				< 10.5 = 88/150 (58.7%)
	White cell count	6.0	1.0-45.0	< 4 in 28/150 (18.7%)
	($\times 10^9$/l)			>10 in 08/150 (5.3%)
				>15 in 04/150 (2.7%)
	Platelets ($\times 10^9$/l)	155	10-725	< 100 in 12/150 (8%)
				> 450 in 36/150 (24%)
	Albumin (g/l)	35	15-48	< 40 in 60/150 (40%)
				< 35 in 34/150 (22.7%)
				< 30 in 26/150 (17.3%)
	Neutrophil count	1.8	0.4-7.5	<4 in 6/150 (4%)
	($\times 10^9$/l)			>7.5 in 3/150 (2%)
	Lymphocyte count	1.43	0.75	<1 in 06/150 (4%)
	($\times 10^9$/l)			>4 in 24/150 (16%)
	Eosinophil count	0.01	0-2.50	<0.4 in 8/150 (5.3%)
	($\times 10^9$/l)			
	Lactate dehydrogenase (U/L)	455	225-3845	>200 in 60/150 (40%)
				>1000 in 11/150 (7.3%)

The above table shows a summary of the relevant blood results. More than 50% of the patients had anaemia. Thrombocytopenia was noted in 8% of the patients, while thrombocytosis was evident in 24% of the patients. Leucopaenia and leucocytosis were uncommon, accounting for 4% and 2% of the patients respectively. Hypoalbuminaemia and an elevated LDH were both present in 40% of the patients, respectively.

Table 21: Distribution of histological subtypes

Histological subtype	Frequency	Percentage	Valid percentage	Cumulative percentage
Mixed cellularity	49	32.7	32.7	32.7
Nodular sclerosis	49	32.7	32.7	65.4
Lymphocyte rich	4	2.7	2.7	68.1
Lymphocyte depleted	7	4.6	4.6	72.7
Un-classified	41	27.3	27.3	100
Total	150	100	100	

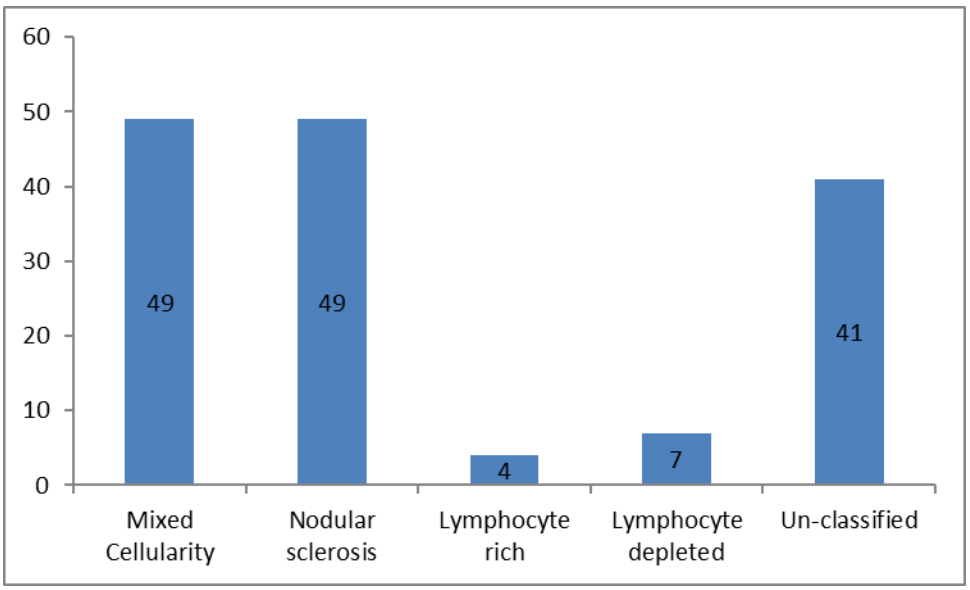

Figure 8: Distribution of histological subtypes

The above diagrams show the breakdown of the distribution of the 150 patients who participated in the survey according to the distribution of histological classification of subtypes. Both Mixed

cellularity and Nodular sclerosis were the predominant subtypes seen, each accounting for 49 patients (32.7%) respectively.

Table 26: True-extranodal disease in HIV seropositive and HIV seronegative patients

Site of disease	Number of patients	HIV Positive	HIV Negative
Pleural effusion	03	01	02
Para spinal mass	02	02	00
Bone lytic lesions	02	02	00
Lung nodules	01	00	01
Breast mass	01	01	00
Tonsillar mass	01	01	00
GIT involvement	01	00	01
TOTAL	**11**	**01**	**01**

3.3 Kaplan- Meier survival curves

Kaplan-Meier survival curves for the entire study population, age group (age <40 years versus age >40 years), early disease versus advanced disease, HIV seropositive versus HIV seronegative status, presence versus absence of 'B' symptoms, histological subtypes and comorbid disease versus no-comorbid disease are all indicated in the figures below.

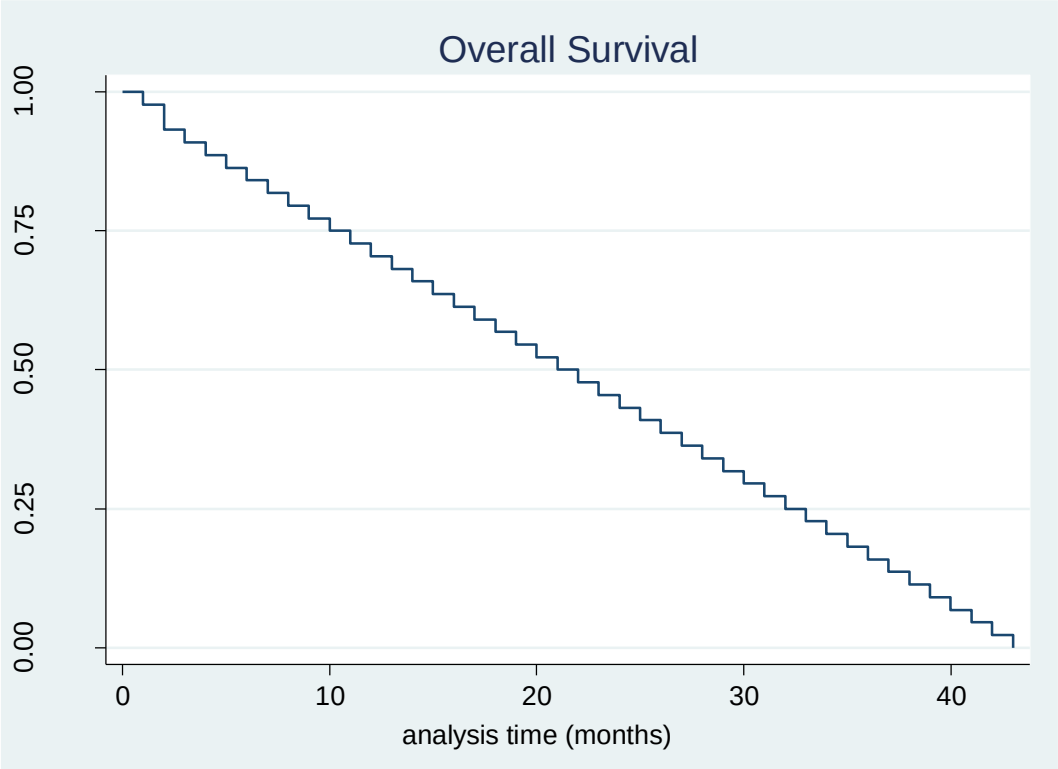

Figure 3: Kaplan Meier survival curve – overall survival

The curve for the overall survival of Hodgkin lymphoma patients shows that the probability of survival gradually declines with time. The median overall survival is 21.5 months.

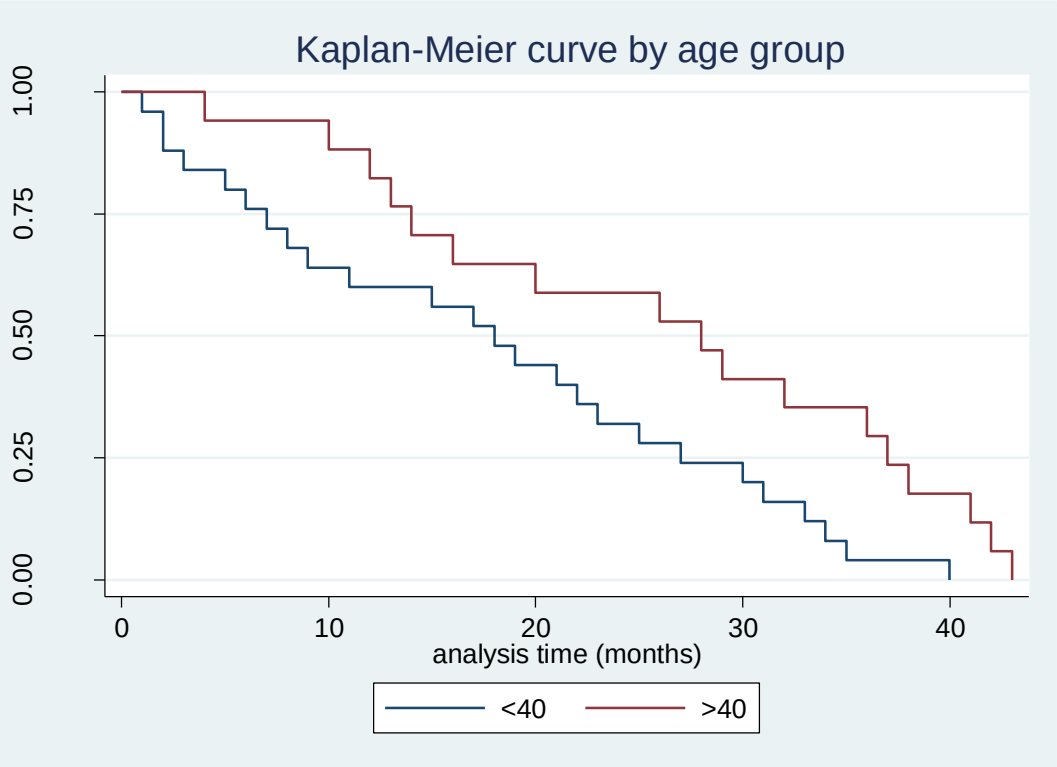

Figure 4: Kaplan Meier survival curve by age group (<40 years vs >40 years)

Figure 10 shows the Kaplan Meier survival curve by patient age group. The figure shows that patients who were > 40 years had a higher probability of survival. This is contrary to older age being an adverse prognostic factor and may be explained by the fact that there were fewer patients that were older than 40 years in this study, and less patients who were HIV seropositive over the age of 40 years.

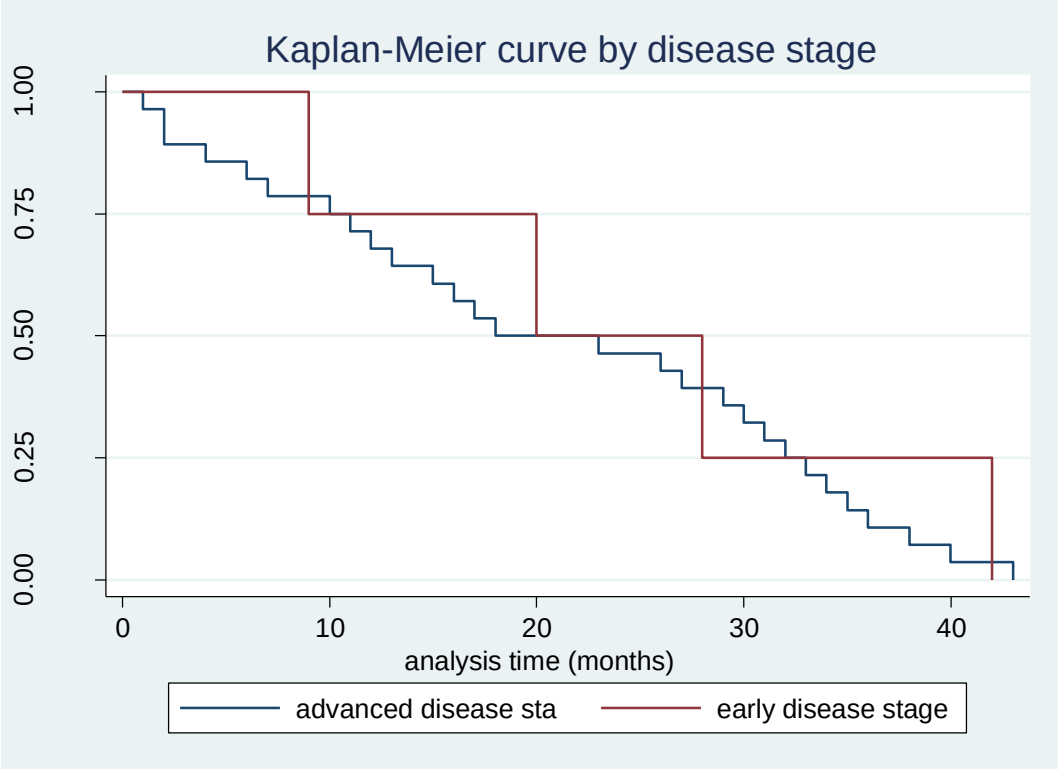

Figure 5: Kaplan Meier survival curve by disease stage (early vs advanced)

Figure 11 shows the Kaplan Meier survival curve by disease stage. Early stage appears to have a better survival. However, with overlap between the two curves, there was no difference in the survival probability of patients with early disease versus those with advanced disease.

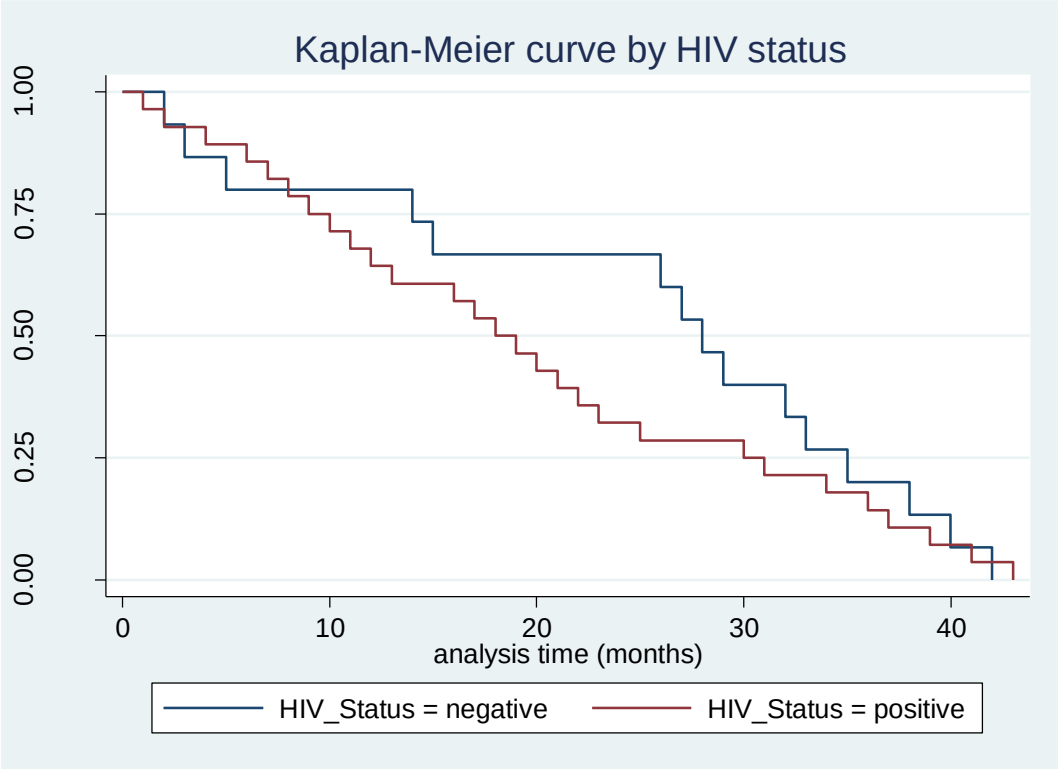

Figure 6: Kaplan Meier survival curve by HIV status (HIV seropositive vs HIV seronegative)

Figure 12 shows the Kaplan Meier survival curve by HIV status. The figure shows an overlap between the two curves in the first 10 months showing that there was no difference in the survival probability of patients with HIV versus those without HIV. However, beyond 10 months, HIV seronegative patients with HL had a higher probability of survival than HIV seropositive patients with Hodgkin lymphoma.

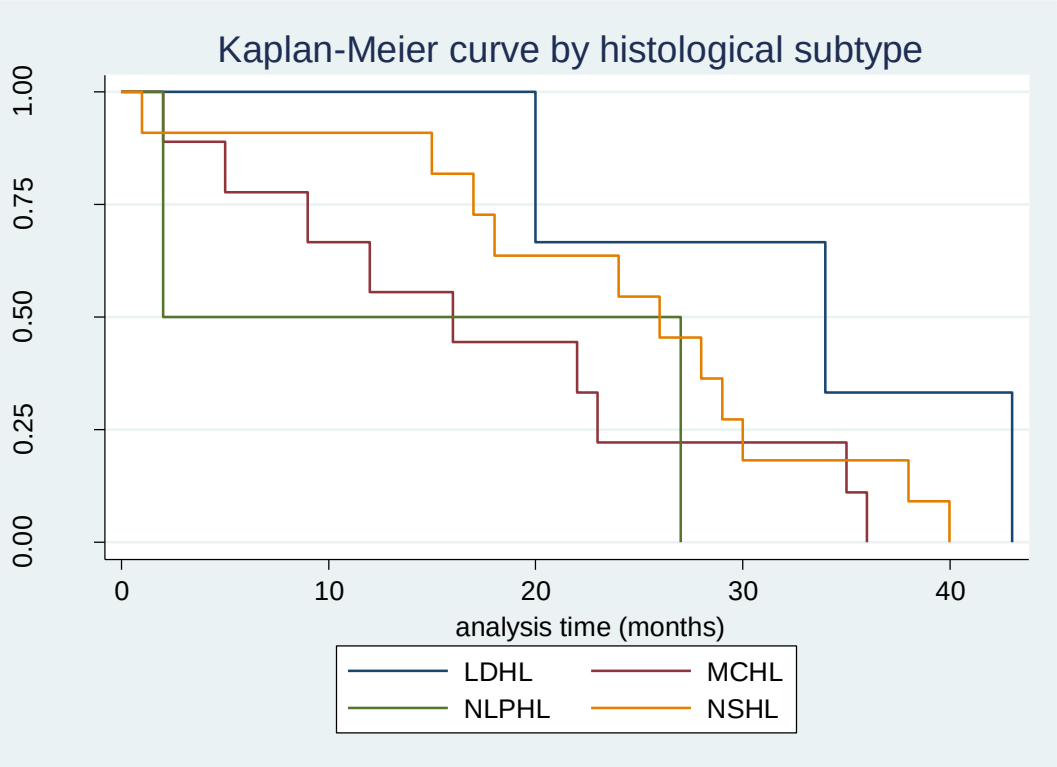

Figure 7: Kaplan Meier survival curve by histological subtypes

Figure 13 shows the Kaplan Meier survival curve by histological subtypes. Patients with lymphocyte depleted histological subtype had a higher probability of survival than those with other histological subtypes. However, the numbers were very small in this category, making the analysis less meaningful.

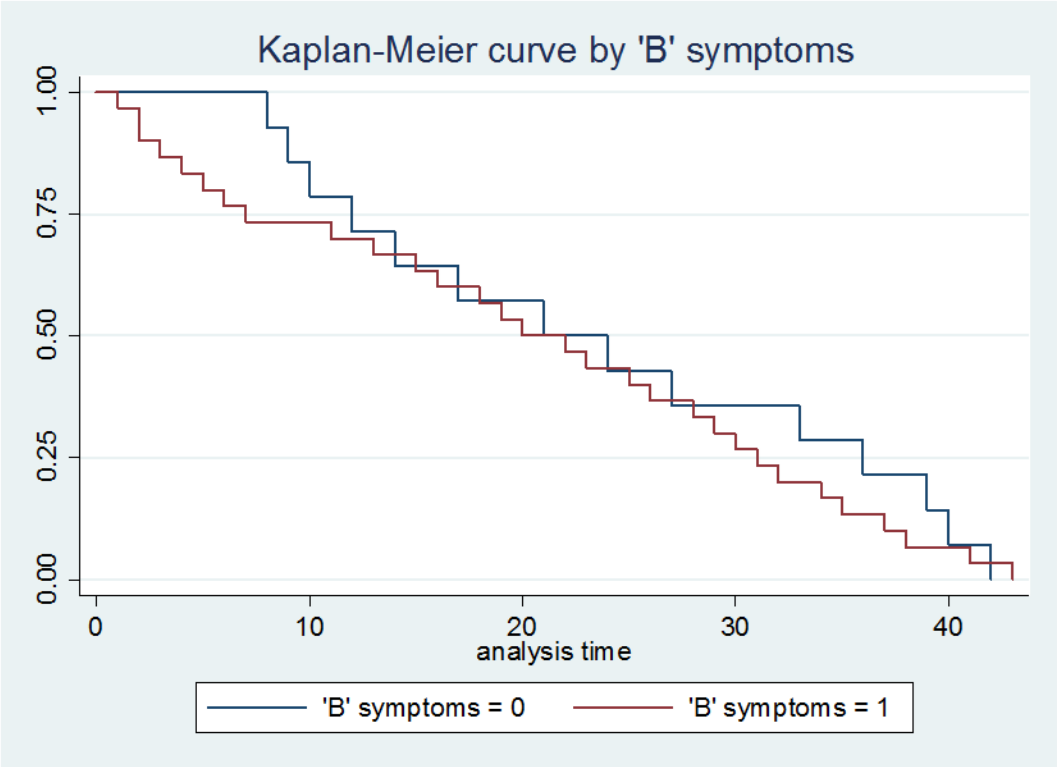

Figure 8: Kaplan Meier survival curve by 'B' symptoms

Figure 14 shows the Kaplan Meier survival curve by 'B' - symptoms. The figure shows that patients without 'B'- symptoms have a higher probability of survival as opposed to patients with 'B'- symptoms in the first 10 months. This pattern changes after 10 months where there is an overlap between the survival probability of patients with 'B'- symptoms and those without. After 30 months, the patients without 'B' - symptoms are likely to have a higher survival probability than patients with 'B'- symptoms.

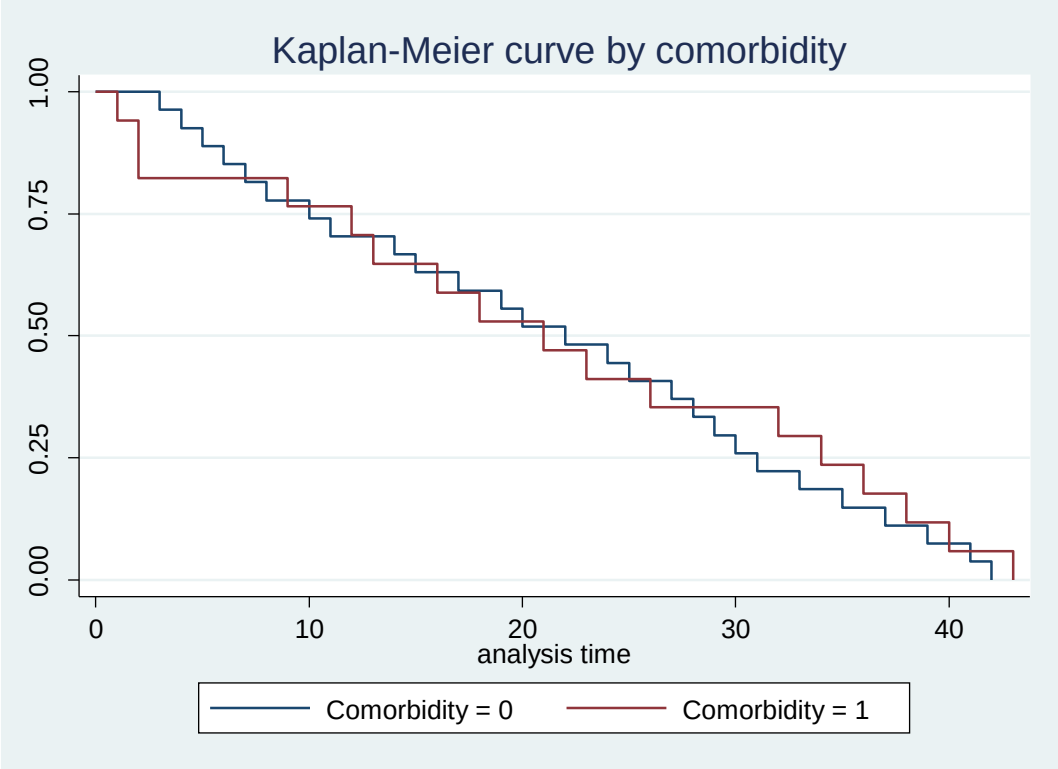

Figure 9: Kaplan Meier survival curve by comorbidity (present vs absent)

Figure 15 shows the Kaplan Meier survival curve by co-morbidity. The figure shows an overlap between the two curves throughout the years showing that there was no difference in the survival probability of patients with co-morbidity compared to those with a co-morbidity.

Table 27: Median survival by clinical characteristics

Characteristic	Median survival (months)	Range (months)
Overall	21.5	1-43
Age		
<40 years	18	1-40
>40 years	28	4-43
Disease stage		
early disease	24	9-42
advanced disease	20.5	1-43
HIV status		
positive	18.5	1-43
negative	28	2-42
Histological subtypes		
Mixed cellularity	16	2-36
Nodular sclerosis	26	1-40
Lymphocyte rich	14.5	2-27
Lymphocyte depleted	34	20-43
B symptoms		
present	21	1-43
absent	22.5	8-45
Comorbidity		
present	21	1-43
absent	22	3-42

The above table shows the median survival estimates of the Hodgkin lymphoma patients based on various demographic and clinical characteristics.

4.0 CHAPTER FOUR: DISCUSSION

4.1 Patient's background in the study

From January 2005 to December 2012 (8 years), a total of 167 newly diagnosed patients with HL were seen (approximately 21 new patients per year). This is higher than the number that was seen in a previous study by Fazel, 2012, conducted at CHBAH, during the period 1990 to 2004, where approximately 11 new patients per year were diagnosed with HL (20).

Of the 167 patients, 17 were excluded due to inadequate/insufficient information/data. The remaining 150 patients were included in this study. Ninety three percent of the 150 patients were of black ethnicity, in keeping with the demographic at CHBAH. There were 84 males (56%) and 66 females (44%), with a male to female ratio of 1.27:1. The median age of the patients was 37 years, with a range of 15-78 years. The peak frequency was in the third and fourth decades of life. This is in contrast to the earlier study done at CHBAH, where the median age was 29 years, and is likely a reflection of the significantly higher contribution from HIV seropositivity (60% compared to 28%) (20). HIV seropositivity was noted in 90 patients (60%), while the remaining 60 patients (40%) were HIV seronegative.

4.2 Clinical manifestations

In general, our patients with HL present late, with advanced stage disease. For the whole group of 150 patients, lymphadenopathy was the most common presenting feature (92.7%), with > 80% (82.7%) having lymphadenopathy in the classically described cervical area. 'B' symptoms were present in 74.7% of the patients. Advanced stage disease (stage III and IV) was noted in 74% of the patients and a performance status of ≥ 2 was evident in 66.7% of the patients. Hepatomegaly was present in 62% while splenomegaly was noted in 37% of the patients. Bone marrow

involvement at presentation was present in 18.7% of the patients. All these clinical features are consistent with late presentations and more advanced stage disease.

4.3 Laboratory results

More than 50% of the patients had anaemia at presentation. Thrombocytopenia was noted in 8% of the patients, while thrombocytosis (reactive) was evident in 24% of the patients. Leucopaenia and leucocytosis were uncommon, accounting for 4% and 2% of the patients respectively. Hypoalbuminaemia and an elevated LDH were both present in 40% of the patients, respectively.

4.4 Histological subtypes of HL

The most common histological subtypes of HL in the study were both Mixed cellularity classical HL and Nodular sclerosis classical HL, with 49 patients (32.7%) in each group. However, in the HIV seropositive group, MCcHL was the most common subtype (36 patients – 40%), compared to the NScHL subtype (21 patients – 33%). Conversely, in the HIV seronegative group, NScHL was more common than MCcHL, being present in 28 patients (46.6%), as compared to 13 patients (21.67%) with MCcHL. An unusual finding was the relatively large number of patients (i.e. 41 patients – 27.3%), in whom the histological subtype was unclassifiable. This is an indication of an increasing number of patients being diagnosed in sites other than lymph nodes, such as the bone marrow and on liver biopsy. This form of diagnosis is more common in patients with HIV seropositivity.

4.5 Comorbid diseases

Comorbid diseases other than HIV and TB were also encountered in this study group. The comorbid diseases include: hypertension, diabetes, stroke and connective tissue disorders. Of these diseases, hypertension (8 patients) and diabetes were the most common. As both these diseases predated the onset of HL and are common diseases seen in the general population, the association is likely to be coincidental. Corticosteroid therapy may have been implicated as being causative, if these conditions occurred as a complication of HL.

4.6 Autoimmune haemolytic anaemia (AIHA) and HL

Autoimmune haemolytic anaemia (AIHA) is rare in HL. It can occur before HL, during or after the diagnosis of HL. Patients with both AIHA and HL are generally older, with a male predominance. NScHL and MCcHL are the most common subtypes, where this association is encountered.

Three patients had AIHA. Two of the patients were HIV seropositive. Of the three patients, two were diagnosed with AIHA prior to the diagnosis of HL, making the association unlikely.

4.7 HL and Connective tissue disease

The association of HL and connective tissue disease is rarely encountered. In our study, two patients had connective tissue diseases (CTD) in association with HL. This included one patient each with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Both the patients were diagnosed with their CTD prior to the diagnosis of HL, making the association unlikely.

4.8 HIV and HL

The last decade has witnessed the emergence of Hodgkin lymphoma occurring with increasing frequency in association with HIV. The relative risk of acquiring HL is 10-20 fold higher with HIV seropositivity, compared to the general population. HIV associated Hodgkin lymphoma is generally more aggressive, presents with advanced stage disease, frequent 'B' symptoms, less favourable histology, more frequent bone marrow involvement and overall, a poorer prognosis compared to Hodgkin lymphoma in HIV seronegative individuals.

A comparison of the HIV seropositive and HIV seronegative patients in our study reveals a statistically significant difference between the histological subtypes (mixed cellularity with HIV seropositivity (p=0.019) and nodular sclerosis with HIV seronegativity (p=0.002), TB association (higher with HIV seropositivity – p=0.001) and more bone marrow involvement with HIV seropositivity (p=0.0007). A poorer prognosis, with a shorter median survival was also noted in HIV seropositive individuals, compared to HIV seronegative individuals (see table 23).

4.9 Hodgkin lymphoma and TB

The association of TB and HL is well described (14, 20, 65, 66). The increased association is due to impaired cellular immunity that predisposes patients with HL to infections like HIV and TB (66). Depressed immunity can also be due to chemotherapy, including the use of corticosteroids, which may facilitate reactivation of dormant TB bacilli and dissemination of infection.

Tuberculosis and HL share similar clinical features such as the presence of constitutional symptoms, lymphadenopathy, bone marrow infiltration and splenomegaly. Both conditions can coexist in the same patient. Lymph node and bone marrow samples may show evidence of both TB and HL.

An association of TB was noted in 39.3% of the patients in our study, with 79.7% of the patients having had a diagnosis of TB prior to lymphoma diagnosis and 20.3% of patients were diagnosed with TB after the lymphoma diagnosis. The association between TB and HL is not surprising in our patients and could be explained on a multifactorial basis – high prevalence of TB in the background population, high HIV seropositivity rate, concomitant chemotherapy and corticosteroid use.

4.10 Treatment

Of the 150 patients in the study, 87.3% received chemotherapy and 12.7% died prior to receiving chemotherapy. The most commonly used initial combination chemotherapy regime was ABVD (Adriamycin, bleomycin, vinblastine, decarbazine) and prednisone. The median number of cycles received was 7.5. However, some patients defaulted and others died before completing their planned number of cycles.

Of the patients that received initial chemotherapy, 22 patients received less than 2 cycles of chemotherapy, 48 patients received 2 or more but less than 8 cycles of chemotherapy, and 61 patients received 8 or more cycles of chemotherapy.

In general, patients with early stage disease received 4-6 cycles of chemotherapy, while those with advanced stage disease received 6-8 cycles of chemotherapy. The patients who relapsed were given second line chemotherapy or considered for high dose chemotherapy followed by an autologous stem cell transplant (see tables 3.24 and 3.25). Of the 150 patients, 48 (32%) are alive, 44 (29.3%) have died and 58 (38.7%) are lost to follow up. Understanding the nature of HL, it is likely that the majority of patients who are lost to follow are alive and in remission.

Table 28: Comparison of Dr Fazel's study - 2012 and my study - 2017

Variable for Comparison	Fazel's Study - 2012	Turatsinze's study - 2017
Time frame	14 years	8 years
Institution	CHBAH	CHBAH
Number of patients	163	150
Gender ratio (M:F ratio)	1.3:1	1.27:1
Median age	29	37
Range	13-87	15-78
HIV seropositivity	28%	60%
Performance status		
≤ 2	90%	48%
> 2	10%	52%
Presence of ' B' symptoms	78%	74.7%
Presence of lymphadenopathy	85%	92.7%
Laboratory features		
Anaemia	-	50%
Thrombocytopenia	-	8%
Leukopenia	-	4%
Increased Albumin and LDH	-	40%
Histological subtypes:		
Mixed cellularity cHL	45%	32.7%
Nodular sclerosis cHL	37%	32.7%
Lymphocyte Rich cHL	3%	2.7%
Lymphocyte depleted cHL	0%	4.6%
Unclassified	15%	27.3%
Outcome		
Alive	9%	32%
Died	31%	29.3%
Lost to follow up	60%	38.7%
Ann Arbor stage		
0-1	5.13%	7.3%
≥ 2	94.87%	92.7%
Bone marrow involvement	26%	18.7%
Tuberculosis in association with HL	32%	20.3%

4.11 Study limitations

Since our study was a retrospective study, there were some limitations. These limitations include:

- Inadequate and missing demographic and clinical data from patient files
- Inadequate and missing blood results, imaging and histology results in the patient files
- Poor compliance and lost to follow up of patients
- Information on treatment, follow up and response to treatment may not have been documented completely in all patients
- Lack of availability of PET/CT scans at initial assessment and at follow up
- Lack of the above information does impact on accurate assessment of treatment response, disease-free survival and overall survival. Moreover, the documentation of long term toxicities of therapy in a potentially curable malignancy may not be adequately reflected.

5. CHAPTER FIVE: CONCLUSION

Hodgkin lymphoma in southern Africa is similar to what has been described in the literature, in regard to many salient features of the disease. However, in our study, there was a high prevalence of HIV and TB, in association with HL. Over the past three decades, there has been a paraigm shift at our institution, from an early period in the 1980's with no HIV seropositivity in association with HL, to <50% in the 1990's and early 2000's, to > 50% in the last decade. The association between HIV and HL has an impact on the adverse clinical presentation and poorer outcome of our patients. Health care workers need to be aware of this emerging and increasing association between HIV and Hodgkin lymphoma, so that patients could be diagnosed early and timeously, and both combination antiretroviral therapy and chemotherapy could be administered concurrently/simultaneously and without delay.

The limitations with regard to the retrospective nature of this study have been mentioned in the last chapter. It is hoped that in future, prospective studies should be undertaken looking at various aspects of HL, including a more detailed study on the impact of HIV on HL.

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APPENDIX A: DATA COLLECTION SHEET

1. PATIENT STUDY NUMBER

2. OCCUPATION (DOMINANT AND RELEVANT OCCUPATIONS)

3. AGE

4. GENDER M F

5. ETHNIC GROUP BLACK ASIAN COLOURED WHITE

6. ECOG PERFORMANCE STATUS 1 2 3 4

7. B SYMPTOMS YES NO

IF YES: - Weight Loss - Night sweats - Fever >38˚C

8. SEVERE PRURITUS YES ☐ NO ☐

9. COMORBID DISEASE (other than HIV or TB)

YES ☐ NO ☐

IF YES – SPECIFY NAME AND DURATION OF DISEASE

10. RELEVANT MEDICATION/EXPOSURE PRIOR TO DIAGNOSIS (e.g. cytotoxic agents, radiation, petroleum toxins)

YES ☐ NO ☐

IF YES GIVE DETAILS

11. LYMPHADENOPATHY AT PRESENTATION

YES ☐ NO ☐

IF YES - DURATION

12. HISTORY OF TUBERCULOSIS YES ☐ NO ☐

- IF YES WHEN WAS THE DIAGNOSIS MADE? PRIOR TO DIAGNOSIS ☐

DURING LYMPHOMA TREATMENT ☐

CURRENTLY ☐

- HOW WAS TB DIAGNOSED

- SITE OF TB

- START DATE AND DURATION OF TREATMENT

-

13. CLINICAL FEATURES AT PRESENTATION

PYREXIAL ☐ PALLOR ☐ PETECHIAE ☐ JAUNDICE ☐

OTHERS ☐ SPECIFY

14. BULK DISEASE YES ☐ NO ☐

IF YES - PERIPHERAL ☐ - CXR ☐

SITE SIZE

15. LYMPHADENOPATHY AT PRESENTATION

YES ☐ NO ☐

IF YES, SITE

16. EXTRA NODAL SITES AT PRESENTATION

YES OR NO		SITES	

- IF YES, DOCUMENT THE SITES, SIZE, SYMMETRY AND ALL THE OTHER RELEVANT CLINICAL CHARATERISTICS (E.G. CONSISTENCY, MOBILITY, TENDERNESS, OVERLYING SKIN ETC.) OF THE LYMPHADENOPATHY

  MENTION ALL THE NEGATIVE PERIPHERAL SITES OF LYMPHADENOPATHY

  MENTION IF THERE IS INVOLVEMENT OF WALDEYER'S RING, INTRATHORACIC INVOLVEMENT – SVC SYNDROME, DE'ESPIANS SIGN AND PEMBERTON'S SIGN, INTRA-ABDOMINAL DISEASE AND IN A MALE THE EXAMINATION OF THE SCROTUM AND TESTES

17. INVOLVEMENT OF LIVER AND SPLEEN

YES OR NO	

IF YES, GIVE DETAILS (SIZE, CHARACTERISTIC ETC.)

18. TRUE EXTRA NODAL SITES AT PRESENTATION (OTHER THAN LIVER, SPLEEN AND BONE MARROW) – SUCH AS CNS, SKIN, BONE, GIT ETC.

YES OR NO		SITE AND DETAILS

19. RADIOLOGICAL FINDINGS

CXR	

SONAR	

CT SCAN	

PET/CT SCAN	

MRI SCAN	

20. ANN ARBOR STAGING

21.

1 ☐ 2 ☐ 3 ☐ 4 ☐ A ☐ B ☐

SUBSCRIPTS: ‘E’, ‘X’

22. BONE MARROW ASPIRATE AND TREPHINE

INVOLVEMENT, YES OR NO ☐

FINDINGS (MENTION OF ANY EVIDENCE OF TB, NON-SPECIFIC GRANULOMAS ETC.)

23. FNA OF NODE YES OR NO

SITE

FINDINGS

24. SUMMARY OF HISTOLOGICAL FINDINGS

SITE, TYPE OF TISSUE, FINDINGS, SPECIAL STAINS, SUBTYPE OF HL

25. **HIV SEROLOGY** - REACTIVE [ ] - NON-REACTIVE [ ]

IF REACTIVE, WHEN (MONTH, YEAR) WAS HIV DIAGNOSED? NOTE CD4 COUNT AT PRESENTATION

- IS PATIENT ON ARV'S? YES [ ] NO [ ]

- IF YES: REGIMEN

DATE OF COMMENCEMENT OF ARV'S

TREATMENT COMPLICATIONS

FOLLOW UP CD4 COUNTS AND VIRAL LOAD

RELATED, COMPLICATION OF TREATMENT, OTHER

26. SURVIVAL

- OVERALL SURVIVAL ☐

- DISEASE FREE SURVIVAL ☐

27. ANY OTHER RELEVANT INFORMATION

APPENDIX B: ANN ARBOR STAGING SYSTEM

Ann Arbor Staging System with Cotswolds' modification	
Stage	**Description**
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	2 or more lymph node regions on the same side of the diaphragm
III	Lymph nodes on both sides of the diaphragm
III1	With splenic hilar, coeliac, or portal nodes
III2	With para-aortic, iliac, or mesenteric nodes
IV	Involvement of extranodal site beyond that designated "E"
Modifying features	
A	No symptoms
B	Fever, drenching night sweats, weight loss >10% in 6 months
X	Bulky disease: greater than one third widening of mediastinum or >10 cm maximum diameter of nodal mass
E	Involvement of single, contiguous, or proximal extranodal site

APPENDIX C: ECOG PERFOMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

APPENDIX D: RESPONSE DEFINITIONS FOR CLINICAL TRIALS

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, Fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.