HODGKIN'S LYMPHOMA IN ADULTS AT CHRIS HANI-BARAGWANATH HOSPITAL:

A FIFTEEN YEAR REVIEW

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine (Internal Medicine).

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ETHICS COMMITTEE APPROVAL

This research was approved by the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (clearance certificate number: M050420).

DECLARATION

I, Fatima Bibi Fazel, 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.

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Fatima Bibi Fazel

The …….. day of ……., 2012

DEDICATION

To my parents, husband, son and daughter

ABSTRACT

Hodgkin's lymphoma (HL) is a lymphoproliferative disorder that was first described by Thomas Hodgkin and Samuel Wilks in the first half of the nineteenth century. It is characterised by the presence of painless lymphadenopathy, usually in the cervical region. Constitutional symptoms are a common presenting feature. Clinical staging is based on the backbone of the Ann Arbor staging classification. Patients with advanced disease often have hepatosplenomegaly and bone marrow infiltration. True extranodal disease is rare. HL is broadly divided into two distinct clinical entities: nodular lymphocyte predominant HL (5%) and classical HL (95%) - which is further subdivided into four groups: nodular sclerosis HL, mixed cellularity HL, lymphocyte-rich HL and lymphocyte-depleted HL. Most patients are treated with combination chemotherapy and involved field radiotherapy. With excellent cure rates of >95% for early stage disease nowadays, the challenge is to minimise the adverse long term effects of chemo-radiotherapy, while at the same time achieving optimal cure rates.

There are clear differences in the demographics and clinical presentation of HL between the developed world and developing countries. Hence, the main aim of this study was to determine the demographics and clinical presentation of HL in a developing, sub-Saharan African population, and to compare these findings with findings elsewhere in the world. Secondary objectives included assessing the treatment used and response to therapy, prognostic factors affecting survival, differences in the presentation between human immunodeficiency virus (HIV) positive and negative individuals, the association of HL with tuberculosis, and the documentation of the long term effects of therapy.

Method: This was a retrospective review of all adult patients diagnosed with HL at Chris Hani-Baragwanath Hospital (CHBH) in Soweto during the period January 1990 – December 2004. *Results:* 163 patients were seen over a fifteen year period. There were 93 males and 70 females, with a Male(M):Female(F) ratio of 1.3:1. The median age at presentation was 29yrs, with an absence of a second peak in older patients. Seventy eight percent of patients had B symptoms and 69% had advanced stage disease at presentation. Nodular sclerosis HL was the

main histological subtype in the younger, HIV negative population. Mixed cellularity HL was the commonest histological subtype seen in older patients and the HIV positive group. Sixty three percent of patients had a complete response to first line therapy, 18% a partial response, 2% stable disease and 17% progressive disease. Prognostic features of statistical significance that negatively affected survival included older patients (>40yrs), patients with advanced stage disease and HIV seropositivity. The histological subtype and presence of B symptoms did not significantly affect outcome. Twenty three percent of the patients were HIV positive, and increasing seropositivity appears to be an emerging trend. *Conclusion:* HL in patients at CHBH displays many clinical characteristics typical of a developing nation, such as the absence of a bimodal age distribution, more B symptoms and more advanced stage disease. The predominance of the more favourable nodular sclerosis histological subtype in the younger, HIV negative population tends to follow the pattern of a developed nation. Older patients, patients with advanced stage disease and HIV positive patients have a poorer outcome. The large number of patients lost to follow up precludes accurate assessment of long term overall survival in the study population, as well as documentation of long term adverse effects/complications of therapy.

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CHAPTER ONE: LITERATURE REVIEW

1.1 INTRODUCTION

Hodgkin's Lymphoma (HL) is a lymphoproliferative disorder that was first described by Thomas Hodgkin and Samuel Wilks in the first half of the nineteenth century (1). In 1832, Hodgkin presented seven autopsy cases with lymphadenopathy, whilst curator of the museum at Guy's Hospital in London. Specimens from three of these cases were preserved in alcohol for many years, and in 1998 Poston proved that two of these original cases were indeed that of HL, as demonstrated by the presence of the classic Reed-Sternberg (RS) cell and its associated marker, CD15 (2,3). Also called lymphogranulomatosis initially, Wilks had named the condition Hodgkin's Disease. However, as the pathognomonic Reed-Sternberg (RS) cell is now known to be of lymphoid origin, the preferred term for the disease is that of Hodgkin's Lymphoma (1).

1.2 PATHOBIOLOGY OF HODGKIN'S LYMPHOMA

While Thomas Hodgkin provided the first macroscopic description of HL in 1832, the "diagnostic" RS cell was first described by both Carl Sternberg and Dorothy Reed independently in 1898 and 1902 respectively (4). The first histologic classification was coined by Jackson and Parker in 1944. This was replaced by the Lukes and Butler classification in 1964. In 1965, the Lukes-Butler classification was simplified at the Rye conference and was used for over 30 years because of its reproducibility and good clinico-pathological correlation. It consisted of four histological subtypes: nodular sclerosis, mixed cellularity, lymphocyte predominant and lymphocyte depletion (4).

With advances in histopathology, the Rye classification was addressed in the revised European-American lymphoma (REAL) classification in 1994. HL was essentially divided into two distinct clinical entities: 1) nodular lymphocyte predominant HL (NLPHL), and 2) classical HL (cHL) which comprises four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-

depleted. Each subtype differs in their clinical features, amount of fibrosis, number of tumour cells, composition of the cellular background and the frequency of Epstein-Barr virus (EBV) infection. The REAL classification still stands, and has been adopted by the World Health Organisation (WHO) scheme (1) (Table 1.1). Two additional groups have been included in the WHO scheme. 'Unclassifiable HL' is used in cases where biopsy material is insufficient, or when the diagnosis of HL is made at an extranodal site. Then there is a group of '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 (4).

Table 1.1: WHO classification of Hodgkin's 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

1.2.1 Nodular lymphocyte predominant Hodgkin's lymphoma

NLPHL comprises about five percent of all HL's. The tumour usually exhibits a nodular growth pattern morphologically. The neoplastic cell is a germinal centre B cell that, unlike Hodgkin and RS (HRS) cells, has maintained its B cell program. Called lymphocyte predominant (LP) cells or popcorn cells, these cells express CD45 and CD20. CD15 expression is negative and CD30 is rarely weakly positive (4). Like germinal centre B cells, LP cells produce immunoglobulin. This is via the expression of transcription factor Oct-2 and its co-activator BOB.1, which is consistently absent from HRS cells. Unlike with cHL, the EBV genome has never been found in LP cells. Gene expression profiling studies have shown that LP cells, like HRS cells, also exhibit constitutive nuclear factor kappa B (NFκB) activity (4).

The microenvironment in NLPHL consists of a mixture of lymphocytes, plasma cells and follicular dendritic cells. The T lymphocytes form characteristic rosettes around the neoplastic LP cells, and also exhibit a classic germinal centre phenotype. They produce a chemokine that is responsible for B cells homing to the lymphoid follicles. The classic T cell rosetting can be used to differentiate cases of NLPHL from T cell/Histiocytic Rich B cell lymphoma (5).

1.2.2 Classical Hodgkin's Lymphoma

1.2.2.1 Pathology of classical HL

The diagnostic tumour cell of cHL is the characteristic multi-nucleated, giant RS cell. 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, and CD15 expression has been found in approximately 80% of patients with cHL. CD20 is less frequently expressed (4). 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 (4). Hence the diagnosis of cHL has to be made on finding the neoplastic cells within an appropriate cellular background. The neoplastic infiltrate of HRS cells makes up only 0.1-10% of the tumour bulk (1). The inflammatory milieu makes up the rest of the tumour. This consists of lymphocytes, plasma cells, eosinophils, histiocytes, neutrophils, fibroblasts and collagen. Variations in the composition of this inflammatory background results in the four histological subtypes of cHL mentioned previously.

Nodular sclerosis HL

Nodular Sclerosis (NS)-cHL is the commonest subtype in the developed world (4). It is characterised by a thickened lymph node capsule from which emanate broad collagen fibres that divide the lymph node into nodules. Also characteristic are lacunar cells - neoplastic cells with cytoplasm that is sensitive to formalin fixation, resulting in peri-nuclear condensation of the cytoplasm with a clear halo closer to the cell membrane. HRS cells are rare. Mummified tumour cells are also seen due to increased apoptosis. Cellular and syncytial variants have been described, where the latter is thought to run a more aggressive clinical course. A grading system for NS-cHL has been proposed by the British National Lymphoma Investigation (BNLI) group. This is based on degree of tumour cellularity, amount of fibrosis and atypia of the neoplastic cells. Its real prognostic value is still to be elucidated in larger series (4).

Mixed cellularity HL

Mixed Cellularity (MC)-cHL is more common in developing countries and in patients with human immunodeficiency virus (HIV) infection. It is characterised by a polymorphous infiltrate of background cells which efface the lymph node architecture. Typical HRS cells are seen, as well as mummified tumour cells. The interfollicular variant is rare, but needs to be differentiated from conditions such as follicular hyperplasia and Castleman's disease (4). The epithelioid cell rich variant has granulomata formation with an epithelioid cell reaction and Langhans cells. It needs to be differentiated from a Lennert's lymphoma (lymphoepithelioid lymphoma). HRS cells are always seen after a careful search.

Lymphocyte-depletion HL

Lymphocyte Depletion (LD)-cHL is the rarest variant which has the worst prognosis. It is identified by a paucity of background lymphocytes with numerous HRS cells. There is a fibrotic and a reticular/sarcomatous variant, which must be differentiated from anaplastic large cell lymphoma.

Lymphocyte-rich HL

Lymphocyte Rich (LR)-cHL consists of a nodular and much rarer diffuse variant. Under low power, the nodular variant may resemble NLPHL. However the immunophenotype of the neoplastic cells resembles that of the classic HRS cell.

1.2.2.2 Biology of classical HL

The Reed-Sternberg cell

Despite the fact that HRS cells constitute a small proportion of the tumour bulk, they are capable of survival and unrestricted tumour growth. Their neoplastic potential has been attributed to two main factors: apoptosis deregulation and constitutive NFκB activity (5). HRS cells have been shown to express c-FLIP constitutively, hence down-regulating Fas and evading apoptosis. NFκB activity is enhanced by various routes such as CD40 ligand and latent membrane protein 1 (LMP-1). Inhibitor of kappa kinase (IκKinase) is activated with liberation of NFκB from its inhibitor, inhibitor of kappa B (IκB) (6). There may also be defects in the IκB family (4). The end result is activation of nuclear transcription factors that prevent apoptosis.

The role of Epstein-Barr virus

Epstein-Barr virus (EBV) integration into the genome of HRS cells has been shown in 20-80% of cases of cHL (4). The frequency of EBV-associated HL varies due to a number of factors. EBV-associated HL is more common in MC versus NS histological subtypes, in developing countries versus developed countries, in paediatric and older patients with HL versus young adults and in patients with immune deficiency states. Almost all patients with HIV infection and HL are EBV positive. HL post transplantation and in patients with congenital immune deficiency syndromes is also usually EBV-associated (6). The exact role of EBV in the pathogenesis of HL is yet to be determined. However, LMP-1 has oncogenic potential by enhancing bcl 2 expression and by acting via the CD40 signalling pathway to evade apoptosis (6).

The tumour microenvironment

Complex interactions between neoplastic cells and the tumour microenvironment aid in tumour survival. HRS cells are capable of recruiting cells from the peripheral circulation by the release of various cytokines and chemokines. Local expansion of the microenvironment is also controlled to a certain extent, and so the inflammatory milieu is manipulated by HRS cells (4).

Of emerging interest is the influence of the microenvironment cellular component on the clinical course of HL. This is of major clinical relevance, since a percentage of patients with HL will not respond to first line therapy, despite cure rates of over 85%. Apart from interim PET scans, there are no other current modalities to assess, early on, tumour responsiveness to therapeutic modalities. Studies by Sanchez-Aguilera et al. and Steidl et al. have identified a gene signature for tumour-associated macrophages (with CD68 expression) that is associated with primary treatment failure (7, 8). Other gene expression profiling studies have further identified signatures associated with good and poor outcome HL. Not only could this be useful to assess treatment responsiveness at the outset, but it may also serve as potential molecular targets for newer treatment modalities.

1.3 INCIDENCE OF HODGKIN'S LYMPHOMA

HL is an uncommon malignancy. The worldwide age-standardised incidence rate in 2008 was 1.0/100,000 (3). The incidence varies geographically, with North America displaying a higher incidence than Japan and China, where the condition is relatively rare. Developing countries may also show an increased incidence compared to developed countries. There may also be regional variations in the incidence of HL within a country. There is a definite increased incidence of HL in acquired immune deficient states such as HIV, congenital immune deficiencies and post solid organ and bone marrow transplants. These cases are usually EBV related. HL is also increased in people with autoimmune disorders or those who have family members with an autoimmune condition. Rare, but well documented, is also a tendency for HL to exhibit a familial aggregation (9-14).

1.4 EPIDEMIOLOGY OF HODGKIN'S LYMPHOMA

Three main age groups are referred to when looking at the epidemiology of HL: 1) childhood HL (CHL); 2) adolescent/young adult HL (AYA HL); and 3) older adult HL (OA HL) (15). These groups differ somewhat in biology, clinical presentation, main histological subtype and prognosis.

CHL represents children ≤14 years of age. This group is characterized by a male predominance, an increased prevalence of MCHL and NLPHL, and a higher association with EBV, compared to AYA HL. The incidence of HL in this age group is higher in developing countries. This may be related to lower socio-economic status and larger family size (15). Overall, the prognosis is very good.

AYA HL, 15-35 years old, usually represents the peak incidence of HL. Adults who are 35-54 years old have quite a similar clinical presentation. There is no significant gender preference. Up to 80% of cases in developed countries are of the nodular sclerosis subtype (16). The association with EBV is less than with childhood and older adult HL. The prognosis is good, with relative five year survival rates of 90% (15).

OA HL patients are 55 years and older. This age group presents with more of a mixed cellularity subtype, an association with EBV in up to 56% of cases, more B symptoms, more advanced stage disease, and overall a poorer prognosis than the other two groups (15).

In developed countries, there is a tendency for HL to exhibit a bimodal age distribution, with peak incidences in the AYA and OA age groups. In developing countries, the second peak in older adults is not as obvious. Also, in some areas like the Middle East and parts of Asia, the initial peak is noticed more in early childhood (17).

Other possible risk factors for HL have been highlighted in the paper by Maggioncalda et al (17). These include: socioeconomic status (SES), with a higher incidence of HL in people of higher SES but a poorer prognosis in patients of lower SES; exposure to pathogens such as measles in childhood, that may potentially reduce the risk of HL; strenuous exercise at least twice a week, that has been shown to decrease the risk of acquiring HL by 40%; an increased risk of HL in

active and passive smokers; and regular low dose aspirin exposure that may reduce the risk of developing HL.

1.5 CLINICAL FEATURES OF HODGKIN'S LYMPHOMA

HL can present in various ways. The presentation may differ slightly depending on the histological subtype, geographical area, age group and immune status of the patient. The clinical presentation of NLPHL will be addressed separately.

The commonest manifestation of HL is that of painless, enlarging lymph node masses, that may wax and wane. In 90% of cases the lymphadenopathy (LN) starts in supradiaphragmatic lymph nodes, usually in the cervical region (18). Less commonly, lymphadenopathy starts below the diaphragm (more common in older patients). The pattern of disease spread is highly predictable, with contiguous spread to centriaxial lymph nodes. Mediastinal LN is thus common (18). Infiltration of the liver, spleen, bone marrow, bone and lungs may also occur. However, as these organs are more deep-seated, the patient may, instead of a mass lesion, present with local organ-specific symptoms such as cough and bone pain, deranged laboratory tests or non-specific constitutional symptoms (18).

Up to one third of patients with HL experience at least one constitutional symptom or B symptom (19). B symptoms are weight loss of >10% body weight in the preceding six months, unexplained fever and drenching night sweats. In general, B symptoms correlate with more advanced disease, bulk disease and a poorer prognosis. Some patients may present initially with B symptoms or fatigue only, thus making the diagnosis of HL more challenging. Other less common systemic symptoms include pruritis and alcohol-induced lymph node pain. However, in some series pruritis has been described in up to 30% of patients with HL (3).

Two types of extranodal involvement by HL are described: 1) Direct local extension from involved lymph nodes or via adjacent lymphatics is more common. Extranodal sites such as the pleura, pericardium, peri-hilar lung, skin, epidural tissue and thyroid are involved in this manner (18). This type of contiguous extranodal involvement does not alter the stage of disease significantly, and therapy may still be directed as for localized disease. 2) Distant extranodal

spread is usually to four main organs: the bone marrow, liver, lung and bone. Distant involvement of other extranodal 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, where true extranodal disease at such unusual sites may be seen more frequently than in HIV negative individuals, it is an uncommon finding.

Autoimmune cytopaenis and other paraneoplastic manifestations are infrequently associated with HL (20). Autoimmune haemolytic anaemia and autoimmune thrombocytopenia, if found to be associated with HL, usually resolve on treatment of the HL (18). Paraneoplastic neurologic manifestations include cerebellar degeneration, subacute myelopathy and motor neuropathies, Guillain-Barre syndrome, and limbic encephalitis. Treatment of the HL usually arrests progression of, and occasionally improves, the neurology (21). Paraneoplastic renal involvement is usually a glomerulonephritis, which can be of many types, such as membranous, minimal change or proliferative (22). It may manifest clinically as a nephrotic syndrome, which may precede the onset of HL by months to years, and may not resolve on treatment of the HL (18).

Skin manifestations of HL may be seen in 13-50% of patients (23, 24). Most cutaneous eruptions are non-specific and can resemble conditions such as dermatomyositis and ichthyosis. Actual skin involvement by HL has been reported in 0.5-7.5% of patients (25). 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. Skin involvement by HL is usually a feature of advanced disease and may imply a poorer prognosis (25).

Other abnormalities that have been reported to be associated with HL include: hepatitis, cholangitis, vasculitis, hypercalcaemia, hypoglycaemia, coagulopathies and haemophagocytosis (26).

1.5.1 Nodular lymphocyte predominant Hodgkin's Lymphoma

NLPHL requires special mention as the clinical presentation differs somewhat from cHL. It tends to involve younger patients, with a male predominance of 2:1. Disease is usually limited, with cervical or inguinal LN as the presenting feature (19). B symptoms, bulk disease and extranodal involvement are unusual. It is an indolent disease, with lymphadenopathy often persisting for a number of years before the diagnosis is made. Cure rates are high with frequent late relapses. Unusual presentations and relapse should be confirmed on biopsy, as the condition may co-exist with a diffuse large B cell Lymphoma or a T cell-rich B cell Lymphoma (18).

1.6 DIAGNOSIS OF HODGKIN'S LYMPHOMA

As mentioned previously, the definitive diagnosis of HL requires histology to identify the characteristic tumour cells (HRS or LP cells) within an appropriate reactive cellular background. Thus a complete excision biopsy of an enlarged lymph node is necessary, so that the sparse tumour cells are not missed and the lymph node architecture can be appreciated (3). This may not always be possible, especially in cases where the biopsy is from an extranodal site, and the diagnosis is then more challenging.

Diagnostic errors in pathological classification have been reported in a number of 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 too invasive, and then the clinician may have to rely on an FNA diagnosis in the correct clinical context. The role of FNA in the diagnosis of HL may change with improvements in flow cytometry methods specific for the detection of HRS cells, such as nine colour assays and gating methods to include the HRS cell, as reported by Fromm, et al. (27). NLPHL will still not be able to be detected in this manner (27).

1.7 STAGING AND INVESTIGATIONS FOR HODGKIN'S LYMPHOMA

Clinical staging of HL is imperative as it directly affects prognosis and the choice of treatment modality. The standard for staging is the Ann Arbor classification and the recent Cotswolds Modification (Appendix 1) (28). The Cotswolds modification takes into account modern imaging with computerized axial tomography (CT) scanning. It allows for the assessment of bulk disease, defined as more than one third of the transthoracic diameter for mediastinal disease, or a peripheral mass of ≥10cm in size. It also differentiates extranodal disease that is due to contiguous spread, from distant extranodal involvement (28).

A thorough history is necessary to determine the presence or absence of B symptoms, performance status of the patient, pruritis, characteristics unique to HL lymph nodes such as change in size, and rarer symptoms like alcohol-induced pain in lymph nodes.

Lymphadenopathy needs to be clearly documented as regions involved, above and below the diaphragm. A chest X-Ray (CXR) will be useful, but a CT scan of the neck, thorax, abdomen and pelvis is mandatory for this. One would also be able to assess on CT scan for the presence of bulk disease and extranodal involvement, whether due to direct extension or distant spread.

A bone marrow (BM) trephine biopsy may indicate bone marrow involvement. Some authors are of the opinion that a bone marrow biopsy may not be necessary in stage IA or IIA disease with no adverse risk factors, as the probability of a positive BM biopsy in these instances is very low (<1%) (28). The pattern of bone marrow involvement in HL is focal, and therefore BM biopsy could easily miss involvement at sites other than the iliac crests. With the increasing use of positron emission tomography with fluorodeoxyglucose (FDG-PET) with CT as part of initial staging to serve as a baseline for comparison to assess treatment response, the question arises as to whether PET/CT can replace BM biopsy (29). Studies have shown that the sensitivity for bone involvement by HL is better with PET/CT than BM biopsy, conventional CT scanning or both (29, 30). A meta-analysis by Pako et al. showed a sensitivity of 76% for FDG-PET, while a combination of later studies showed a sensitivity of 85.7%, and indicated that only 1.1% of BM involvement would be missed if BM biopsy was omitted (29, 31). The 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 involvement was assessed. However, only in 14% of these patients (seven patients) did the stage change from limited stage to advanced disease, thus potentially warranting a change of therapy (30).

Other helpful tests would include a full blood count with a differential, blood urea and electrolytes, liver function tests, erythrocyte sedimentation rate (ESR), serum calcium, uric acid and lactate dehydrogenase (LDH) levels, T cell subsets, immunoglobulin levels and, in the appropriate setting, an HIV test.

The role of PET/CT in the staging of Hodgkin's Lymphoma

The use of positron emission tomography with fluorodeoxyglucose (FDG-PET) in the initial staging of HL is not part of routine practice. PET/CT is more sensitive than conventional CT scanning, picking up 25-30% more disease (32). However, while this may upstage a patient, it may also result in overtreatment and additional related toxicity. In favourable, early stage disease on conventional CT scan only, cure rates are >95% already. 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 currently limited to clinical trial settings and situations where CT scan findings in limited-stage disease are equivocal or radiation field planning is difficult (32).

1.8 MANAGEMENT OF HODGKIN'S LYMPHOMA

The modern management of HL has resulted in excellent cure rates, making long term complications of chemo-radiotherapy a reality and an important consideration as part of disease management. However, despite overall high cure rates of 70-85%, a significant proportion of patients will still have primary refractory disease (5-10%), or relapse after a complete cure (10-30%) (33). The focus and challenge of HL management these days is on efforts to minimize long term toxicities of treatment, while at the same time achieving optimal cure rates and survival.

1.8.1 Risk stratification of patients

While the search continues for clinically useful biological markers that would determine at the outset a patient's response to conventional therapies (e.g. CD 68 positive macrophages), there are a few clinical prognostic markers that are useful in grouping patients according to the severity of their disease and their risk of disease recurrence. This is the current basis for risk stratification of patients into different treatment groups. Patients with Ann Arbor stages I and II fall into limited/early stage HL, while those with stages III and IV have advanced disease.

The German HL Study Group (GHSG) and the European Organisation for Research and Treatment of Cancer (EORTC) have both developed a prognostic scoring system for patients with early stage HL that differs only slightly in terms of the criteria used (Appendix 2) (33). Patients with Ann Arbor stages I-IIA have early stage favorable HL. Patients with stage IIB HL and any one or more of the following risk factors of bulky mediastinal disease, high ESR, ≥3-4 lymph node sites involved, extranodal disease and massive splenic disease, will fall into the category of early stage unfavourable HL. The GHSG classifies patients with stage IIB disease and bulky mediastinal disease or extranodal involvement into the advanced group.

Patients with advanced disease have been further risk stratified, and an International Prognostic Scoring system (IPS)/Hasenclever index, (developed in 1998), is used in this subgroup of patients (Appendix 3) (33, 34). The IPS involves seven variables, each of which independently affects patient outcome. Patients with no risk factors have a five year freedom

from progression (FFP) of 84%, while those with five or more variables have a five year FFP of 42% (33).

1.8.2 Risk adapted treatment

The risk stratification of patients into the above-mentioned subgroups, has allowed for more specific tailoring of treatment modalities and intensities, with the aim of avoiding the overtreatment of low risk patients and the under-treatment of high risk patients, while at the same time attempting to minimize the long term toxicities of chemo-radiotherapy.

Early stage Hodgkin's Lymphoma

For early stage favourable HL, combined modality therapy (CMT) has been shown to be superior to chemotherapy alone (35). Extended field radiotherapy only for early stage disease is no longer used, due to high treatment-related toxicity and high relapse rates. The current standard of care is to administer two cycles of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) followed by 20Gy of involved field radiotherapy (IFRT). More than 95% of patients can be cured with this approach. A large study by the GHSG involving 1,370 patients showed no difference in response to treatment, progression free survival (PFS) and overall survival (OS) with two cycles versus four cycles of ABVD and 20Gy versus 30Gy of IFRT (33).

For early stage unfavourable HL, CMT is also the standard of care, with four cycles of ABVD followed by 30Gy IFRT. The five year progression-free survival (PFS) is about 85-90% (35). Intensification of chemotherapy using two cycles of escalated BEACOPP (bleomycin, etopiside, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone) with two cycles of ABVD versus four cycles of ABVD in 1,655 patients showed an improved freedom from treatment failure (FFTF) at the expense of increased treatment toxicity with escBEACOPP, with no improvement in OS (33).

Advanced stage Hodgkin's Lymphoma

Numerous chemotherapy regimens have been compared for the treatment of advanced HL over the past few years. The results of many randomized trials have shown the best results with

ABVD (33). The five year PFS rates are around 70% (35). In addition to the efficacy of ABVD, it is also easy to administer and is well tolerated by patients. The use of escBEACOPP compared to ABVD, may result in improved PFS, but it is still unclear whether overall survival is improved (35). The problem with escBEACOPP is increased myelosuppression in the short term and infertility in the long term, making it a less feasible option in younger patients. It has also been associated with an increased incidence of myelodysplasia and acute leukaemia, though the numbers to date are small.

The role of radiotherapy in advanced disease is not as clear as in early stage disease. A randomized EORTC trial showed no benefit from radiotherapy in terms of disease recurrence for patients in complete remission (CR), but patients in partial remission (PR) had a clear benefit. The GELA group confirmed this finding for patients in CR. Initial results from the GHSG HD15 trial, using FDG-PET to guide consolidation radiotherapy, has shown a possible role for radiotherapy in PET positive patients with residual active disease (35).

1.8.3 Response adapted treatment and the use of interim PET/CT scans

While the use of clinical prognostic indices is helpful in grouping patients for risk stratified therapy, it does not take into account individual variations in response to treatment. Interim PET scans may complement and possibly supercede the value of prognostic scoring systems. FDG-PET performed early on in treatment may provide some guidance as to the chemo-sensitivity of a tumour and to the risk of relapse.

PET/CT scanning in patients with HL is of particular use for a couple of reasons. FDG-PET scans are able to distinguish metabolically active lymph nodes that are due to disease, from normal lymph nodes. FDG-PET can also reliably determine whether a residual mass (quite common in HL) consists of fibro-necrotic scar tissue or viable tumour cells. Accurate localization of disease is possible with the use of integrated PET/CT scanners.

As with any new modality, it is important to understand the limitations of FDG-PET and to await the results of ongoing randomized trials to assess its appropriate use in clinical practice. FDG-PET has a high negative predictive value (NPV) and a weaker, more variable positive

predictive value (PPV). Hence, while a negative PET scan may be more reliable and clinically useful, a positive scan needs to be interpreted with caution. False positive PET scans may be due to infection, inflammation and supraclavicular brown fat. A negative PET scan also does not totally exclude active tumour due to the limit of resolution of current scanners (36).

Early stage Hodgkin's Lymphoma

Since cure rates are high with current recommendations for treatment of this sub-group of patients, the question arises as to whether IFRT can be totally omitted to further minimize the adverse long term effects of treatment. Eighty percent of patients with early stage disease have a PET negative response after two to three cycles of ABVD, and their PFS will be 95% whether treated with further chemotherapy or radiotherapy (32).The HD6 trial showed a small reduction in five year FFP in patients with limited, non-bulky disease treated with six cycles of ABVD alone (87%), compared to those in whom radiotherapy was added (93%), but better overall survival in the ABVD group (37). The feeling is that a modestly inferior PFS may be acceptable with the omission of radiotherapy, as toxicity will be reduced and effective second line treatment is available for the small number of patients who will relapse. Currently, three large randomized trials are assessing the need for radiation or further chemotherapy or just observation, based on PET findings after two to three cycles of ABVD. The final results of these trials are eagerly awaited.

Advanced disease

Gallamini et al. showed initially that the use of PET post cycle two chemotherapy could predict the outcome for patients with advanced HL. In 260 poor risk patients they found that those who were PET negative had a two year PFS of 95%, as opposed to PET positive patients whose two year PFS was 13% (38). Interim PET positive patients are therefore at higher risk of relapse than interim PET negative patients. This observation could potentially serve as a guide for escalation or de-escalation of chemotherapy in individual patients. However, imaging has been difficult to interpret consistently, and a significant proportion of PET positive patients will still be cured by continuing their original treatment regimen, rather than escalating treatment

intensity with added toxicity. Thus, interim PET scanning is not recommended for advanced stage HL, except in the context of a clinical trial (32).

1.8.4 End of treatment PET/CT

In patients with advanced disease, PET/CT is useful in assessing residual masses at the end of chemotherapy. Due to the high NPV of PET, patients with a negative scan at the end of chemotherapy can be assumed to be in complete remission (CR). Treatment can be stopped in these patients, as further chemotherapy or radiotherapy has been shown to be of no benefit. About 25% of patients with a residual mass at the end of chemotherapy will be PET positive. These patients are currently treated with radiotherapy, despite the knowledge that a certain percentage of scans will be false positive, and some of these masses may be radio-resistant (as chemo-resistance and radio-resistance often co-exist). Results of current trials addressing this issue will hopefully clarify further management (32).

1.8.5 Management of refractory/relapsed disease

Five to ten percent of patients will have primary refractory disease. The prognosis for these patients is poor, as second line chemotherapy has not been able to achieve good cure rates, with long term disease free survival (DFS) in only five to ten percent of patients (39). High dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is the treatment of choice in these patients.

About 10-30% of patients who have achieved a complete remission (CR) will relapse. The risk of relapse is highest in the first one to two years, and is very low at 10 years post CR. At 10-15 years post treatment for HL, the concern about the adverse long term effects of therapy administered supercedes that of relapse. More than 80% of patients in first relapse will respond to salvage chemotherapy, with a median survival of four years. There has been no direct comparison between the various salvage regimens, so no regimen is preferred. Despite good responses to salvage chemotherapy, patients still relapse and succumb to disease progression and treatment complications. Hence, most patients with relapsed disease are now managed with HDCT and ASCT if eligible. Phase II studies and two randomized trials have confirmed an

improved outcome with ASCT compared to conventional chemotherapy, with both trials showing a three year event free survival of more than 50% in the transplant arms (40, 41).

1.8.6 The role of stem cell transplantation in the management of HL

As mentioned above, HDCT and ASCT is now the standard of care for patients in first relapse. A subset of patients (usually those with localized disease at relapse), may however still benefit from radiotherapy. For patients with primary refractory disease, the outcome after HDCT and ASCT is not as promising as in patients who relapse. However, this sub-group of patients may still have a 20-30% chance of cure with ASCT after failing first and second line chemotherapy (42).

PET/CT scanning may have a role to play prior to using highly toxic therapy in patients considered for transplant. PET can be used to assess response to second line chemotherapy prior to HDCT and ASCT. A positive PET scan prior to transplant is associated with a higher relapse rate and a poorer outcome post ASCT. However, not all patients with a positive PET scan will relapse post transplant (7-56% 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 best currently available chance of cure (32).

For patients who relapse after ASCT, the possibility of an allogeneic stem cell transplant (allo-SCT) exists. 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 (42). The increasing practise 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 a lower transplant-related mortality. The increased incidence of chronic graft versus host disease (GVHD) in RIC allo-SCT resulted in lower relapse rates, and this was associated with an improved PFS and OS (42). The possibility of a 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 the allo-SCT setting as well.

1.8.7 Novel therapies in the management of Hodgkin's lymphoma

The development of novel, targeted therapies offers some hope for patients who are chemo-resistant or cannot tolerate the toxicity of conventional regimens.

Monoclonal antibodies

Preparations of monoclonal antibodies to CD30 were previously disappointing due to low responses and high toxicity. Current preparations are much more promising and better tolerated. Brentuximab vedotin is an antibody-drug conjugate comprising an anti-CD 30 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 (43).

Histone deacetylase (HDAC) inhibitors

Panobinostat showed an overall response rate of 27% in 129 patients who failed ASCT. The median PFS was 5.7 months (44).

Mammalian target of rapamycin (mTOR) inhibitors

Everolimus is an mTOR inhibitor that showed an overall response rate of 47% in patients who had relapsed disease. Eight patients had a PR and one patient a CR, with four of these patients being free from progression at 12 months (45).

Rituximab

Rituximab, a chimeric monoclonal antibody to CD 20, has shown good responses in patients with relapsed and refractory NLPHL. Similar good results were seen in patients with cHL who had multiple relapses. However, these responses have been short-lived. Furthermore, patients

with NLPHL who are treated with Rituximab may relapse with a CD 20 negative T cell-rich B cell NHL (46).

Other agents

Cytotoxic agents such as bendamustine, vinorelbine and gemcitabine have produced responses in patients with HL who have been heavily pretreated. The immunomodulatory agent lenalidomide has also shown promising results when used as a single agent, and trials are ongoing in relapsed HL patients and as part of combination chemotherapy in elderly patients with HL (3).

1.8.8 Management of nodular lymphocyte predominant HL

NLPHL is of an indolent nature, with a 10 year OS of about 90%. For patients who have localized disease that has been fully excised, a 'watch and wait' approach is thus reasonable. Patients with localized disease may also benefit from 20-30Gy of IFRT, with the 10 year PFS for stage I being 85% and 65% for stage II disease (35). Patients with more advanced disease are usually treated with combination chemotherapy as in cHL. Rituximab is often added to ABVD. A study of single agent Rituximab in patients with relapsed disease has shown an overall response rate of 94%, but early recurrence. Trials to optimize chemotherapy (with Rituximab) are in progress (33).

1.8.9 Management of the elderly patient with HL

With the second peak in incidence of HL in developed countries in patients over 60 years of age, special consideration needs to be given to the management of HL in this sub-group. Elderly patients with HL tend to do worse than their younger counterparts. DFS and OS rates are about 20% lower than for younger patients with HL. There are a few reasons for this. Older people have more co-morbid disease, e.g. cardiovascular and respiratory. The elderly patient with HL presents with more adverse risk factors. Older patients also generally tolerate cytotoxic chemotherapy poorly, posing a challenge to administer chemotherapy with an intention to cure. Similarly, salvage regimens may be intolerable to the elderly patient. A small study of CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy in elderly

patients has shown a three year PFS of 82% and OS of 91% (47). It is hoped that newer agents such as monoclonal antibodies, which are better tolerated, provide a new avenue for the optimal management of the elderly patient with HL.

1.9 LATE EFFECTS OF TREATMENT FOR HODGKIN'S LYMPHOMA

Acute toxicity from HL therapy is not very different from the treatment of other cancers. Side effects that are dose-limiting include myelosuppression, specific side effects of chemotherapy such as neurotoxicity of vinca alkaloids, and direct organ toxicities from radiation therapy.

More unique to the management of HL is the long term sequelae of chemotherapy, radiation therapy and stem cell transplantation. The reason for this is that most patients with HL are young, and with the excellent cure rates of 70-85% (and more with early stage favourable disease) nowadays, patients are living much longer and hence the late effects of treatment are more apparent.

In 1962, Kaplan developed the concept of extended field radiotherapy (EFRT) for the treatment of HL. The five year survival for this previously lethal disease increased to 70% for patients with localized disease (48). In the 1970's, MOPP (mechlorethamine, oncovin, procarbazine, prednisone) chemotherapy was used and in the 1980's, ABVD was introduced for patients who were resistant or refractory to MOPP. Stem cell transplantation also became available as a treatment option. By the 1990's, the late effects of chemo-radiotherapy became more apparent (49).

A number of late effects of therapy for HL are noted. These complications vary between individuals, based on the period in which the patient was treated and on the modality of treatment that the patient received. All patients should be made aware of these possible late complications, preferably prior to commencing treatment, but definitely at the end of treatment so that adequate follow-up and screening is facilitated. A brief overview of specific complications is given below and some guidelines for screening, so that complications may be detected early.

1.9.1 Secondary malignancies

Secondary cancers are usually due to radiotherapy (RT). They are responsible for most of the morbidity and mortality experienced by HL survivors. The cumulative incidence of developing a second malignancy is 11% at 20 years and 26% at 30 years post treatment. The commonest malignancies are solid organ tumours such as non-melanoma skin cancer, lung cancer, breast cancer and colo-rectal cancer. Sarcomas and non-HL may also occur. These cancers manifest at a median of 14.3 years after treatment, and the risk continues to rise with time (50). Adolescent females are at greatest risk for breast cancer, especially those who have received mantle radiotherapy at doses of >30Gy (15).

Myelodysplasia and acute leukaemia are usually due to the use of alkylating agents in combination chemotherapy such as MOPP and BEACOPP. The median latency is three years, with a usual initial presentation within 10 years (49).

The introduction of involved field radiotherapy (IFRT) and the recent concept of involved node radiotherapy (INRT) has resulted in substantially reduced volumes of radiation to the lungs, heart and breast tissue, for patients previously receiving mantle RT. The standard of care for early stage disease is 20Gy of IFRT, so radiation doses are even reduced. This results in breast tissue receiving 80% less of the radiation exposure than with previous mantle RT. These measures have shown to reduce the risk of a second malignancy (48).

For patients at increased risk of breast cancer, monthly breast self examination and annual clinical examination is recommended. Annual mammography should be performed eight years post treatment or from the age of 25, whichever is later (51).

Patients must be advised to use sun-protective measures and monthly skin self-examination, with recommended annual dermatologic assessment of skin lesions.

For patients who received pelvic, abdominal or spinal RT >30Gy, colo-rectal screening should commence at the age of 35 or 15 years post treatment and repeated with a frequency depending on initial findings (52).

Patients must stop tobacco use, as this further increases the risk of lung cancer.

1.9.2 Cardiovascular disease

Long term cardiac effects may be due to mainly mediastinal RT or anthracycline use, and have a latency of 10 years. The cumulative risk of cardiac disease is 5-10% at 15 years, 16% at 20 years and 34% at 30 years (53-55).

Almost half of cardiac complications are due to accelerated coronary artery disease caused by mediastinal RT at doses of >35Gy. The use of IFRT often involves the superior one third of the heart, and hence the coronary arteries are still within the radiation field. However, IFRT and current recommended treatment doses have reduced cardiac exposure by 60% (48). The use of involved node RT may have a role to play in limiting coronary artery radiation exposure, but it is unclear whether this should be the standard of care currently. Established risk factors for coronary artery disease further accelerate the atherosclerotic process.

Myocardial perfusion may also be affected by mantle RT, causing left ventricular (LV) dysfunction. Anthracycline therapy may cause LV dysfunction and congestive cardiac failure more than one year after treatment if doses above the limit for toxicity (e.g. >550mg/m^2 for a drug such as adriamycin) are administered. However, a significant proportion of patients receiving less than the toxic dose will develop subclinical cardiomyopathy at a median follow up of eight years after treatment (49).

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

Patients at risk for cardiovascular disease need to be advised not to smoke, and existing risk factors need to be aggressively managed. Screening may commence 10 years post treatment with a baseline stress test and echocardiogram. Echocardiogram will not only detect valvular

lesions, but may also provide insight as to LV function. There is evidence that early anti-failure therapy, such as the use of angiotensin coverting enzyme (ACE) inhibitors and carvedilol, for asymptomatic LV dysfunction may prevent progression of cardiomyopathy (56).

Careful clinical examination is mandatory to assess for non-coronary vascular disease, where bruits or absence of pulses will warrant doppler imaging.

1.9.3 Thyroid disease

Up to one third of patients may develop thyroid abnormalities. The commonest manifestation is hypothyroidism, which may be subclinical. RT damages the thyroid vasculature. Paediatric patients are much more sensitive to these effects. Other manifestations may be Grave's disease, thyroiditis, multinodular goiter, adenoma, malignancy and rarely secondary hypothyroidism.

Patients should have annual thyroid examination and thyroid function tests (49). Subclinical hypothyroidism must also be treated with eltroxin, to avoid over-stimulation of a gland that is already prone to malignancy. A palpable nodule needs to be investigated in its own right.

1.9.4 Infertility

With a peak incidence of HL in patients in their reproductive years, infertility is an issue that cannot be ignored. The culprits are usually alkylating agents, and hence ABVD is a more appropriate choice of chemotherapy in younger patients, rather than BEACOPP and the previously used MOPP regimen. Pelvic RT and total body irradiation also cause damage to the gonads. Premature menopause may occur as a result of ovarian failure.

Patients need to be informed as to the risk of infertility prior to therapy, and treatment needs to be tailored to preserve fertility or avoid permanent effects if possible. Males should be informed of the option of sperm banking. Premature menopause needs to be managed in its own right, especially with measures to protect against osteoporosis.

1.9.5 Other late effects

Pulmonary disease may be due to mediastinal RT or the use of bleomycin, usually at a dose of >400mg. Elderly patients may have an idiosyncratic reaction to bleomycin at lower doses (57). Pulmonary manifestations include interstitial pneumonitis, pulmonary fibrosis and acute respiratory distress syndrome.

Chronic fatigue is a common manifestation in over one third of patients. It may persist for long after treatment is completed. The cause is unclear, but may be cytokine related. Reversible causes need to be investigated and treated.

Psychosocial issues have a direct impact on health-related quality of life. HL survivors may experience anxiety, depression and post traumatic stress disorder symptoms long after treatment has been completed. It is important to enquire about social support, financial worries and return to work and school/studies at follow up visits.

Impaired immunity may persist despite treatment discontinuation and cure of HL. Patients should receive the influenza vaccine annually, and those who have received splenic irradiation or had a splenectomy must receive pneumococcal, meningococcal and haemophilus vaccinations.

1.10 HIV AND HODGKIN'S LYMPHOMA

HL and HIV both present with a peak incidence in young adults, and so it was initially thought that the co-existence of these two conditions was purely co-incidental. However, with the advent of anti-retroviral (ARV) therapy, patients with HIV began to live longer, and HL was seen with an increased incidence even in these older patients. 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. Some of these differences are highlighted below.

1.10.1 Incidence and epidemiology

HL is a non-AIDS-defining cancer, with a ten-fold increased incidence in HIV positive patients compared to the general population (9, 58). While AIDS-defining cancers like NHL and Kaposi's sarcoma are decreasing in incidence with the advent of highly active anti-retroviral therapy (HAART), the incidence of non-AIDS-defining cancers like HL, anal carcinoma, lung cancer and hepatocellular carcinoma is on the rise (59).

Powles et al confirmed in their prospective cohort of 11,112 HIV positive patients with cancer, that HAART was associated with an increased risk of HL (60). A possible explanation is that immune reconstitution facilitated by HAART results in an influx of CD4 cells and other inflammatory cells into the tumour microenvironment, and that these provide proliferation signals for the HRS cell.

Almost all cases of HIV-HL are EBV associated. The impaired immunity in HIV allows for uncontrolled proliferation of EBV. The EBV latent membrane protein 1 (LMP-1) is found in practically all tissue samples of HIV-HL. LMP-1 is responsible for constitutive NFkB expression that results in activation of signalling pathways responsible for cell growth and decreased apoptosis.

1.10.2 Pathology

Most cases of HIV-HL in the pre-HAART era were of the mixed cellularity and lymphocyte depleted subtypes of classical HL. These were cases that were associated with marked immune

suppression. With the advent of HAART, mixed cellularity HL still remains the commonest histological subtype in HIV-HL, but nodular sclerosis HL is increasing in incidence again (59).

1.10.3 Clinical Features

HIV-HL displays an aggressive clinical course. Most patients present with B symptoms and advanced stage disease. Extranodal involvement is common, present in 17-62% of patients in a number of studies, with the commonest extranodal site being the bone marrow (40-59%), followed by the liver (17-40%) and then the spleen in 20-30% of cases (9). HAART exposure prior to the diagnosis of HL may modify the clinical picture somewhat. Data from the Italian Cooperative Group on AIDS and Tumours (GICAT) showed that patients who were on HAART already at the time of HL diagnosis were older, had less B symptoms, had higher leucocyte and neutrophil counts, and higher haemoglobin levels (58).

1.10.4 Management

Supportive measures

The optimal management of the HIV-HL patient requires supportive measures, in addition to chemotherapy. Patients should ideally be on HAART and, depending on the CD4 count, chemoprophylaxis for opportunistic infections such as pneumocystis jerovecii pneumonia may need to be instituted. Growth factor support is often required, as these patients tend to tolerate chemotherapy less well and often have bone marrow involvement by HL with impaired reserve.

Specific treatment

As most patients have advanced disease, treatment usually involves combination chemotherapy. Regimens such as ABVD, EBVP, MOPP/ABV hybrid and Stanford V have all been used. Remission rates and overall survival are generally lower than for the general population (9). Special considerations in this group include potential interactions between anti-retrovirals and anti-infectives with chemotherapy.

The benefits of HAART

Patients on HAART do better than HAART-naïve patients. HAART allows for the delivery of standard doses of chemotherapy on time, and there is less morbidity from opportunistic infections. In a study by the Spanish group GESIDA, patients on HAART had higher complete remission rates, and this translated into better overall survival rates (61). HAART has also allowed for the option of salvage therapy by autologous stem cell transplantation in relapsed patients with HIV-HL. However, patients on HAART still do worse than their HIV negative counterparts (9).

The role of PET scans

The role of PET scanning in HIV-HL has yet to be clearly defined. PET scans have to be interpreted with great care. HIV positive patients may have positive PET scans for reasons other than malignancy. Areas of increased uptake in the lung and oesophagus may be due to HIV-related infections. Nodal uptake may also be due to opportunistic infections such as tuberculosis and other malignancies like Kaposi's sarcoma (58). Baseline PET scans prior to treatment may be useful in this setting.

1.11 TUBERCULOSIS AND HODGKIN'S LYMPHOMA

The association between tuberculosis (TB) and malignancy is well documented. This association is even more significant with HL, as demonstrated by Kaplan et al in a large series of 201 patients with malignancy (62). The increased incidence of TB in HL is for a number of reasons. Patients with HL have impaired cellular immunity, which predisposes them to infection with intracellular organisms such as mycobacterium species (63). Furthermore, the chemotherapy used to treat the HL contributes to the immune suppression, facilitating reactivation of dormant TB bacilli and dissemination of infection. This association between TB and HL may be further enhanced by the co-existence of HIV infection in areas where the condition is epidemic.

TB and HL have a similar clinical presentation with regards to constitutional symptoms, the presence of lymphadenopathy and possibly hepatosplenomegaly, bone marrow involvement and overlapping CXR and CT scan features. Some of the skin manifestations of HL may also mimic scrofuloderma that is seen in TB (25). Both conditions may also present with granulomatous reactions histologically in LN and the bone marrow, which may be necrotising in HL as well as in TB. This clinical overlap often leads to a delay in the diagnosis of either condition if they co-exist. Furthermore, TB presenting during or after the treatment of HL may be confused with refractory or relapse of HL respectively (64).

While three-dimensional single-proton emission computed tomography (3D-SPECT) and FDG-PET scans may be useful, they cannot fully differentiate metabolically active tissue due to infection, from malignancy. A case report by Bakheet et al, demonstrated generalized intense FDG-PET uptake by lymph nodes due to TB in a patient with breast malignancy, which was initially confused for metastatic disease or lymphoma (65). Visual interpretation with quantitative analysis and specific cut-off values may help with the specificity of PET scans. However, the most sensitive and specific means of differentiating TB from HL is by tissue biopsy (64, 25). Both conditions can co-exist in the same LN or bone marrow sample. The pathologist needs to look carefully for HRS cells with characteristic staining properties, and perform stains for acid-fast bacilli, cultures for mycobacterium TB and in difficult cases, polymerase chain reaction (PCR) to identify TB organisms.

It is 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 the interpretation of PET scans in the patient with TB and malignancy, thus hopefully providing the clinician faced with diagnostic and management dilemmas with more specific and less invasive solutions.

CHAPTER TWO: PATIENTS AND METHODS

2.1. Study design and population

This is a retrospective study of all adult patients (according to hospital admission criteria - males over the age of 12 and females over the age of 14) presenting at Chris Hani-Baragwanath Hospital, Clinical Haematology Unit, with a confirmed histological diagnosis of Hodgkin's lymphoma, during the period January 1990 to December 2004.

2.2. Methods

Each patient's haematology file was reviewed in great detail. Demographic, clinical, laboratory (including histology), radiographic and management parameters for each patient were documented on a standardised data collection sheet. Response to treatment, complications, relapse (where applicable), date last seen, date of death (where applicable) and overall survival were also documented.

2.3. Data analysis

Data was recorded in an EXCEL spreadsheet and analysed in Stata by a statistician. Missing data was excluded from the analysis. Continuous variables such as age, duration of lymphadenopathy, blood parameters and number of chemotherapy cycles, were reported as a median with the range and/or interquartile range. Age distribution between HIV positive and negative patients was compared using the non-parametric Wilcoxin rank-sum test. Frequencies of categorical variables such as gender, B symptoms, performance status, site of lymphadenopathy, etc. were compared using the Pearson Chi-Squared test. When sub-groups of patients were compared for categorical variables, the Fisher's exact test was used. A life table analysis and Kaplan-Meier survival curves were used to assess overall survival, and to determine prognostic variables affecting survival. Where survival between groups of patients was compared, the stratified log-rank test (stratified for age) was used. A p-value of <0.05 was considered to be significant for all tests used.

CHAPTER THREE: RESULTS

3.1. Patient characteristics

A total of 163 patients with HL were seen between January 1990 and December 2004. The median age was 29 years (range 13-87yrs). The inter-quartile range (IQR) was 23-39 years. There was no clear evidence of a second peak in incidence in older patients, as demonstrated by the histogram below (Figure 3.1). Thirty seven patients (23%) were over the age of 40 years.

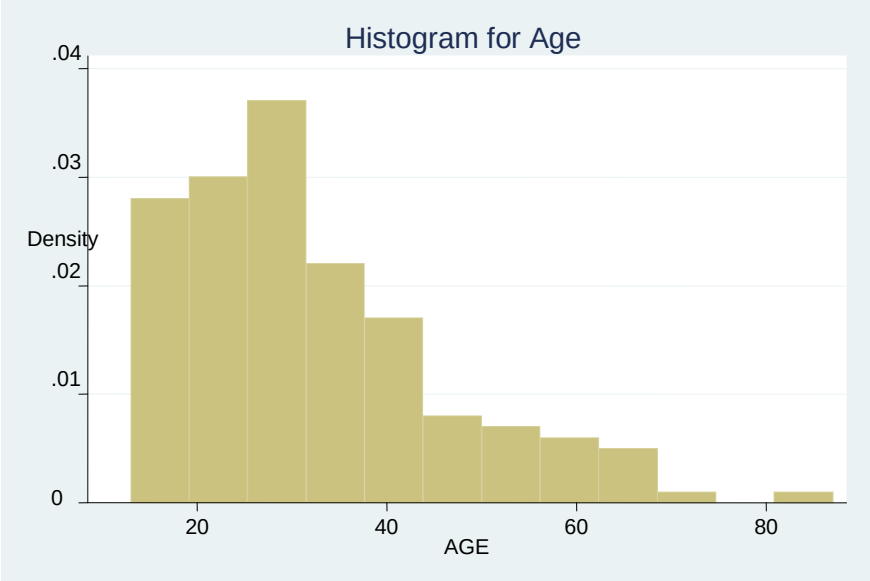


Figure 3.1: Histogram for age

There were 93 males (M) and 70 females (F), with a M:F ratio of 1.3:1. One hundred and fifty patients were Black (145 were South African; two were from Mozambique, two from Swaziland and one from Lesotho; all employed in South Africa), six patients were Indian (South African born), four patients were Coloured, one patient was Caucasian and two patients were classified as 'other' – one of whom was Moroccan and the other from the Comores; both residing in South Africa.

3.2. Clinical features

Performance status (PS) was assessed using the Eastern Cooperative Oncology Group (ECOG) grading system (Appendix 4). The PS was known in 132 patients. Most patients had a PS of 0 and 1 (see Figure 3.2 below).

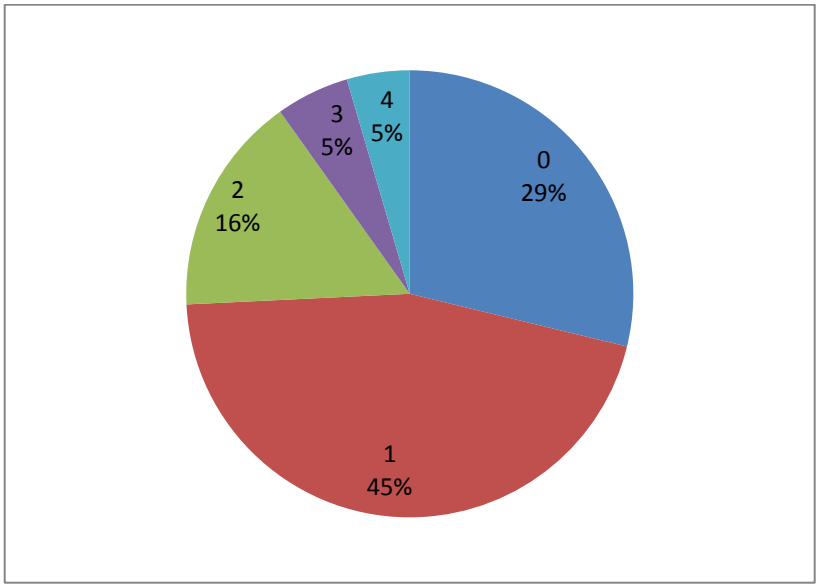


Figure 3.2: Distribution of performance status

B symptoms were defined as unexplained weight loss of more than 10% body weight in the preceding six months, drenching night sweats, and unexplained fever of >38^{o}C in the previous two to four weeks for which there was no other cause. The presence or absence of B symptoms was known in 156 patients. Thirty four patients (22%) had no B symptoms, while 122 patients (78%) had at least one or more of the above-mentioned B symptoms. Twenty one of 154 patients (14%) complained of severe pruritis.

Forty one of 161 patients (26%) had a history of tuberculosis (TB). Nine patients (6%) had TB prior to the diagnosis of HL (five were much earlier in childhood). Of the remaining 32 patients (20%), the diagnosis of TB and HL was simultaneous in eight patients, TB was diagnosed whilst on treatment for HL in 19 patients, TB was diagnosed on relapse of HL in one patient and four patients had TB whilst in remission from HL. Six of the 32 patients also had a history of TB prior to the diagnosis of HL, and thus had recurrent TB. Eleven of 41 patients (27%) with TB were also

HIV positive (forty six patients (28%) in the study were HIV positive; see page 51). Seventeen of 32 patients had pulmonary TB only, three patients had TB meningitis, three patients had TB lymphadenitis, three patients had TB of the bone marrow only, and six patients had disseminated TB (four were HIV positive).

The median duration of lymphadenopathy (LN) or symptoms relating to HL prior to presentation to hospital was five months (range 0.3-132mnths; IQR of 3-11mnths). The characteristics of LN at presentation are highlighted in Table 3.1 below. Most patients presented with involvement of supra-diaphragmatic LN, including the cervical region. Generalised lymphadenopathy was defined as involvement of three or more lymph node regions. Bulk disease was defined as involvement of more than one third of the transthoracic diameter for mediastinal LN, or a peripheral lymph node mass of ≥10cm, and could be evaluated in 151 patients. In the 10 patients who had no LN, the diagnosis of HL was made at an extranodal site. Distribution of LN could not be accurately evaluated in 16 patients (10%) because imaging results were not available for these patients.

Table 3.1: Characteristics of lymphadenopathy at presentation

Characteristic	**Number of patients**	**Percentage**
Supra-diaphragmatic LN	129	79%
Cervical LN	125	78%
Sub-diaphragmatic LN only	8	5%
Generalised LN	86	53%
No LN	10	6%
Non-evaluable	16	10%
Bulk disease	26	17%

Hepatomegaly was present in 61 of 149 patients (41%) at presentation. The hepatomegaly was clinically present in 54 of these patients (36%), and radiological findings (ultrasound or CT scan imaging) concurred in 20 of these patients (13%). The remaining seven patients had

hepatomegaly on imaging only. Six of 143 patients (4%) had liver lesions, described as hypo-echoic lesions on sonar or hypodensities in the liver on CT scan. Three patients had large liver masses on imaging. The liver and spleen characteristics of the nine patients with liver lesions/masses are noted in Table 3.2.

Table 3.2: Liver and spleen characteristics in patients with liver lesions/masses

Patient with liver lesions/masses	Hepatomegaly	Abnormal liver function test	Splenomegaly	Splenic lesions
1	Yes	Yes	Yes	Yes
2	Yes	No	Yes	Yes
3	Yes	Yes	Yes	Yes
4	Yes	Yes	No	Yes
5	No	No	No	No
6	Yes	Yes	No	No
7	Yes	Yes	Yes	No
8	Yes	Unknown	Yes	No
9	No	No	No	Yes

Deranged liver function tests (LFT) such as raised ALP/GGT or ALT/AST were noted in 50 of 151 patients (33%). In 24 patients with hepatomegaly, LFT's were normal. Nine patients with abnormal liver function tests (LFT) had no hepatomegaly.

Sixty of 148 patients (41%) had splenomegaly. The spleen was clinically enlarged in 47 patients (32%), with radiological concurrence (sonar/CT scan) in 26 of these patients (18%). In 13 patients (9%), there was radiological splenomegaly only. Two patients had a massive splenomegaly. Thirty four patients (24%) had splenic lesions, defined as hypo-echoic lesions on sonar or hypodensities in the spleen on CT scan.

Thirty nine patients (26%) had bone marrow infiltration by HL. Thirteen patients (11%) had definite granulomas in the bone marrow. One bone marrow was reported by the pathologist as 'suspect' for a granuloma. Fifteen of 152 patients (10%) had extranodal disease at sites other than the liver, spleen or bone marrow. In eight of these patients, extranodal involvement was by contiguous spread, viz. five with paraspinal masses and three with pleural effusions (proven

on cytology or biopsy to be HL). One patient with a pleural effusion had proptosis of the right eye, but there was no confirmatory imaging. Three of the 15 patients (20%) were HIV positive. Table 3.3 highlights the sites of extranodal involvement and HIV status of patients.

Table 3.3: Distribution of extranodal sites of disease and HIV status

Site of disease	Number of patients	HIV status
Paraspinal mass	5	One patient positive
Pleural effusion	3	Negative
Lytic lesions in bone	2	Negative
Lung nodules	2	Negative
Breast mass (bulk disease)	1	Negative
Tonsillar mass	1	Positive
Gastro-intestinal involvement	1	Positive

One hundred and fifty six patients were evaluable for staging of disease, which was assessed according to the Cotswolds modification of the Ann Arbor staging system (Appendix 1). Staging modalities included clinical examination, CXR and abdomino-pelvic ultrasound or CT scan with contrast – which was the preferred modality, depending on the period of presentation and the modality that was available at that time. Bone marrow aspirate and trephine was done routinely as part of staging. Eight patients (5%) had stage I disease, 41 (26%) stage II disease, 48 (31%) stage III disease and 59 (38%) stage IV disease (Figure 3.3). Limited/early stage disease, defined as stage I and II disease, was present in 31% of patients. Advanced disease, defined as stage III and IV disease, was present in 69% of patients.

Histological subtype was noted according to the Rye classification initially and later the WHO classification of HL. Fifty eight patients (37%) had nodular sclerosis HL (NSHL), 71 patients (45%) mixed cellularity HL (MCHL), five patients (3%) NLPHL (two were actually lymphocyte predominant according to the Rye classification), 23 patients (15%) were 'unclassifiable' and one patient had indeterminate histology. There were no reported cases of lymphocyte-rich HL (LRHL) and lymphocyte-depleted HL (LDHL) in the study population.

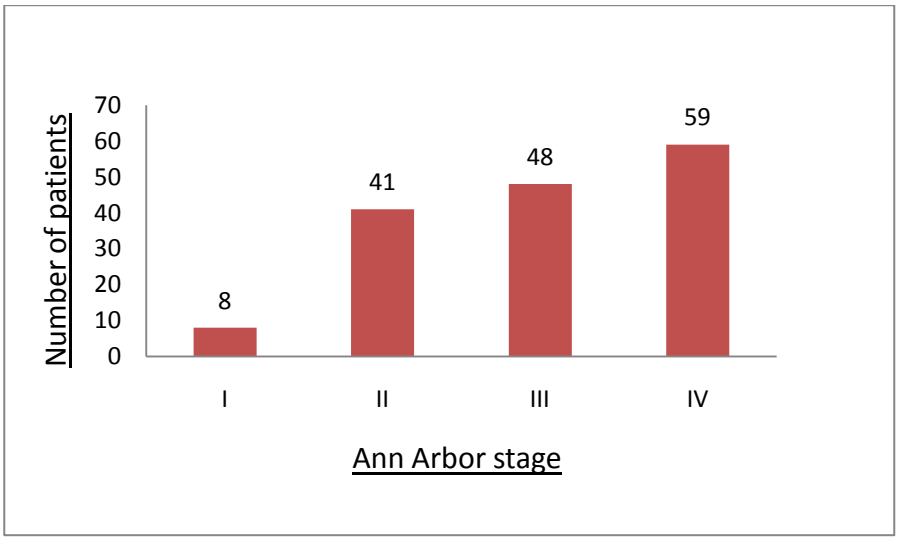


Figure 3.3: Distribution of disease stage

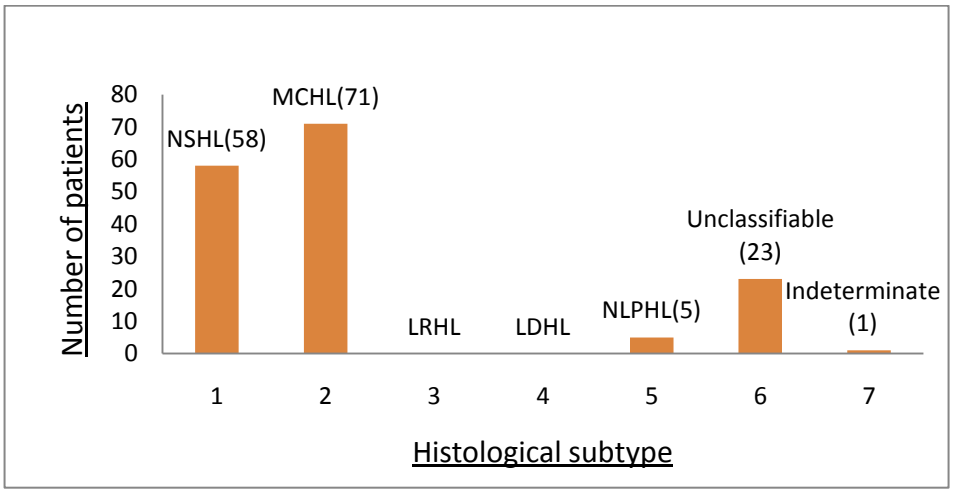


Figure 3.4: Distribution of histological subtypes in the study population

NSHL was the commonest subtype in younger (<40yrs), HIV negative patients (see Figure 3.5). MCHL was the commonest histological subtype seen in older (>40yrs), HIV negative patients, as well as in the HIV positive group (Figures 3.6 and 3.7).

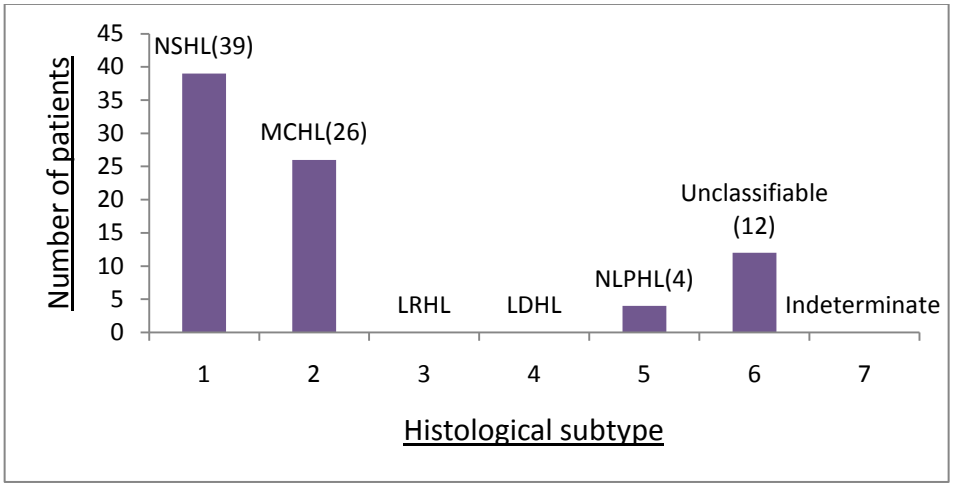


Figure 3.5: Distribution of histological subtypes in younger (≤40yrs), HIV negative patients

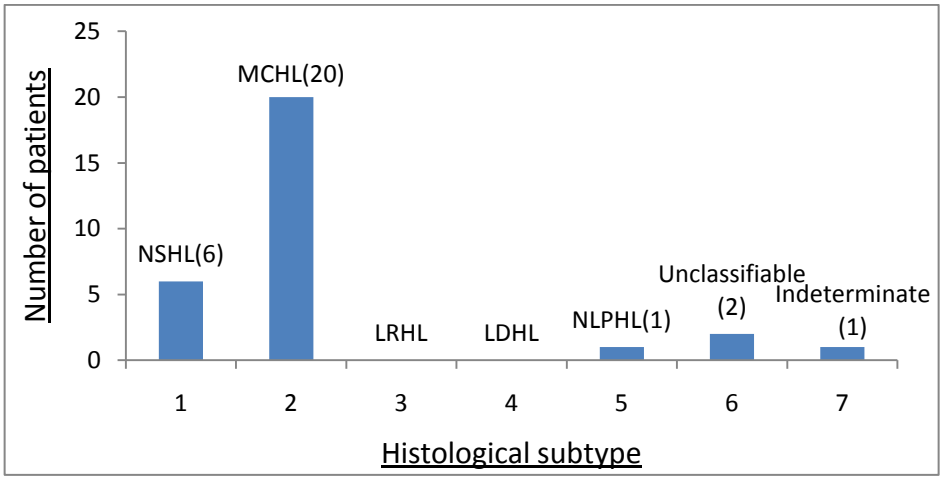


Figure 3.6: Distribution of histological subtypes in older (>40yrs), HIV negative patients

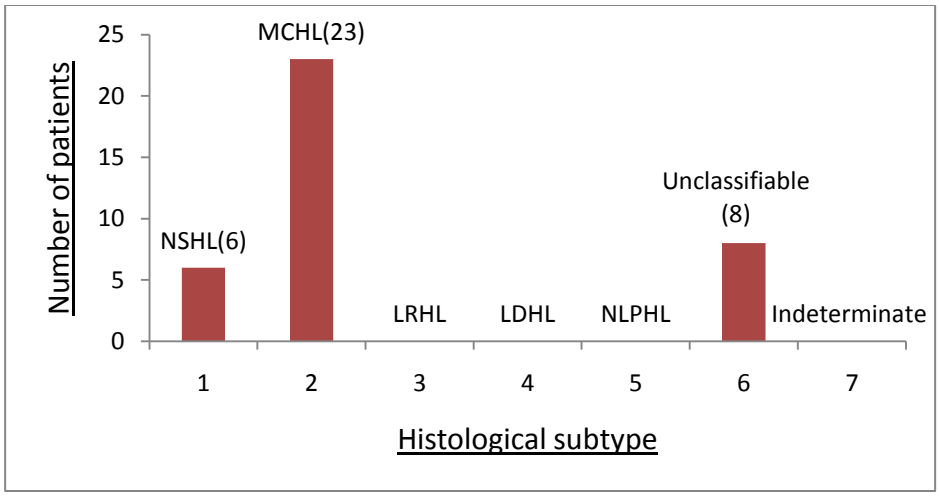


Figure 3.7: Distribution of histological subtypes in the HIV positive population

3.2.1 Uncommon clinical manifestations

Four patients were Coombs positive. Three of the four patients had clinical evidence of haemolytic anaemia. Two patients had a simultaneous diagnosis of AIHA (autoimmune haemolytic anaemia) and HL. One patient developed AIHA on relapse of HL. One patient presented with a pathological fracture of the right neck of femur. One patient had marked cholestasis with a sclerosing cholangitis diagnosed on liver biopsy. One patient presented with a simultaneous diagnosis of HL and chronic lymphocytic leukaemia (CLL).

3.2.2 Clinical presentation of nodular lymphocyte predominant HL

Two patients had lymphocyte predominant HL according to the Rye classification, and three patients were classified as NLPHL according to the current WHO classification. Patient numbers were too small to make any comparisons with classical HL or with NLPHL seen elsewhere. Patient characteristics of this sub-group are shown in Table 3.4.

Table 3.4: Patient characteristics of nodular lymphocyte predominant Hodgkin's lymphoma histological subtype

Characteristic	**Number of patients**
Total number of patients	5
Male / Female	3 / 2
HIV status	All negative
B symptoms	3
Performance status: 0 1 2 3	2 1 1 1
Duration of LN (range)	10-132 months
Early stage disease	2
Advanced disease	3
Bone marrow involvement	0/4 patients
Bulk disease	0
Extranodal disease	2 (paraspinal masses)
Complete remission	3
Relapse	2/3 (both in year two of remission)
Outcome: Dead Lost to follow-up	2 (OS = 872d and 2520d) 3

3.3. Blood results

Haemoglobin (Hb), white cell count (WCC), eosinophil, lymphocyte and platelet counts, albumin, lactate dehydrogenase (LDH) and B_2 microglobulin levels were recorded as medians and ranges. Categories of blood counts, LDH and B_2 microglobulin levels were documented according to laboratory reference values (see table below). Categories of Hb, WCC, lymphocyte count and serum albumin were also documented according to the International Prognostic Scoring System.

Table 3.5: Summary of blood results

Blood parameter	Median	Range	Categories
Haemoglobin (g/dl)	10.05	2 - 16.1	<14 in 82/92 males (89%) <12 in 56/68 females (82%) <10.5 in 93/160 (58%)
White cell count ($\times 10^9$/l)	7.5	0.3 - 34.4	<4 in 31/159 (20%) >11 in 45/159 (28%) ≥15 in 19/159 (12%)
Lymphocyte count ($\times 10^9$/l)	1.42	0 – 7.5	>4 in 8/149 (5%) <1 in 48/149 (32%) <0.6 in 15/149 (10%)
Eosinophil count ($\times 10^9$/l)	0.00	0 – 2.04	>0.4 in 15/149 (10%)
Platelet count ($\times 10^9$/l)	333	16 – 889	<100 in 15/159 (9%) >450 in 49/159 (31%)
Albumin (g/l)	32	18 - 52	<40 in 121/150 (81%)
Lactate dehydrogenase (U/L)	586	256 - 4251	>500 in 86/121 (71%) >1000 in 16/121 (13%)
B_2 microglobulin (mg/l)	2.6	0.1 – 22.51	>2.2 in 65/104 (63%)

Most patients had anaemia. Leucocytosis and thrombocytosis were present in almost one third of patients. Eosinophilia was present in 10% of patients. Leucopenia was more common than thrombocytopenia. Lymphopenia was common, documented in almost one third of patients. Most patients had low albumin levels. LDH levels were raised in more than two thirds of patients. Raised B_2 microglobulin levels were also fairly common.

3.4. Treatment

One hundred and sixty patients (98%) received combination chemotherapy as part of first line treatment. Two patients died of pneumonia, prior to receiving any form of anti-neoplastic therapy. In a third patient, it was unclear if any treatment was received prior to demise. Echocardiograms were not done routinely prior to commencing chemotherapy. Patients who had echocardiograms included those patients presenting over the age of 45 years, patients with a history of underlying cardiovascular disease, patients who had received cumulative doses of anthracyclines and were due to receive a further course of chemotherapy, and patients in whom cardiac examination was abnormal.

The median number of chemotherapy cycles received at first course was eight (IQR 4-10). According to treatment protocols at the time, patients with early stage disease generally received six to eight cycles of BCVPP (BCNU, cyclophosphamide, vincristine, procarbazine, prednisone) and patients with advanced disease generally received eight to twelve cycles of combination ABVD and BCVPP (depending on individual responses). ABVD (six to eight cycles) for early stage disease was introduced much later in the study period. Drug dosages were attenuated for HIV positive patients, and individualised according to CD4 counts. Forty six patients (28%) received BCVPP only, 20 patients (12%) received ABVD only, and 88 patients (54%) were given individualised combinations of ABVD and BCVPP. Six patients (4%) received other forms of combination chemotherapy such as CHOP.

Combined modality treatment was not the standard of care for early stage disease. In patients who received radiotherapy as part of treatment, DXT was administered post chemotherapy to those who had localised residual disease, and as sandwich therapy (between chemotherapy cycles) or post chemotherapy to sites of bulk disease. Patients who presented as medical emergencies due to superior vena cava syndrome and spinal cord compression received urgent DXT prior to chemotherapy. Twenty four patients (15%) in the study received radiotherapy as part of first line combined modality treatment. No patients received radiotherapy alone as treatment.

Ten patients (6%) were considered for HDCT and ASCT as part of salvage therapy. Of these patients, six were transplanted; two at a referral centre and four at Chris Hani-Baragwanath Hospital (CHBH). In the remaining four patients, it was unclear if they were transplanted, as these were earlier patients who were referred to another tertiary centre at the time, and were lost to follow up. In the transplanted patients, two died at the referral centre post transplant (cause unclear) and one patient died at CHBH from severe neutropenic sepsis with positive blood cultures for Methicillin Resistant Staphylococcus Aureus (MRSA) in the post transplant period. Of the remaining three patients who were transplanted at CHBH, all achieved a complete remission. Two are lost to follow up, but remained in remission for the four years of follow up. One patient still follows up at our clinic and continues to be in remission for more than eight years.

Of the patients with NLPHL, both patients who presented with paraspinal masses received radiotherapy as part of initial combined modality treatment. One patient died from septic complications of paraplegia, and the other was lost to follow-up after radiotherapy. One patient died of influenza pneumonia (H1N1); he was in complete remission from HL. One patient who achieved a complete remission did not relapse in the 10 years of follow up. The fifth patient was lost to follow-up after relapse of disease; her remission status was unclear.

3.5. Treatment response

Response to initial treatment was assessed using the modified Cheson criteria for malignant lymphoma (Appendix 5). Cheson's criteria were modified according to the imaging modalities available at the time of assessment. Measures of response included clinical assessment, CXR, abdomino-pelvic ultrasound, CT scan, gallium/PET scan and repeat bone marrow trephine (if initially involved).

Response was assessed on completion of first line treatment, and in the patients who died or defaulted on chemotherapy, the response to treatment was assessed at demise or when the patient was last seen, respectively. Treatment response was assessed as non-evaluable (NE) if patients died or were lost to follow up too early in the course of treatment for assessment, or if clinical examination alone was insufficient (in patients who had no further imaging, or repeat bone marrow trephine in cases of bone marrow involvement).

Table 3.6 summarises treatment responses for HIV negative patients, HIV positive patients and one patient in whom it was unclear when HIV was contracted. More HIV positive patients died during chemotherapy than HIV negative patients. Default rates on chemotherapy were quite high, accounting for almost one third of patients. Many patients had NE response assessments; this was especially true for the HIV positive group. Complete response rates for the two groups were similar (these findings are discussed in sections 4.5 and 4.8.3). When only patients with evaluable disease response were assessed, the rate of a complete response (CR) was 63%, partial response (PR) was 18%, stable disease (SD) was 2% and progressive disease (PD) was 17% (see Figure 3.8).

Table 3.6: Treatment response for HIV negative and HIV positive patients

Patient groups (number induced)	**Subgroups**	**Treatment response***
HIV negative (n=123)	Died on treatment = 18 (15%)	PD = 5 NE = 13
	Defaulted treatment = 34 (27%)	CR = 1 PR = 7 PD = 7 NE = 19
	Completed treatment = 71 (58%)	CR = 49 PR = 9 SD = 2 PD = 5 NE = 6
	Total = 123	CR = 50 (41%) PR = 16 (13%) SD = 2 (1%) PD = 17 (14%) NE = 38 (31%)
HIV positive (n=36)	Died on treatment = 9 (25%)	CR = 1 PR = 1 NE = 7
	Defaulted treatment = 12 (33%)	CR = 1 PR = 1 PD = 1 NE = 9
	Completed treatment = 15 (42%)	CR = 12 PR = 1 NE = 2
	Total = 36	CR = 14 (39%) PR = 3 (8%) PD = 1 (3%) NE = 18 (50%)
HIV status unclear (n=1)	Completed treatment = 1	CR = 1
Total population (n=160)	Total = 160	CR = 65 (41%) PR = 19 (12%) SD = 2 (1%) PD = 18 (11%) NE = 56 (35%)

*CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease

Response types for the 104 patients who could be clearly evaluated are depicted in Figure 3.8 below.

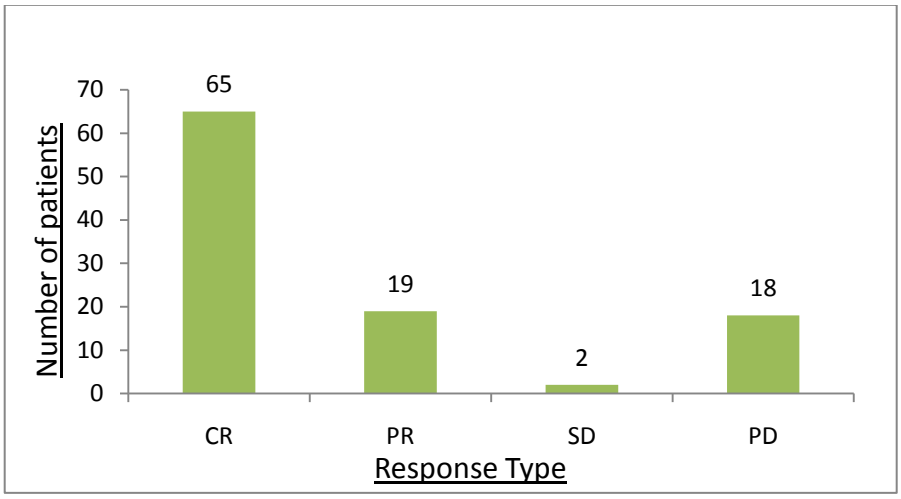


Figure 3.8: Initial response to treatment

Table 3.7 highlights response assessments for disease stage and chemotherapy regimen used. Of the patients with progressive disease, 82% had advanced stage disease. There were no significant differences for treatment response between the two age categories.

Table 3.7: Response assessments for disease stage and chemotherapy regimen

Response type	Early stage disease	Advanced disease	BCVPP only (n=28)	ABVD only (n=6)	BCVPP and ABVD (n=62)
CR	69%	58%	68%	83% (5)	63%
PR	24%	17%	25%	17% (1)	18%
PD	7%	25%	7%	-	19%

Relapse of HL after first line therapy was assessable in 58 out of 65 patients who achieved a CR. Seven patients were lost to follow-up soon after achieving a complete remission. Thirty patients did not relapse within at least one year of follow up. Twenty eight patients relapsed after first line treatment. Of the patients who relapsed, the median time to first relapse (DFS to CR-1) in 23 of these patients was 420 days (range 52-2739).

3.6. Complications

Complications were documented in 60 patients. 83% of these patients had advanced disease, and 17% had limited stage disease. Most complications were acute complications related to HL. Specific therapy-related complications were either acute or delayed (long term). Table 3.8 summarises these complications.

Table 3.8: Complications related to Hodgkin's lymphoma and its treatment in the study population

Complication	**Number of patients**
Acute complications related to HL	
Marked cytopaenias from bone marrow infiltration (requiring blood product/growth factor support)	11
Superior vena cava syndrome	7
Parasthesiae/paraplegia from paraspinal mass	7
Recurrent chest infections (not related to TB)	5
Persistent pleural effusion requiring pleurodesis	4
Deep vein thrombosis	4
Autoimmune haemolytic anaemia	3
Chicken pox	2
Herpes zoster (HIV negative)	2
Acute hepatitis	1
Pathological fracture neck of femur	1
Psychosocial	5
Major depression	1
Specific treatment-related complications	
Acute: Chemotherapy-induced pneumonitis	1
Radiation-induced pneumonitis	1
Haemorrhagic cystitis post autologous stem cell transplantation	1
Dilated cardiomyopathy	1
Delayed: Hypothyroidism	2
Glioblastoma multiforme	1
Adenocarcinoma of the lung	1

3.7. Outcome and factors affecting survival

Currently, 15 patients (9%) are confirmed to be alive. Fifty one patients (31%) have died. Ninety seven patients (60%) could not be traced and are lost to follow up. At last visit or upon demise, 65 patients (40%) were not in remission from their disease, 56 patients (34%) were in complete remission, and in 42 patients (26%) their remission status was unclear. Findings from a life table analysis of survival times for patients who achieved an initial complete remission, a partial remission, and those with progressive disease are highlighted in Table 3.9 below. Patients in CR did not reach 50% survival, and patients in PR did not reach 25% survival. Seventy five percent of the total number of patients who were assessed for treatment response were alive at 63 months, and the population did not reach 50% survival in the analysis time.

Table 3.9: Survival times for patients in complete remission (CR), partial remission (PR) and those with progressive disease (PD)

Response category(n)	75% alive	50% alive	25% alive
CR (65 patients)	90 months	-	-
PR (19 patients)	30 months	77 months	-
PD (18 patients)	13 months	34 months	115 months
Total (102 patients)	63 months	-	-

Kaplan-Meier survival plots for the entire study population, age categories, HIV categories, disease stage categories, histological subtypes and B symptoms are in the figures below. Older patients (>40yrs), HIV positive patients and patients with advanced disease (stages III and IV) had comparatively poorer survival rates, that reached statistical significance. Patients with B symptoms tended to do worse than patients without B symptoms, but this did not reach statistical significance. Comparison of nodular sclerosis, mixed cellularity or unclassifiable histological subtypes did not appear to significantly affect outcome either.

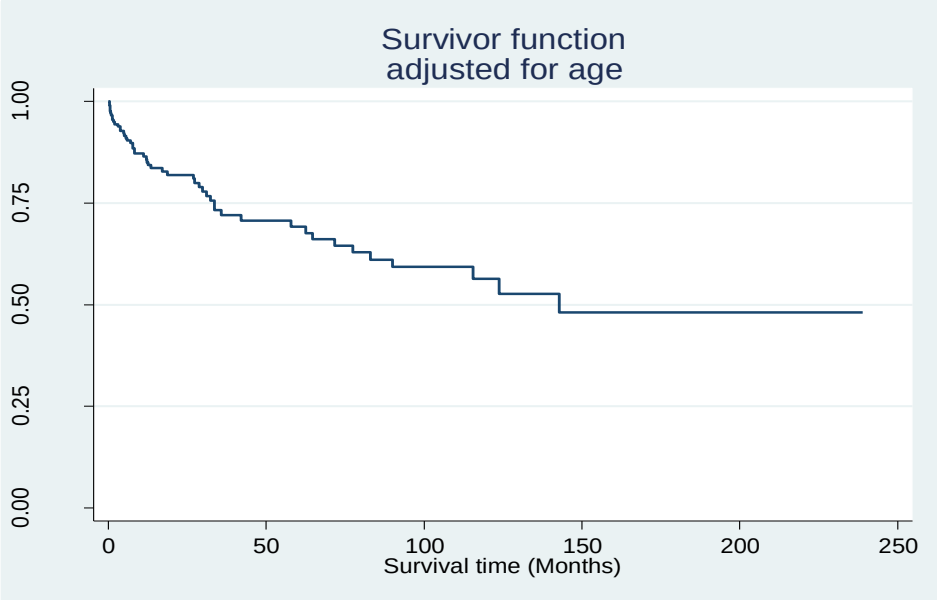
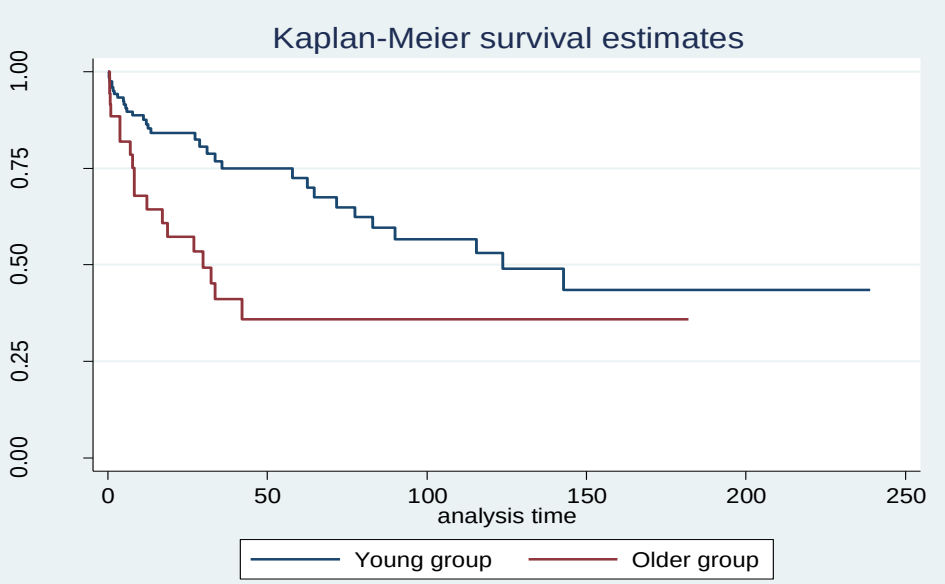
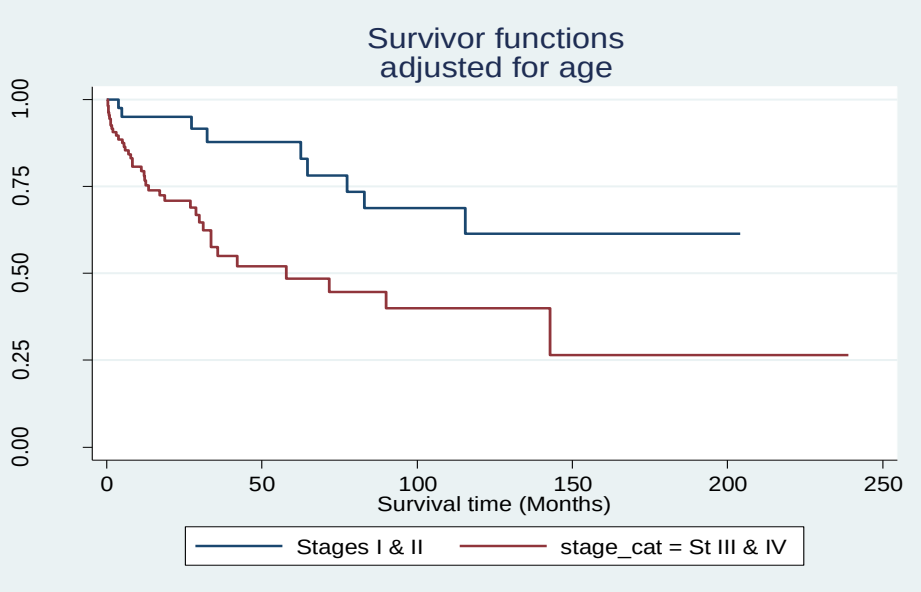


Figure 3.9: Kaplan-Meier survival plot for the study population



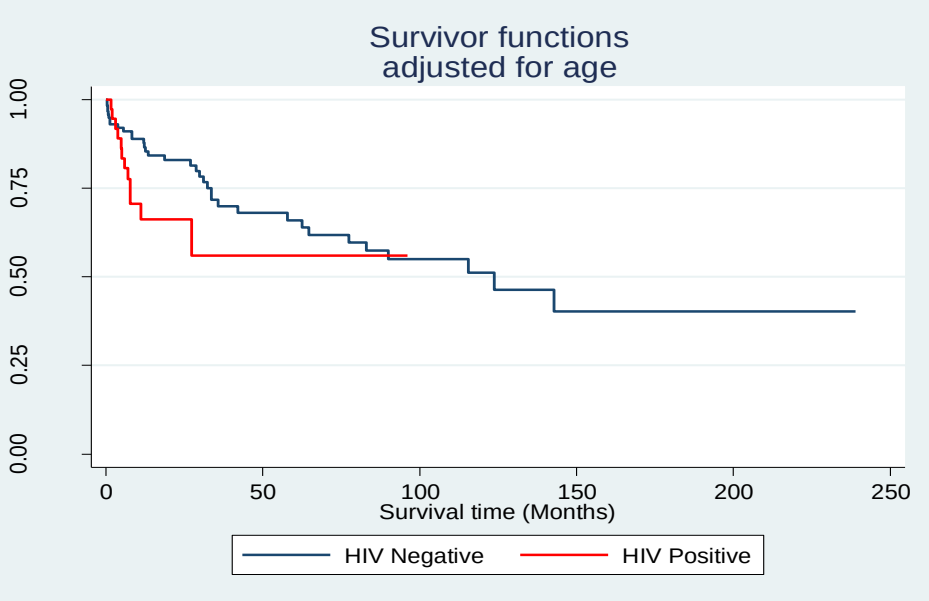
*p value = 0.0041

Figure 3.10: Kaplan-Meier survival plot for younger (≤40yrs) vs older patients (>40yrs)



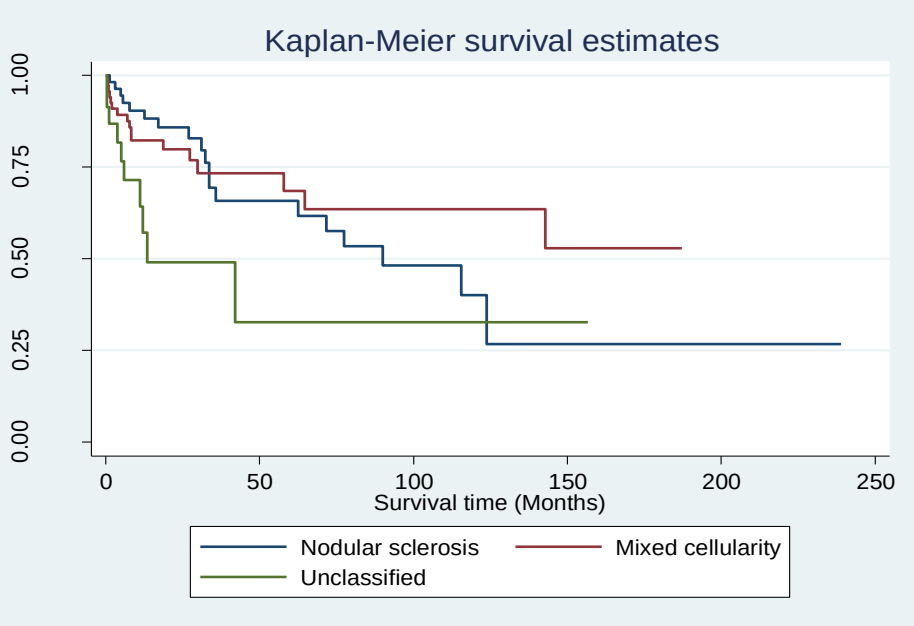
*p value = 0.0018

Figure 3.11: Kaplan-Meier survival plot for early vs advanced stage disease



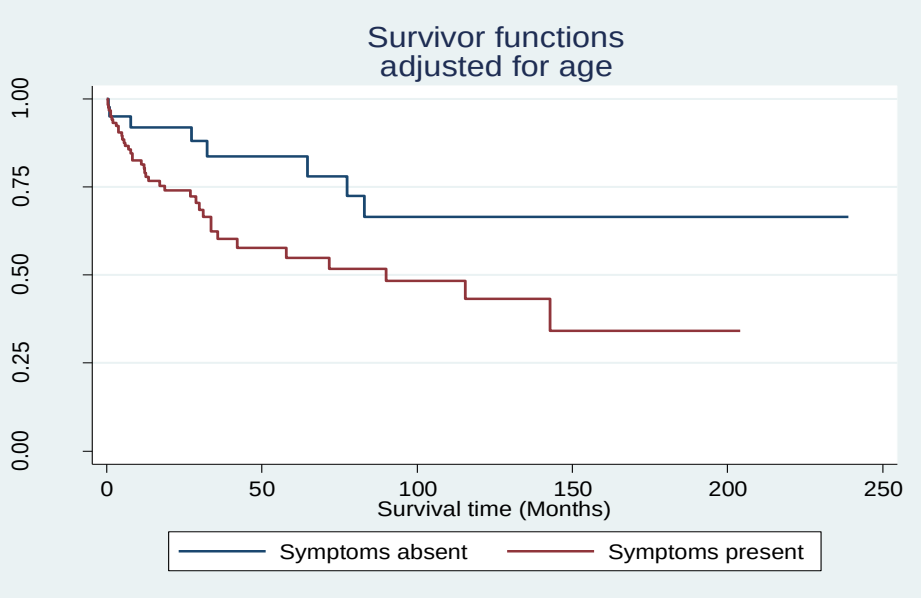
*p value = 0.0073

Figure 3.12: Kaplan-Meier survival plot for HIV negative vs HIV positive patients



*p value = 0.075

Figure 3.13: Kaplan-Meier survival plot for histological subtype



*p value = 0.108

Figure 3.14: Kaplan-Meier survival plot for patients with no B symptoms vs B symptoms

3.8. Patient subgroups

3.8.1. Early stage disease vs advanced disease

Patients with Ann Arbor stage I and II were grouped as limited/early stage disease (ESD). Patients with Ann Arbor stage III and IV were grouped as having advanced stage HL (AD). Disease stage was evaluable in 156 patients. More patients had advanced stage disease. Patients with AD had more B symptoms and a slightly poorer performance status at presentation than patients with ESD. MCHL was slightly more common than NSHL in patients with AD. Further comparisons are highlighted in the table below and will be discussed later.

Table 3.10: Clinical and laboratory characteristics of patients with early stage disease vs advanced disease

	Early Stage Disease	**Advanced Disease**
Number of patients (%)	49 (31%)	107 (69%)
B symptoms	25 (53%)	92 (88%)
Performance status : 0 1 2 3 4	58% 35% 7% 0% 0%	14% 51% 20% 8% 7%
Bulk disease	13 (28%)	13 (13%)
Subtype: NSHL MCHL	40% 52%	36% 40%
Hb <10.5 g/dl	23%	72%
WCC ≥15×10^9/l	4%	15%
Lymphocyte count <0.6×10^9/l	4%	11%
Albumin <40g/l	56%	89%
LDH >500U/l LDH >1000U/l	63% 8%	77% 17%

3.8.2 Younger patients (≤40yrs) vs older patients (>40yrs)

Patients were grouped into two age categories for purposes of analysis, with 40 years being the cut-off age. The most striking observation was the predominance of MCHL as the main histological subtype in older patients. B symptoms were equally prevalent in both age groups. Findings are highlighted in the table below.

Table 3.11: Clinical characteristics of younger patients vs older patients

	Younger patients (≤ 40yrs)	**Older patients (> 40yrs)**
Number of patients	125/162 (77%)	37/162 (23%)
Advanced disease	81/121 (67%)	25/34 (74%)
B symptoms	93/119 (78%)	28/36 (78%)
Performance status: 0 1 2 3 4	28% 49% 14% 4% 5%	32% 35% 23% 10% 0%
Bulk disease	20 (17%)	6 (17%)
Histological subtype: NSHL MCHL	51 (41%) 48 (39%)	7 (21%) 23 (68%)

3.8.3. HIV negative vs HIV positive patients

Forty six patients (28%) in the study were HIV positive. Six patients had a prior diagnosis of HIV (more than one year). In 31 patients, HIV was diagnosed simultaneously with HL. Eight patients contracted HIV after their HL was diagnosed. In one patient, the timing of the HIV diagnosis was unclear. There was no HIV result for one patient. These last ten patients were omitted for statistical analysis. Hence 37 patients were analysed in total.

Similarities and differences between the HIV positive and negative groups are noted in Table 3.12. Both groups had similar median ages at presentation of HL (see box-whisker plot and histogram below). HIV positive patients were concentrated in the third and fourth decades.

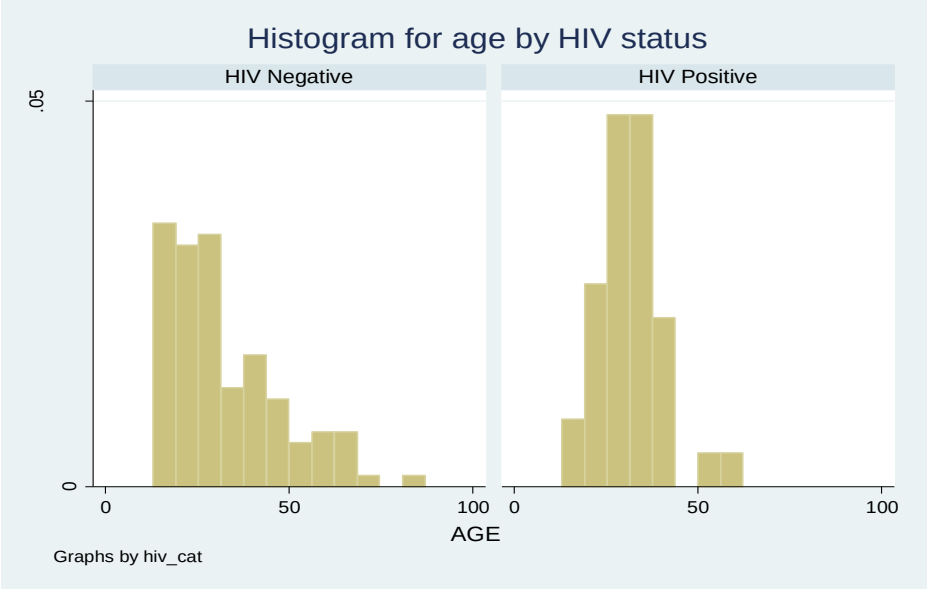


Figure 3.15: Histogram for age by HIV status

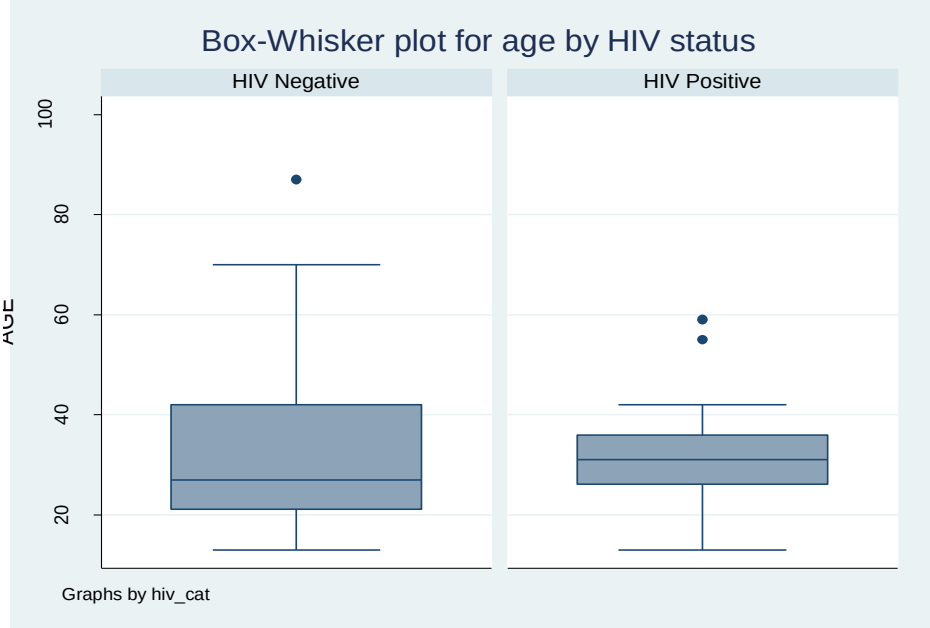


Figure 3.16: Box-Whisker plot for age by HIV status

Table 3.12: Clinical characteristics of HIV positive vs HIV negative individuals

	HIV positive	**HIV negative**
Number of patients	46 (28%) / (37 analysed)	116 (71%)
Age (median/range)	30yrs (range 13-59)	29yrs (range 13-87)
Male:female ratio	1.8 : 1	1.2 : 1
CD4 count at presentation ($\times 10^6$/l)	Median = 186 Range = 32-769 IQR = 98-246	N/A
B symptoms	27 (77%)	86 (78%)
Performance status: 0 1 2 3 4	29% 46% 21% 0% 4%	29% 47% 14% 7% 3%
Advanced disease	28 (78%)	74 (67%)
Bulk disease	4 (11%)	22 (21%)
Bone marrow infiltration	15 (43%)	21 (20%)
True extranodal disease	4 (13%)	13 (12%)
Histological subtype: NSHL MCHL Unclassifiable	6/36 (17%) 22/36 (61%) 8/36 (22%)	45/110 (41%) 46/110 (42%) 14/110 (13%)
TB: Total number of patients Past infection Active disease Post treatment for HL	11/46 (24%) 3/11 (27%) 7/11 (64%) 1/11 (9%)	30/115 (26%) 6/30 (20%) 21/30 (70%) 3/30 (10%)
Treatment response: CR PR PD NE	14/36 (39%) 3/36 (8%) 1/36 (3%) 18/36 (50%)	50/123 (41%) 16/123 (13%) 17/123 (14%) 38/123 (31%)

The HIV positive group had a higher male: female ratio, more advanced stage disease, a much higher incidence of bone marrow involvement by HL and a predominance of MCHL, when compared to the HIV negative group. The incidence of B symptoms and extranodal involvement (excluding liver, spleen and bone marrow) was similar in both groups. The association with TB was similar for the two population groups. TB was most frequently associated with HL in both HIV positive and HIV negative patients (slightly more in the negative group).

Five of the thirty seven HIV positive patients received ARV's. One patient was on ARV's prior to to the diagnosis of HL (in private), one patient started ARV's whilst on chemotherapy for HL and three patients received ARV's whilst in remission from HL. Four patients who were referred to the HIV clinic for ARV's were lost to follow up. All these patients were in remission from HL. One patient refused referral for ARV's due to social issues.

Thirty six patients received induction therapy. One patient had disseminated Kaposi's sarcoma and died of pneumonia prior to any chemotherapy.

Twelve of the 37 patients (32%) have died. Of these patients, nine died early in the course of their disease, whilst receiving chemotherapy (see Figure 3.12, Kaplan-Meier plot). Two patients died from HIV-related complications (pneumocystis jerovecii pneumonia), whilst in remission from HL. Twenty four patients (65%) were lost to follow up. Nine of these patients were in complete remission from their HL at last visit. One patient with HIV-HL is currently confirmed to be alive and is in complete remission.

CHAPTER FOUR: DISCUSSION

4.1. Patient characteristics in the study population

Chris Hani-Baragwanath Hospital is a tertiary government referral hospital in Soweto. Thus, most of the patients in the study were from the south of Johannesburg, mainly Soweto. Other patients were referred from nearby areas, and a handful of patients were from neighbouring countries such as Zimbabwe, Swaziland and Mozambique; hence the preponderance of Black patients in the study population. Many patients were also of poor socio-economic standing. The analysis is therefore fairly representative of a developing, Black population from sub-Saharan Africa.

The population group studied included adult patients as classified by hospital admission criteria. The youngest patient was 13 years old and the very young paediatric population was not really assessed here. Seventeen patients (10%) were younger than 18 years, and 28 patients (17%) were younger than 20 years. Fifty percent of adult patients with newly diagnosed HL at Chris Hani-Baragwanath Hospital from 1990-2004 were aged between 23-39 years. This concurs with the peak incidence of HL in young adults, found elsewhere in the world. The absence of a bimodal presentation, without a second peak in older patients, follows the pattern of most developing countries. Furthermore, the population, consisting primarily of Black South Africans, did not exhibit a tri-modal peak as noted in US Black males (3).

As patients in our setting generally tend to present with malignancies about a decade earlier than in developed countries, and the data failed to show a peak in older patients, patients over the age of 40 years were grouped as older patients for purposes of comparison in the study. The cut-off age of 40 years was used for younger patients. Twenty three percents of patients were in the older age group.

The absence of a marked gender preference, with a M:F ratio of 1.3:1, is typical of HL in adults.

4.2. Clinical features

The majority of patients presented with an ECOG performance status (PS) of 1, followed by a PS of 0. Thus most of the patients, despite some late presentations to hospital and a significant number of patients with advanced disease, were quite well on presentation. B symptoms were prominent, reported in up to 78% of patients. This is much higher than the figure of 35% quoted in the paper by Connors (18), but fairly similar to a small paediatric study from Mali (66). Fourteen percent of patients had severe pruritis, one of whom was treated by dermatologists for intractable pruritis for two years before the diagnosis of HL was made. Thus, the diagnosis of HL must be entertained in a patient with unexplained pruritis.

As it was difficult to accurately document the actual prevalence of TB in the study population, patients were divided into HIV positive and HIV negative groups, and further subdivided into those with a past history of TB, patients with active TB and HL, and patients who had TB post treatment for HL (Table 3.12). The background prevalence of TB in South Africa for 2010 was 795/100 000 population (67). The strong association with TB for the HL study population (26% of patients in total) is likely to be a combination of the background prevalence of TB in the community, as well as an increased incidence of TB in patients with HL (as most patients in the study had active TB) and, more recently, the co-existence of HIV with HL. TB was extra-pulmonary in 15 of 32 patients (disseminated in six patients), and this may suggest impaired immune status from HL and, in some patients, co-existing HIV infection.

The median duration of lymphadenopathy (LN) or symptoms relating to HL (five months) was moderate, but the range was quite vast, with some patients still presenting fairly late to hospital. The majority of patients presented with supra-diaphragmatic lymphadenopathy, which is well described in the literature. Almost all of these patients had involvement of cervical lymph nodes. Thus, supra-diaphragmatic lymphadenopathy in the absence of accompanying cervical LN was highly unlikely to be due to HL. In more than half of the patients, lymphadenopathy was generalized at presentation. Thus, localized disease at presentation of HL was not a common finding in the study group. This was in keeping with the higher proportion of patients presenting with advanced stage disease.

Hepatomegaly and splenomegaly were equally common in the study population. The occurrence of splenic and liver lesions, possibly indicating involvement by disease, closely matched frequencies quoted in the literature, with splenic lesions being four times more common than liver lesions (19). The most common deranged liver function test (LFT) was a mildly raised ALP/GGT.

Some enlarged livers and deranged LFT's resolved before treatment for HL. Other reasons for hepatomegaly and abnormal LFT's included liver congestion from severe anaemia in a number of patients, superior vena cava syndrome in patients with massive mediastinal disease, and occasionally fatty infiltration of the liver in HIV positive patients. This might explain why clinical and radiological correlation of hepatomegaly was poor, as some of these conditions may have been reversed prior to imaging. Though the correlation between clinical and radiological splenomegaly was better than for hepatomegaly, the fact that a number of clinically enlarged spleens were not detected radiologically cannot be explained.

Short of a liver biopsy (which can also miss disease), actual involvement of the liver by HL is otherwise difficult to diagnose. HL may present in various ways in the liver, e.g. severe hepatitis, fulminant liver failure and marked cholestasis (68). A number of patients had mildly deranged ALP/GGT with no obvious cause, which resolved on treatment of HL. One of the study patients had a marked cholestatic picture, and was diagnosed with a sclerosing cholangitis on liver biopsy (see uncommon clinical manifestations below). A few patients in the study had a mild hepatitic picture for which no drug or viral cause was evident. One patient had a severe hepatitis; again no clinical cause was evident except for underlying HL.

Table 3.2 was an attempt to exhibit a correlation between liver lesions, hepatosplenomegaly, deranged LFT's and splenic lesions. Hepatomegaly was present in seven out of nine patients with liver lesions/masses, but there was no clear correlation between liver lesions and deranged LFT's, splenomegaly or splenic lesions. Thirty nine percent of patients with hepatomegaly had normal LFT's (probably for some of the reasons mentioned earlier), while 18% of patients with abnormal LFT's had no hepatomegaly; thus, most patients with deranged LFT's on presentation were likely to have hepatomegaly.

The majority of patients in the study had advanced stage disease at presentation. This is in keeping with disease presentation in most developing countries, including parts of Africa (69, 70). Stage IV disease was mainly due to bone marrow involvement at presentation and was less often due to liver and distant extranodal involvement. One third of bone marrow trephines contained granulomas, which were often difficult to differentiate from TB. TB was actively sought at other sites, and if clinically proven and CXR features were suggestive of TB, anti-TB therapy was instituted as well.

Comparisons were drawn mainly between NSHL and MCHL, as these two histological subtypes were the most commonly seen. For the whole group, MCHL was slightly more common than NSHL, appearing to follow the pattern of a developing nation. However, when subgroups of patients were analysed, more marked differences in the frequencies of NSHL and MCHL became evident. When the younger, HIV negative population was assessed, NSHL was the commoner subtype, though still not as predominant as in first world populations. There was no female preference for NSHL in general. In keeping with findings elsewhere, MCHL was the commonest histological subtype seen in older patients and in the HIV positive population (Figures 3.4–3.7).

4.2.1 Uncommon clinical manifestations

HL and primary sclerosing cholangitis

The association of HL and primary sclerosing cholangitis is rare, but well documented (26). An observation of three cases by Man et al. showed that, in all three cases, HL was diagnosed years after the diagnosis of sclerosing cholangitis (71). The study patient had a simultaneous diagnosis of both conditions, the sclerosing cholangitis being diagnosed on liver biopsy, and the HL diagnosed on a lymph node biopsy.

Richter's transformation of chronic lymphocytic leukaemia (CLL) to HL

Richter's transformation of chronic lymphocytic leukaemia (CLL) to HL has been well described in the literature, occurring with a frequency of 15% of all transformations (72). Often the diagnosis of HL is made months to years after the diagnosis of CLL. However, the two conditions

can also be diagnosed simultaneously. Sometimes, the HL clone may share features with the CLL clone. EBV proliferation is thought to play a role in the development of HL. Purine nucleoside analogues used to treat CLL have been implicated as well, but this has not been consistently proven (73). This type of secondary HL has a poorer prognosis than de novo HL, with median OS rates of 0.8 years (74). The study patient had a simultaneous diagnosis of CLL and HL. HL was diagnosed on LN biopsy and CLL was diagnosed on the staging bone marrow that was done. Unfortunately, the patient defaulted therapy after five cycles of combination BCVPP and ABVD (five months after diagnosis). Clinically, at last visit, neither the HL nor the CLL were in remission.

Autoimmune haemolytic anaemia

Autoimmune haemolytic anaemia (AIHA) is rare in HL (75). It can occur at any time in the course of HL: it may precede HL, be diagnosed simultaneously with HL, present upon relapse of HL or present even when HL is in remission (76). A large study of 1029 patients with HL showed an overall incidence of AIHA of less than one percent. Patients with AIHA on presentation of HL appeared to have a unique clinical profile, viz. older patients with more advanced disease and non-nodular sclerosing histological subtypes (75). Another smaller review, showed a male preponderance for AIHA in HL (76). The study patient profile, though small, may support this finding as two of the patients were male and one was female. However, two patients were in the younger age group, and one patient had early stage disease. One patient had NSHL and two patients had MCHL. None of the patients were HIV positive, but one patient did have a simultaneous diagnosis of TB, which can also be associated with an AIHA. A positive Coombs test does not always accompany clinically evident haemolytic anaemia, as was noted in one patient from the study population.

4.2.2 Nodular lymphocyte predominant HL

Patient numbers for this histological subtype (five in total) were too small to draw any adequate conclusions from the findings (see Table 3.4). However, some of the clinical features did differ from the classic description in the literature. No patients had localized disease, and the two patients with early stage disease had stage II disease. Three patients had advanced

disease and B symptoms. The extra-nodal presentations (viz. paraspinal masses) seen in two patients, were also unusual for this histological subtype. The demise of a patient many years later from influenza pneumonia, whilst in remission from HL, further emphasizes the prolonged immune suppression that patients with HL experience, as well as the need for annual influenza vaccination even for patients in remission.

4.3. Blood results

Most patients presented with anaemia (see Table 3.5). Leucocytosis was mainly on the basis of a neutrophilia, and was not always due to sepsis. Leucopenia and thrombocytopenia were mainly due to bone marrow infiltration by HL. The high B_2 microglobulin level of 22.51 was recorded in a patient with renal impairment.

Variables of the IPS were documented, as more study patients had advanced stage disease. Of the patients with haemoglobin levels of <10.5g/l, 83% had advanced disease (p value=0.000). A white cell count of $\geq 15 \times 10^9$/l was not common, but higher white cell counts were seen in patients with advanced disease without statistical significance (p value=0.058). Low lymphocyte counts did not appear significant. Albumin levels were <40g/l in most patients, including a large percentage with early stage disease. This may be a reflection of the lower albumin levels generally seen in our patients.

4.4. Treatment

More than half of the patients in the study received individualised combinations of BCVPP and ABVD. This is a reflection of the number of patients with advanced disease who were treated as per protocol at the time. Only a few patients received ABVD alone as first line chemotherapy, because BCVPP was initially first line therapy in patients with early stage disease. Current trends are changing though.

Patients were referred to another tertiary institution for radiotherapy. Timing of the radiotherapy depended on the clinical presentation of the individual patient. Involved field radiotherapy was not part of routine practice at the time and patients who received radiotherapy in the study need to be followed up closely for long term complications.

Not many patients were transplanted at CHBH in the early days, and a number of patients were referred to another tertiary centre at the time. The first autologous stem cell transplant in a patient with HL at CHBH was in the year 2000. An increasing number of patients are currently receiving HDCT and ASCT at the CHBH and are the subject of a recent review, the abstract of which was presented at the South African Stem Cell Transplantation Society (SACeTS) Conference in Cape Town in February, 2012 (77). The use of ASCT as salvage therapy in HL in our setting will be a promising study for the future.

4.5. Treatment response

Modified Cheson's criteria were used to assess response after first line therapy. A number of patients could not be assessed for treatment response, either because clinical examination alone was insufficient for an assessment, or because patients died early, or were lost to follow-up early in their treatment.

Complete response (CR) rates were lower than those described in the literature (see Table 3.6 and Figure 3.8). This is probably a reflection of the large number of patients in the population that had advanced stage disease at presentation. Furthermore, in a number of patients, compliance during treatment was erratic, and as a result treatment was often interrupted and not administered on time. Socio-economic circumstances often prevented patients from keeping to their exact follow-up dates, and also contributed to the large number of patients who defaulted on chemotherapy (fifty four percent of patients completed initial treatment). This might also partly account for the higher number of patients with progressive disease.

The forty four percent of patients who died or defaulted on treatment accounts for the large percentage of non-evaluable (NE) treatment responses (much higher in the HIV positive group). Eighteen of 34 patients who defaulted chemotherapy, did so after cycle six of chemotherapy, and these patients may have actually been in remission from their disease.

When only patients with evaluable disease response were assessed, overall response rates were much better – 81% (63% CR and 18% PR).

Of note was that progressive disease (PD) was more prevalent in the advanced stage group (p value=0.065). Age category did not affect treatment response.

CR rates were quite similar for patients treated with BCVPP alone and those treated with combination ABVD and BCVPP (see Table 3.7). Randomised trials comparing similar regimens (MOPP vs ABVD alternating with MOPP) have shown superiority of the alternating regimen in terms of CR rates, FFP and OS (33). The findings in this study are probably because combination ABVD and BCVPP was used mainly in patients with advanced disease, while BCVPP alone was used mainly in early stage disease. Patients with ESD had slightly better CR rates than those

with AD (though this was not statistically significant). ABVD alone was used in too few patients to really compare with other regimens.

Fifty eight of 65 patients who achieved a CR could be assessed for relapse of disease. Twenty eight of these patients relapsed. Of the patients who relapsed, the median time to first relapse (DFS to CR-1) in 23 of these patients was 420 days (range 52-2739).

4.6. Complications

The high rate of acute complications related to HL, such as severe cytopaenias and superior vena cava syndrome (see Table 3.8), may be an indication of the aggressive/advanced nature of the disease at presentation in the study population.

Though the acute therapy-related complications were less common, some important points can be noted from these. The development of a subclinical cardiomyopathy has been well described in patients who receive moderate doses of anthracyclines not exceeding the limit of toxicity, usually at a median of eight years follow-up (49). The study patient developed an overt cardiomyopathy (with recurrent episodes of congestive heart failure) early in the course of her treatment, not having reached toxic doses of anthracycline therapy, and prior to receiving mantle field radiotherapy. She was a young female in her early twenties with no overt risk factors for cardiac disease. The development of subclinical hypothyroidism after radiotherapy in this patient may have potentially worsened the cardiac manifestations later on.

The patient who developed a chemotherapy-induced pneumonitis was a seventy year old elderly female. The most likely cause in this patient was an idiosyncratic reaction to bleomycin. This complication has been well described in elderly patients and needs to be considered when deciding on chemotherapy in the older patient with HL. The same patient developed an adenocarcinoma of the lung 14 months after treatment for HL was completed. This complication was more likely related to the strong smoking history of the patient, as it presented fairly soon after chemotherapy. There was no history of thoracic radiation for HL, but alkylating agents were part of chemotherapy. Whether the presentation of the lung malignancy was accelerated by HL or its therapy provides some food for thought.

The presentation of a glioblastoma multiforme occurred in a patient who was initially treated with combination chemotherapy for HL at the age of 13, and then again upon relapse 7.5 years later. He had no history of cranial irradiation. Glioblastoma multiforme is a well documented second malignancy in patients surviving cancer. Usually, but not always, it is associated with radiation, either to the cranium or rarely to sites adjacent to the spine, including mediastinal radiotherapy (78, 79). The patient was followed up for his intra-cranial malignancy by the neurosurgeons, and was unfortunately lost to follow-up at the clinical haematology department.

The study population is now at the time for surveillance for long term complications of therapy. Unfortunately, most patients have been lost to follow-up, and our personal experience regarding long term toxicity of treatment modalities used in our patients has been very limited.

4.7. Outcome and factors affecting survival

The five year overall survival for the population assessable for treatment response was 75%. Initial response to treatment had some impact on patient survival, with patients who achieved a CR not reaching 50% survival, and those who achieved a PR not reaching 25% survival in the life table analysis (see Table 3.9). Older patients, patients with advanced disease and HIV positive patients had significantly poorer survival rates (see Figures 3.9-3.14).

Almost a third of patients have died. Contributing factors are probably the high number of patients with advanced disease and the erratic follow-up for treatment in a number of patients.

All the patients who are alive are currently in remission from their disease. The high rate of patients who are lost to follow up is cause for concern, especially since these patients cannot be monitored for therapy-related complications. Furthermore, it does make accurate assessment of disease free progression and overall survival problematic, which will impact on the optimal management of our patient population in the future.

4.8. Patient sub-groups

4.8.1. Early stage disease vs advanced disease

Table 3.10 summarises the characteristics of the two groups. A large number of patients (69%) had advanced stage disease on presentation. This did not include stage IIB patients with extra-nodal and bulk disease who, according to the GHSG, would also be classified as having advanced disease. This presentation is consistent with studies in other parts of Africa (69, 70). B symptoms were present in almost all patients with AD. All the study patients with a performance status of 3 and 4 had AD, suggesting that some of these patients were (expectedly) more ill at presentation. Conversely, patients with early stage disease were relatively well at presentation to hospital. Haemoglobin levels of <10.5g/dl were seen in a significant number of patients with AD compared to early stage disease (p value = 0.000). While most patients with AD had albumin levels less than 40g/l, a number of patients with ESD had low albumin levels too, and the difference was not statistically significant. As expected, higher LDH levels (>1000U/l) were recorded in the group with advanced disease, indicating higher disease burden. Interestingly, no histological subtype preference was seen, indicating that advanced stage was a feature of the study population in general. Patients with AD had significantly poorer survival than patients with ESD (Figure 3.11).

4.8.2. Younger patients (≤40yrs) vs older patients (>40yrs)

While the classification of older patients was not the same as in the literature (where patients over the age of 55-60 years are classified as older), significant comparisons could be made, indicating that perhaps the cut-off age of 40 years is acceptable for analysis in our population (see Table 3.11). Older patients had more advanced stage disease, which is well described. Mixed cellularity HL was by far the commonest histological subtype, which is also well documented in older patients elsewhere. B symptoms and bulk disease were equally prevalent in older and younger patients. Also, there were no marked differences in performance status at presentation. Older patients had a significantly poorer survival outcome than younger patients (Figure 3.10).

4.8.3. HIV positive patients vs HIV negative patients

The first study patient diagnosed with HIV and HL was in 1994. Over the 15 year study period, 23% of newly diagnosed patients with HL were HIV positive (37 patients in total). This is similar to the prevalence rate of HIV-HL of 19.5% found by Stein et al. in a South African cohort, which included patients from our centre, for the period 1995-2004 (80). In a recent two year review at CHBH from July 2008 to June 2010, the HIV sero-prevalence of newly diagnosed patients with HL was 67% (9). This is a reflection of the marked increase in prevalence of HIV infection in South Africa during these two different study periods. The prevalence of HIV in South Africa in 1995 was 4.5%, and in 2011 it was 10.6% (81).

The median age at presentation for HIV-HL was 30 years (IQR 25-36yrs). Most patients were young, highlighting the peak incidences for both HL and HIV in younger patients. However, even fewer HIV positive patients were older than 40 years, probably because most patients at the time of the study were ARV naïve and did not live long. The box-whisker plot and histogram for age by HIV status demonstrates these similarities and differences quite clearly (Figures 3.15 and 3.16).

The slight male predominance for HIV-HL in the study population is unexplained. The 2008-2010 review at CHBH showed a slight male predominance (M:F ratio of 1.1:1). The marked male predominance of more than 80% found in other series probably reflects the high prevalence of HIV in intravenous drug users and homosexual males, while the main mode of transmission in South Africa is by heterosexual contact (9). Also, the HIV prevalence in South Africa is higher in females than males: 10.9% vs 9.1% in 2005 and 12.6% vs 9.2% in 2011 (81).

Most patients with HIV-HL had B symptoms and advanced stage disease. However, the prevalence of B symptoms was the same as in the HIV negative population, while the percentage of HIV positive patients with advanced disease was higher than in the HIV negative patients (see Table 3.12).

The median CD4 count at presentation was lower than that quoted in most studies, but consistent with the findings at CHBH in 2008-2010 (9). All the patients, except for one, were

ARV naïve at the time of diagnosis of HL. This is probably because 31 of the 37 patients had a simultaneous diagnosis of HIV and HL. Furthermore, anti-retroviral (ARV) therapy was only made available to patients at CHBH towards the end of 2004. Though 45% of the patients in the later review were on ARV's, those patients still had lower CD4 counts at diagnosis of HL.

MCHL was the commonest histological subtype seen in HIV-HL, with an even higher incidence than in the recent series at CHBH (9). NSHL was the second commonest histological subtype. Surprisingly, there were no patients with lymphocyte depleted HL (LDHL), and this could not be explained, as this subtype is supposed to be seen with an increased incidence in HIV-HL. A number of patients had disease that could not be classified, and whether some of these were actually of the lymphocyte depleted subtype needs to be considered. The recent 2008-2010 series of HIV-HL from CHBH showed a prevalence of LDHL of eight percent (2/24 patients), and more recently, unpublished data has revealed another patient with HL of the lymphocyte depleted subtype who has been diagnosed at CHBH.

The high incidence of bone marrow involvement is typical of HIV-HL. Of the patients with other extra-nodal sites of disease, one had gastro-intestinal involvement and one patient a tonsillar mass. These are unusual sites of extra-nodal presentation for HL, which is also well described in HIV-HL.

The percentage of patients with TB was similar for the HIV positive and HIV negative groups, and this is probably a reflection of the high background prevalence of TB in the community in general (see Table 3.12). Slightly more HIV negative patients had active TB than HIV positive patients. The reason for this is probably that there were many more HIV negative than HIV positive patients in the study. In the 2008-2010 review of HIV-HL at CHBH, the proportion of patients with TB, and active TB, in HIV-HL was more than double than in the HIV-HL study population here (59% vs 24% and 38% vs 15%). This is most likely a reflection of the increased background prevalence of TB from 377/100 000 population in 1995 to 795/100 000 population in 2010 (67).

Overall response rates (CR and PR) were only slightly better for the HIV negative group compared to the HIV positive group – 54% vs 47% (see Table 3.12). The reason for this is

probably that the HIV positive group was much smaller than the HIV negative group, and fifty percent of the HIV positive group also had a NE treatment response. The large number of HIV positive patients with a NE treatment response can be attributed to the patients who died and defaulted early on during treatment.

More HIV positive patients died on treatment than HIV negative patients. Nine out of twelve HIV positive patients who died in the study, died on chemotherapy, and seven of these patients died early on within four cycles of chemotherapy. The fact that the majority of these patients had bone marrow involvement by HL and were not on HAART must have contributed to these deaths, as six of these patients died from worsening cytopenias on chemotherapy, and sepsis consequent on the neutropenia.

Almost a third of HIV-HL patients have died. The majority of these patients died early on during the first course of chemotherapy (despite attenuated doses of chemotherapy). This is clearly demonstrated in the Kaplan-Meier survival plot (Figure 3.12). Clearly demonstrated in the plot also, is the significantly superior survival of HIV negative patients over HIV positive patients in the study (p value = 0.0073).

4.9. Study limitations

Being a retrospective study, there were some limitations.

As data was collected from patient records, there was always an element of some missing data for each variable. Fortunately, patient numbers were large enough to still make reasonable inferences from the data.

Erythrocyte sedimentation rate (ESR) results were not available for a number of patients, and it would have been useful to assess their utility as part of the IPS in patients with advanced disease, especially in patients with concomitant HIV or TB, as both these conditions can raise the ESR. Similarly, EBV studies were not done routinely at the time, and these would have been useful to assess positivity in the study population, especially the HIV positive group.

PET scans have become available at the CHBH in the last few years only, and therefore criteria for treatment response assessments had to be modified according to imaging modalities available at the time for each patient. An attempt was made to be as uniform as possible when assessing the treatment responses. Therefore, a number of patients could not be included for assessment of treatment response, as clear assessments could not always be made on available data/imaging.

The large number of patients who are lost to follow-up has impacted on the accurate assessment of treatment response, disease-free survival and overall survival. It has also resulted in limited experience regarding the long term toxicities of treatment modalities used in the study population.

CHAPTER FIVE: CONCLUSION

The main aim of this study was to document the demographics and clinical features of adult patients with Hodgkin's lymphoma at CHBH, and to compare these findings with findings elsewhere in the world. This study has shown that the presentation of HL in adults at CHBH exhibits shared characteristics of developed and developing nations, though mainly those of a developing nation. Another important finding was the higher prevalence of TB in the study population (HIV positive and negative patients) compared to the background prevalence in the community, supporting the positive association of HL and TB. The initial response to treatment impacted on survival, with patients achieving a complete response to treatment displaying longer survival times than those with a partial response, who had better survival times than patients with progressive disease. Other prognostic factors affecting survival in the study population included age of patient, stage of disease and HIV status.

New trends in the management of HL at CHBH are emerging. With the increasing use of HDCT and ASCT in patients with relapsed/refractory disease at CHBH, it will be interesting to assess the impact on patient outcome in the future. The increasing availability of PET/CT scans for response assessment will aid in the optimal management of our patient population, whilst at the same time limiting treatment-related toxicity. Furthermore, the increasing numbers of patients with HIV-HL, as well as the accessibility to combined anti-retroviral therapy (cART) for all these patients, is now revolutionising the management of this subgroup of patients at CHBH, and it will be interesting to reassess disease characteristics and outcome for these patients in the future.

The large number of patients lost to follow-up continues to be cause for concern, especially since many of these patients are probably well and disease outcome and therapy-related complications cannot be adequately assessed. The importance of completing treatment and continuing long term follow-up needs to be stressed to patients at all times, and contact details for patients need to be carefully documented and updated at each visit.

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APPENDICES

APPENDIX 1

Ann Arbor staging classification (Cotswolds modification) (28)

Stage 1 Invovement of a single lymph node (LN) region/structure (eg. spleen, thymus, waldeyer's ring) or single extralymphatic site (1E)

Stage II Involvement of 2 or more LN regions on the same side of the diaphragm; localised involvement of 1 extranodal organ/site and LN regions on the same side of the diaphragm (IIE); number of anatomical sites indicated by a subscript, eg. II_3

Stage III Involvement of LN regions/structures on both sides of the diaphragm, which may also be accompanied by localised involvement of an extranodal organ/site (IIIE), involvement of spleen (IIIS) or both (IIISE)

III_1 ± involvement of spleen, splenic hilar, celiac or portal nodes

III_2 With involvement of para-aortic, iliac or mesenteric nodes

Stage IV Diffuse involvement of 1 or more extranodal sites (eg. bone marrow, liver or other extranodal sites not contiguous with LN – *cf*. 'E' below).

A Absence of constitutional symptoms

B Fevers >38^{o}C, weight loss >10% in 6 months or drenching night sweats

Additional subscripts applicable to any disease stage:

X Bulky disease (widening of mediastinum by >33% or mass ≥10cm)

E Involvement of a single extranodal site contiguous or proximal to known nodal site

APPENDIX 2

Unfavourable criteria for limited stage Hodgkin's lymphoma (33)

GHSG	EORTC
Large mediastinal mass	Large mediastinal mass
High ESR	High ESR
≥4 sites	≥3 site
Age ≥50	Extranodal disease
	Massive splenic disease

GHSG = German Hodgkin Study Group

EORTC = European Organisation for Research and Treatment of Cancer

ESR = erythrocyte sedimentation rate

APPENDIX 3

International prognostic scoring system (IPS) / Hasenclever index for advanced Hodgkin's lymphoma (33)

Adverse Prognostic factors

1) Age ≥45 years

2) Stage IV

3) Male sex

4) White blood count ≥15 000 cells/µl

5) Lymphocyte count <600 cells/µl or <8%

6) Albumin <4.0 g/dl

7) Haemoglobin <10.5 g/dl

Number of factors	5 year FFP (%)	5 year OS (%)
(Outcome according to prognostic score)		
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
≥5	42	56

FFP = freedom from progression

OS = overall survival

APPENDIX 4

WHO / ECOG performance status (19)

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, eg. light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

APPENDIX 5

Revised response criteria for malignant lymphoma, 2007

RESPONSE	*DEFINITION*	*NODAL MASSES*	*SPLEEN, LIVER*	*BONE MARROW*
CR	Disappearance of all evidence of disease	- FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative - 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 measuable 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; 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 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		
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 identifed node>1 cm in short axis Lesion PET positive if FDG-avid lymphoma or PET positive prior therapy	>50%increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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