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Mature T-cell and natural killer Cell neoplasms at Chris Hani Baragwanath Academic Hospital

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Mature T-cell and Natural Killer Cell Neoplasms at Chris Hani Baragwanath Academic Hospital

AYESHA OMAR

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

Johannesburg, 2019

ETHICS COMMITTEE APPROVAL

This research was approved by the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (clearance certificate number: M131117).

DECLARATION

I, Ayesha Omar, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (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.

……

Ayesha Omar

Date: …….

DEDICATION

I dedicate this research report to my husband, children, parents and patients.

ACKNOWLEDGEMENTS

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

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ABSTRACT

Introduction

Non-Hodgkin Lymphoma (NHL) is the most common haematological malignancy encountered in adults at Chris Hani Baragwanath Academic Hospital.

Worldwide, there has been an increase in the incidence of NHL. This is related to the increased use of iatrogenic immunosuppression, environmental factors such as exposure to radiation and other occupational hazards including pesticides and herbicides, and most importantly in our setting, exposure to viruses such as HIV. The increase in incidence is particularly true with regard to B-cell NHL.

Non Hodgkin Lymphoma (NHL) constitutes a heterogeneous group of clonal lymphoid neoplasms of B-cell, and T-cell/NK-cell origin. Each of these two broad immunophenotypic categories is further subdivided into precursor or peripheral/mature subtypes.

This study was aimed at retrospectively exploring the mature or peripheral T-cell/NK-cell lymphoid neoplasms in adults, as seen at the Clinical Haematology Unit, Department of Medicine, Chris Hani Baragwanath Hospital (CHBAH) during the period 01/01/2004 to 01/01/2015 (12 years).

Patients and Methods

The study entailed a retrospective review of patient records with mature/peripheral T-cell/NK-cell NHL as indicated above. Descriptive analysis was conducted through the computation of frequency tables for categorical variables and appropriate measures of central tendency i.e. mean ± SD/median (IQR) for continuous variables. Kaplan Meier survival curves were plotted to

determine the survival probability of the patients based on demographic and clinical characteristics.

Results

A total of 52 patients were included in the study. Ninety four percent were of black ethnicity, in keeping with the patient demographics at CHBAH. There were 30 females (58%) and 22 males (42%), with a female to male ratio of 1.4:1. The median age of the patients was 46 years, with a range of 21-82 years. The peak frequency of NHL was in the fifth decade of life. HIV seropositivity was noted in 11 patients (21%). For the whole group, cutaneous manifestations were the most common presenting feature (73%). Other dominant clinical features were 'B' symptoms (65%), hepatomegaly (40%), bone marrow involvement (39%), lymphadenopathy (29%) and splenomegaly (27%). Advanced stage disease was seen in 50% of the patients with PTCL and 42% of the patients with CTCL. An ECOG performance status of ≤ 2 was noted in the vast majority of patients (86.5%). PTCL (63%) was more common than CTCL (37%). The most common histological subtypes in the PTCL patients were PTCL, NOS; ALCL and ATLL, while in the CTCL patients, MF and SS were the only subtypes noted.

Combination chemotherapy was the mainstay of treatment for PTCL, while skin directed therapies and chemotherapy were used in patients with CTCL. The response to treatment was more favourable in the CTCL group.

Of the 52 patients, 14% are alive, 65% have died and 21% are lost to follow up. The median overall survival of the patients was 14 months.

Conclusion

The T-cell/NK-cell lymphoid neoplasms account for only 7% of the lymphoid neoplasms seen in adults at CHBAH, as compared to 10-15% quoted in the literature. At CHBAH, patients present at a younger age, with a female predominance. The majority of the patients with the mature/peripheral T-cell/NK-cell lymphoid neoplasms have a PTCL (63%), while the CTCL are present in 37% of the patients. The subtypes of PTCL are similar to that described in the literature, with a noticeable paucity of the AITL and NK-TCL subtypes. PTCL when compared to CTCL, are statistically significantly different in that they present with lesser patients with an ECOG PS of 1 and 2 (p=0.030), have more 'B' symptoms (94% vs 16%; p=0.00), have less cutaneous involvement (58% vs 100%; p=0.01), more frequent hepatomegaly (52% vs 21%; p=0.042), a higher association with HIV (30% vs 5%; p=0.04), poorer response to treatment and a poorer outcome (lower median survival rate of 6 months, compared to 39 months).

TABLE OF CONTENTS

ETHICS COMMITTEE APPROVAL i

DECLARATION ii

DEDICATION iii

ACKNOWLEDGEMENTS iv

ABSTRACT v

TABLE OF CONTENTS viii

LIST OF TABLES xi

LIST OF FIGURES xiii

LIST OF ACRONYMS/ ABBREVIATIONS xiv

1.0. CHAPTER ONE: LITERATURE REVIEW 1

1.1. Introduction 1

1.1.1. Overview of Lymphoma 1

1.2. Epidemiology of T-cell Lymphoma 2

1.3. Pathogenesis of Peripheral T-cell Lymphoma 2

1.4. Classification of T-cell Lymphoma 3

1.4.1. T-cell/ Natural Killer cell Non-Hodgkin Lymphoma 6

1.4.1.1. Peripheral T-cell Lymphoma Not Otherwise Specified (PTCL, NOS) 8

1.4.1.2. Angioimmunoblastic T-cell Lymphoma (AITL) 8

1.4.1.3. Systemic Anaplastic Large Cell Lymphoma 9

1.4.1.4. Adult T-cell Leukaemia / Lymphoma 12

1.4.1.5. Extranodal Natural Killer T-cell Lymphoma, Nasal Type 13

1.4.1.6. Hepatosplenic T-cell Lymphoma 14

1.4.1.7. Enteropathy associated T-cell Lymphoma 15
1.5. Clinical Features of T-cell Lymphoma 17
1.6. Diagnosis and Staging of Peripheral T-cell Lymphoma 18
1.7. Management of T-cell Lymphoma 19
1.8. HIV and T-cell Lymphoma 20
1.9. TB and T-cell Lymphoma 20
1.10. Cutaneous T-cell Lymphoma (CTCL) (Extra-Nodal) 21
1.10.1. Pathogenesis of Cutaneous T-cell Lymphoma 25
1.10.2. Classification of Cutaneous T-cell lymphoma 26
1.10.3. Clinical presentation of Cutaneous T-cell lymphoma 28
1.10.4. Diagnosis of Cutaneous T-cell Lymphoma 28
1.10.5. Treatment of Cutaneous T-cell lymphoma 30
2.0. CHAPTER TWO: PATIENTS AND METHODS 33
2.1. Study Design 33
2.2. Study Population 33
2.3. Methods and Procedures 33
2.4. Sampling 34
2.5. Data Management 34
2.6. Data Analysis 34
3.0. CHAPTER THREE: RESULTS 36
3.1. Demographics 36
3.2. Comorbidities 39
3.3. Clinical features 42

3.4. Subtypes of T-cell and NK-cell Non-Hodgkin lymphoma 43
3.5. Comparison between the Cutaneous and Peripheral T-cell lymphomas 44
3.6. Comparison of results by HIV status 48
3.7. Kaplan Meier survival curves 51
4.0. CHAPTER FOUR: DISCUSSION 57
4.1. Patient demographics 57
4.2. Clinical manifestations 59
4.3. Laboratory Results 59
4.4. Comorbid diseases 60
4.5. HIV and Tuberculosis 60
4.6. Treatment 61
4.7. Study Limitations 62
5.0 CHAPTER FIVE: CONCLUSION 63
REFERENCES 64
APPENDIX A: Normal blood parameters 70
APPENDIX B: Data collection sheet 71
APPENDIX C: Histology form 75
APPENDIX D: Revised response criteria for Malignant Lymphoma, 2007 79
APPENDIX E: Ethics approval 80
APPENDIX F: Ethics approval continued 81
APPENDIX G: Turn-it in report 82

LIST OF TABLES

Table 1.1: WHO Classification of the Mature T-cell and NK-cell neoplasms (2008) 4

Table 1.2: WHO Classification of the Mature T-cell and NK-cell neoplasms (2016) 5

Table 1.3: Clinical features of ALK-positive and ALK-negative ALCL (systemic type) and PTCL, NOS 10

Table 1.4: ATLL: Classification and characteristics 13

Table 1.5: Eastern Cooperative Oncology Group - measure of functional status 17

Table 1.6: Ann Arbor staging system (Cotswold Modification) 19

Table 1.7: Staging of Cutaneous T-cell Non-Hodgkin Lymphoma 27

Table 1.8: Revised staging of MF and SS based on the ISCL 27

Table 1.9: Algorithm for the diagnosis of MF developed by the ISCL 29

Table 1.10: Summary of the available treatments for patients with MF and SS 30

Table 3.1: Gender distribution 36

Table 3.2: Distribution of patients by ethnicity 37

Table 3.3: ECOG performance status 38

Table 3.4: Distribution of patients by comorbidity, excluding HIV and TB 39

Table 3.5: TB in association with T-cell/NK-cell Lymphoma 40

Table 3.6: Diagnosis of TB 41

Table 3.7: Distribution of patients by HIV status 41

Table 3.9: Clinical features 43

Table 3.10: Subtypes of T-cell and NK-cell NHL 43

Table 3.11: Comparison of the Cutaneous and Peripheral T-cell lymphomas 44

Table 3.12: Comparison of laboratory features between Cutaneous and Peripheral T-cell NHL 45

Table 3.13: Comparison of Cutaneous and Peripheral T-cell NHL - HIV, TB and Outcome..... 46

Table 3.14: Comparison of HIV sero-positive and HIV sero-negative Peripheral T-cell lymphoma patients 48

Table 3.15: Means and Medians for Overall Survival 51

Table 3.16: Means and Medians for Overall Survival by disease stage 52

Table 3.17: Means and Medians for Overall Survival by age group 53

Table 3.18: Means and Medians for Overall Survival by HIV Status 54

Table 3.19: Means and Medians for Overall Survival by patient group 56

LIST OF FIGURES

Figure 3.1: Gender distribution 36

Figure 3.2: Distribution of patients by ethnicity 37

Figure 3.3: ECOG performance status 38

Figure 3.4: Distribution of patients by comorbidity, excluding HIV and TB 39

Figure 3.5: TB in association with T-cell Lymphoma 40

Figure 3.6: Distribution of patients by HIV status 41

Figure 3.7: Distribution of patients on cART 42

Figure 3.8: Kaplan Meier overall survival curve 52

Figure 3.9: Kaplan Meier survival curve by disease stage 53

Figure 3.10: Kaplan Meier survival curve by age group 54

Figure 3.11: Kaplan Meier survival curve by HIV status 55

Figure 3.12: Kaplan Meier survival curve by patient group 56

LIST OF ACRONYMS/ ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AITL	Angioimmunoblastic T-cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic lymphoma kinase
ATLL	Adult T-cell Leukaemia/ Lymphoma
BMAT	Bone Marrow Aspirate and Trephine
cART	Combination Antiretroviral Therapy
cALCL	Cutaneous Anaplastic Large Cell Lymphoma
CHBAH	Chris Hani Baragwanath Academic Hospital
CHOEP	CHOP plus etoposide
CHOP	Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisone
COP-BLAM-V	Cyclophosphamide, Oncovin (Vincristine), Prednisone, Bleomycin Adriamycin (Doxorubicin), Procarbazine
CT	Computerised Tomography
CTCL	Cutaneous T-cell Lymphoma
CNS	Central Nervous System
CVAD	Cyclophosphamide, Vincristine, Adriamycin (Doxorubicin), Dexamethasone
EATL	Enteropathy Associated T-cell Lymphoma
EBV	Epstein - Barr virus
ECP	Extracorporeal Photopheresis

ECOG	Eastern Cooperative Oncology Group
EPOCH	Etoposide, Prednisone, Oncovin (Vincristine), Cyclophosphamide Hydroxydaunorubicin (Doxorubicin)
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FTCL	Follicular T-cell Lymphoma
GI	Gastrointestinal
HDAC	High Dose Ara C (Cytosine Arabinoside)
HDAC	Histonedeactetylase
HHV-8	Human Herpesvirus 8
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HSTCL	Hepatosplenic T-cell Lymphoma
HTLV-1	Human T-cell lymphotropic virus-1
ICE	Ifosfamide, Carboplatin, Etoposide
IEL	Intraepithelial lymphocyte
IFN-α	Interferon alpha
IFNγ	Interferon-gamma
IPI	International Prognostic Index
ISCL	International Society for Cutaneous Lymphoma
IVAC	Ifosfamide, Etoposide, Cytarabine
LDH	Lactate Dehydrogenase
LyP	Lymphomatoid Papulosis
MEITL	Monomorphic Epitheliotropic Intestinal T-cell Lymphoma

MF	Mycosis Fungoides
MRI	Magnetic Resonance Imaging
NBUVB	Narrowband Ultraviolet B light phototherapy
NK	Natural Killer
NK/T-NT	NK/T-cell lymphoma nasal type
NHL	Non-Hodgkin Lymphoma
NOS	Not Otherwise Specified
PD-1	Programmed cell-Death-1
PET	Positron Emission Tomography
PEACE-BOM	Prednisone, Etoposide, Adriamycin (Doxorubicin), Cyclophosphamide Bleomycin, Oncovin (Vincristine), Methotrexate
PIT	Prognostic Index for T-cell lymphoma
ProMACE/CytaBOM	Cyclophosphamide, Adriamycin (Doxorubicin), Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate, Prednisone
PS	Performance status
PTCL	Peripheral T-cell Lymphoma
PUVA	Psoralen and Ultraviolet A light phototherapy
REAL	Revised European American Lymphoma
SCT	Stem Cell Transplant
SS	Sezary Syndrome
TB	Tuberculosis
TCR	T-cell Receptor
TIA-1	T-cell restricted Intracellular Antigen

TLR	Toll-like receptor
TSEBT	Total Skin Electron Beam Therapy
VAMP	Vincristine, Adriamycin (Doxorubicin), Methotrexate, Prednisone
WHO	World Health Organization

1.0. CHAPTER ONE: LITERATURE REVIEW

1.1. Introduction

In this introductory chapter, the background and literature review for the study are presented. It includes a brief overview, pathogenesis, review of classification systems, clinical presentation, diagnosis, and management of the common peripheral and cutaneous T-cell lymphomas. The relationship between T-cell lymphomas and HIV and TB are also covered in this overview.

1.1.1. Overview of Lymphoma

According to the World Health Organisation (WHO) classification, mature lymphoid neoplasms are divided into 5 major categories: Mature B-cell neoplasms, Mature T-cell and Natural Killer (NK) – cell neoplasms, Hodgkin Lymphoma (HL), Histiocytic and dendritic cell neoplasms and Post transplantation lymphoproliferative disorders (PTLDS) (1, 2).

Of the two main categories of lymphoma, Hodgkin Lymphoma (HL) constitutes approximately 20% of lymphoid neoplasms, whereas Non-Hodgkin Lymphoma (NHL) comprise approximately 80% of all lymphoid neoplasms. Furthermore, of the NHL, 80-95% are B-cell derived and 10-15% are of T-cell / Natural killer (NK-cell) derivation (1, 2, 3).

T-cell/NK-cell lymphoma is further classified into precursor types i.e.: NK-cell, T lymphoblastic lymphoma/leukaemia and peripheral or mature T-cell lymphoma. Where the T-cell/NK-cell lymphomas arise from the lymph nodes, they are referred to as nodal, whereas those that affect mainly the skin are referred to as the cutaneous types (1, 4, 5).

The subject of this MMED covers only the peripheral or mature T- cell and NK cell lymphomas and does not include the precursor T-cell lymphomas, B-cell lymphomas, Hodgkin Lymphoma and Histiocytic and dendritic cell neoplasms.

1.2. Epidemiology of T-cell Lymphoma

Non-Hodgkin lymphoma (NHL) is ranked as the 7th most common cancer in the USA (6). In comparison to B-cell Lymphoma, data regarding the epidemiology and risk factors of the T-cell Lymphomas is limited. The frequency of occurrence of T-cell Lymphoma is lower than that of B-cell Lymphoma (6). T-cell lymphomas account for 10-15% whereas B-cell lymphomas account for 80-85% of all NHL (3, 6). In addition, Cutaneous T-cell Lymphoma (CTCL) is relatively rare in comparison to Peripheral T-cell Lymphoma (PTCL). These two subtypes of T-cell lymphoma are differentiated by their phenotypic, diagnostic, prognostic, and molecular aspects. The incidence and survival rate of PTCL and CTCL subtypes are influenced by environmental, medical, lifestyle and genetic factors, as well as gender, race, ethnicity and residential location (6).

The rarity of T-cell Lymphoma proves to be a challenge. Large cohorts of patients are required to provide greater insight into the epidemiology, demographics, clinical features, management and treatment of the T-cell lymphomas (6).

1.3. Pathogenesis of Peripheral T-cell Lymphoma

Peripheral T-cell Lymphomas (PTCLs) are heterogeneous tumours which have unique clinical and biological features. The pathogenesis of PTCL is not entirely clear. Recent studies have revealed several mechanisms that could contribute to the pathogenesis of peripheral T-cell transformation. These mechanisms include the following:

- Deregulation of signalling pathways controlling T-cell development, differentiation, and maturation.
- Alterations of the peri-tumour microenvironment, and

virus-mediated changes in T-cell biology, in particular, Epstein Barr Virus (EBV) and Human T-cell lymphotropic virus-1 (HTLV-1) which may induce T-cell transformation (7, 8, 9).

Insights into the pathogenesis may assist in prognosticating the disease and providing more innovative therapies globally (9).

1.4. Classification of T-cell Lymphoma

The T-cell Lymphomas have evolved over the past few decades bringing with it a number of different classifications (10, 11, 12). In 1994, the Revised European-American Classification of Lymphoid Neoplasms (REAL) applied immunophenotypic and genetic factors in identifying distinct clinico-pathologic entities amongst the Non-Hodgkin Lymphomas (10).

The World Health Organisation (WHO) lymphoma classification is based upon the REAL classification. It was published in 2001 and updated in 2008 and includes many different subtypes of lymphoma. The latest classification groups lymphomas according to their cell types. The principle of the classification is based on the recognition of distinct diseases according to a combination of features including: morphology, immunophenotype, genetic, molecular and clinical features (see table 1.1 below) (11). Furthermore, the 2016 revision of the WHO classification of lymphoid neoplasms brings with it numerous advances in the classification of nodal, extra nodal and NK-cell neoplasms as well as the introduction of new entities (see table 1.2 below) (2).

Table 1.1: WHO Classification of the Mature T-cell and NK-cell neoplasms (2008) (Adapted from Campo E, et al.) (1)

Mature T-cell and NK-cell neoplasms	
T-cell prolymphocytic leukemia	
T-cell large granular lymphocytic leukemia	
Chronic lymphoproliferative disorder of NK cells*	
Aggressive NK cell leukemia	
Systemic EBV+ T-cell lymphoproliferative disease of childhood	
Hydroa vacciniforme-like lymphoma	
Adult T-cell leukemia/lymphoma	
Extranodal NK/T-cell lymphoma, nasal type	
Enteropathy-associated T-cell lymphoma	
Hepatosplenic T-cell lymphoma	
Subcutaneous panniculitis-like T-cell lymphoma	
Mycosis fungoides	**Cutaneous involvement**
Sézary syndrome	
Primary cutaneous CD30+ T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	**Cutaneous involvement**
Primary cutaneous anaplastic large cell lymphoma	
Primary cutaneous gamma-delta T-cell lymphoma	
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*	
Primary cutaneous CD4+ small/medium T-cell lymphoma*	
Peripheral T-cell lymphoma, NOS	
Angioimmunoblastic T-cell lymphoma	
Anaplastic large cell lymphoma, ALK^+positive	
Anaplastic large cell lymphoma, ALK^-negative	

*NK- Natural Killer; EBV- Epstein Barr Virus; NOS- Not Otherwise Specified; ALK- Anaplastic lymphoma kinase

Table 1.2: WHO Classification of Mature T-cell and NK-cell neoplasms (2016) (Adapted from Swerdlow SH, et al.) (2)

Mature T-cell and NK-cell neoplasms	
T-cell prolymphocytic leukemia	
T-cell large granular lymphocytic leukemia	
Chronic lymphoproliferative disorder of NK cells	
Aggressive NK-cell leukemia	
Systemic EBV+ T-cell lymphoma of childhood*	
Hydroa vacciniforme–like lymphoproliferative disorder*	
Adult T-cell leukemia/lymphoma	
Extranodal NK-/T-cell lymphoma, nasal type	
Enteropathy-associated T-cell lymphoma	
Monomorphic epitheliotropic intestinal T-cell lymphoma*	
Indolent T-cell lymphoproliferative disorder of the GI tract*	
Hepatosplenic T-cell lymphoma	
Subcutaneous panniculitis-like T-cell lymphoma	
Mycosis fungoides	**Cutaneous involvement**
Sezary syndrome	
Primary cutaneous CD30+ T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	
Primary cutaneous anaplastic large cell lymphoma	
Primary cutaneous gamma delta T-cell lymphoma	
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	**Cutaneous involvement**
Primary cutaneous acral CD8+ T-cell lymphoma*	
Primary cutaneous CD4 small/medium T-cell lymphoproliferative disorder*	
Peripheral T-cell lymphoma, NOS	
Angioimmunoblastic T-cell lymphoma	
Follicular T-cell lymphoma*	
Nodal peripheral T-cell lymphoma with TFH phenotype*	
Anaplastic large-cell lymphoma, ALK^+ , Anaplastic large-cell lymphoma, ALK^-	
Breast implant–associated anaplastic large-cell lymphoma*	

*NK- Natural Killer; EBV- Epstein Barr Virus; GI- Gastrointestinal; NOS- Not Otherwise Specified; ALK- Anaplastic lymphoma kinase

Some of the salient differences between the 2008 and 2016 classifications include the following:

- Due to genetic mutations, Follicular T-cell Lymphoma (FTCL) and Angioimmunoblastic T-cell lymphoma (ATCL) have been unified under a common heading.
- In 2016, there are improved criteria aiding in the recognition of Anaplastic Large Cell Lymphoma (ALCL).
- In lymphomatoid papulosis (LYP), there have been additional subtypes identified.
- A new entity has been described as breast implant-associated ALCL, which is associated with breast implants.
- Two other new entities have been added, viz., indolent T-cell Lymphoproliferative disorder of the GI tract and primary cutaneous acral $CD8^+$ TCL.
- It is now apparent that two subtypes of Enteropathy associated T-cell lymphoma (EATL) exist: Type I which is linked to celiac disease and Type II which shows no association with celiac disease (2).

1.4.1. T-cell/ Natural Killer cell Non-Hodgkin Lymphoma

T-cell lymphomas account for approximately 10-15% of all NHL (6). Mature T-and natural killer (NK)-cell lymphomas have 21 distinct disease types, according to the latest classification ranging from indolent cutaneous lymphomas to more aggressive lymphoid malignancies (2). The majority of these lymphomas exhibit extranodal disease. There are also phenotypic variations in different geographical locations due to the various risk factors associated with T-cell lymphoma, such as Epstein-Barr Virus (EBV) and human T-cell lymphotropic virus -1 (HTLV-1). HTLV-1 is found more commonly in Asia, therefore exhibiting a higher incidence of Adult T-cell leukemia/lymphoma (ATLL) in this location.

The T-cell lymphomas can broadly be divided into i) primarily leukaemic, ii) nodal or iii) extranodal (cutaneous) varieties (albeit with some overlap). Examples of some of these entities are indicated below:

A) LEUKAEMIC

1. Sezary Syndrome (SS)
2. Adult T-cell Leukaemia

B) NODAL

1. Peripheral T-cell Lymphoma, Not Otherwise Specified (PTCL, NOS)
2. Angioimmunoblastic T-cell lymphoma
3. Systemic Anaplastic Large Cell Lymphoma (ALCL)

Less common types

4. Adult T-cell leukaemia/lymphoma
5. Extranodal NK/T-cell lymphoma, nasal type
6. Hepatosplenic T-cell lymphoma
7. Enteropathy associated -T cell lymphoma

C) CUTANEOUS

1. Mycosis Fungoides (MF)
2. Sezary Syndrome
3. CD 30 + lymphoproliferative disease

1.4.1.1. Peripheral T-cell Lymphoma Not Otherwise Specified (PTCL, NOS)

Peripheral T-cell Lymphoma, not otherwise specified (PTCL, NOS) constitutes a group of aggressive lymphomas that are derived from T-cells and NK cells that arise from lymphoid tissues outside of the bone marrow such as lymph nodes, spleen, gastro-intestinal tract, and skin (5).

It is the commonest subtype of the peripheral or mature T-cell lymphomas, accounting for approximately twenty five percent of all the peripheral or mature T-cell lymphomas. Adults around the age of sixty are mainly affected, with a male predominance (see table 1.3). The disease is evident in all parts of the world. Patients usually present with advanced stage disease. Adverse prognostic factors include the presence of B-symptoms, bulky disease, poor performance status and extra nodal disease. PTCL, NOS is a diagnosis of exclusion, after considering the other peripheral or mature T-cell lymphomas. Malignant T-cells are evident morphologically and immunophenotypically. The immunophenotype of PTCL, NOS is CD4 positive and CD8 negative. Despite anthracycline based combination chemotherapy, PTCL, NOS has an aggressive clinical course. This aggressive nature is manifest even in lower risk patients, where 60-70% are likely to relapse in the first 5 years (5, 13, 14, 15).

1.4.1.2. Angioimmunoblastic T-cell Lymphoma (AITL)

Angioimmunoblastic T-cell lymphoma (AITL) was first described in 1974 as an aggressive disease of the elderly, characterised by diffuse lymphadenopathy, hepatosplenomegaly, anaemia and hypergammaglobulinemia (5). Patients may present with comorbidities like autoimmune disease. These include Coomb's-positive autoimmune haemolytic anaemia, immune thrombocytopenia, mixed cryoglobulinemia with associated vasculitis and autoimmune arthritides. Infections like HIV and hepatitis have been seen in patients with AITL although no definite connection has been

established. EBV-infected lymphocytes are seen in nearly all cases of AITL. Patients with AITL can develop second primary lymphomas that are of B-cell origin and driven by EBV infection. There are variable histologic appearances which can resemble both malignant and benign conditions. Immunophenotyping shows CD3 positive, CD4 positive and CD8 negative T-lymphocytes. The course of AITL is moderately aggressive with an overall 5-year survival of approximately 30 percent. Therapies for AITL range from corticosteroids to anthracycline-based combination chemotherapy (5, 14, 16).

1.4.1.3. Systemic Anaplastic Large Cell Lymphoma

Anaplastic large cell Lymphoma (ALCL) comprises 2 percent of all NHL in the United States. ALCL has 3 clinically distinct subtypes: Systemic ALK-positive ALCL, Systemic ALK-negative ALCL and primary cutaneous ALCL (17).

Based on the International Peripheral T-cell Lymphoma Project, the median age of ALK^+ patients was 34 years, while those who were ALK^- had a higher median age of 58 years. In both subtypes, there was a male predominance of 1.7:1 (ALK^+) and 1.5:1 (ALK^-), respectively (17). In the majority of patients the disease affects the lymph nodes and skin but may also arise in the lung, gastrointestinal tract, or bone (17).

Both systemic varieties are treated as aggressive lymphomas. The ALK positive ALCL patients respond better to chemotherapy, while ALK negative ALCL patients are more likely to relapse within five years and may require other modalities of treatment, including stem cell transplantation (SCT) (17).

Table 1.3: Clinical features of ALK-positive and ALK-negative ALCL (systemic type) and PTCL, NOS. (Adapted from Savage KJ, et al) (17)

Clinical features	ALK-positive (%)	ALK-negative (%)	p-value[a]	PTCL, NOS (%)	p-value[b]
Total number of cases	87 (55)	72 (45)	-	331	
Median age (years)	34	58	.0001	57	0.30
Age <60 years	74 (86)	42 (58)	<.0001	170 (50)	0.21
Male: female	1.7:1	1.5:1	.74	1.9:1	.41
STAGE					
I or II	30 (35)	30 (42)	.38	102 (31)	.18
III	25 (29)	15 (21)		87 (26)	
IV	31 (36)	27 (37)		145 (43)	
Elevated LDH	31 (37)	31 (46)	.28	158 (49)	.62
Performance status >2	30 (35)	21 (30)	.56	60 (18)	.02
Nodal only disease	39 (54)	38 (49)	.52	124 (42)	.07
Extranodal sites >1	17 (19.5)	15 (21)	.84	99 (29)	.15
Bulky disease > 10 cm	17 (21)	6 (11)	.17	19 (7)	.25
B-symptoms	52 (60)	41 (57)	.72	118 (35)	.0004
Hemoglobin <110 g/L	17 (27)	18 (32)	.54	61 (22)	.11
Platelets $<150\times10^9$/l	6 (10)	6 (11)	.83	64 (24)	.03
IPI 0, 1	40 (49)	27 (41)	.50	88 (28)	.066
2	18 (22)	13 (20)		111 (35)	
3	12 (15)	16 (24)		71 (22)	
4, 5	12 (14)	10 (15)		48 (15)	
5 y FFS %	60	36	.015	20	.012
5 y OS %	70	49	.016	32	.032
5 y FFS by IPI %					
0, 1	80	62		35	
2	61 p <.001[c]	44 p = .0015[c]		16 p <.001[c]	
3	23	16		13	
4, 5	25	13		8	
5y OS by IPI %					

0,1	90	74		52	
2	68 p <.001[c]	62 p <.001[c]		33 p <.001[c]	
3	23	31		16	
4,5	33	13		13	

Notes: [a]ALK-positive vs. ALK-negative Anaplastic lymphoma kinase

[b]ALK-negative vs. PTCL-NOS. Peripheral T-cell lymphoma, not otherwise specified

[c]Comparison of IPI - International prognostic index) risk groups within specified subtypes

FFS: failure-free survival; OS: overall survival; PS: performance status; LDH: lactate dehydrogenase

ALK- positive ALCL occurs more commonly than ALK-negative ALCL. Immunohistochemically, the large lymphoid cells show strong expression of the cytokine receptor CD30. ALCL also frequently express CD25 and HLA-DR. In 60 percent they also express CD3, CD43 and CD45RO. Additionally, in one third of cases they express neither B-cell nor T-cell markers and are labelled undetermined. Combination anthracycline based chemotherapy regimens is the current standard of care. Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisone (CHOP) chemotherapy remains the first line chemotherapy. ALK positive disease responds well to CHOP or CHOEP (CHOP plus etoposide). In contrast, ALK negative patients may be more likely to relapse with these treatments and may require high dose chemotherapy followed by stem cell transplantation. For relapsed or refractory systemic ALCL, a number of other drugs have been approved by the Food and Drug Administration (FDA) of the United States, including romidepsin, belinostat, pralatrexate and brentuximab (13, 17).

CD 30 positivity in ALCL indicates a better prognosis. Translocation (2; 5) is helpful in differentiating between Hodgkin lymphoma and t(2;5)-positive ALCL, as both diseases may be CD30 positive (18).

1.4.1.4. Adult T-cell Leukaemia / Lymphoma

Adult T-cell leukaemia/lymphoma (ATLL) was first described in Japan in 1977 (19). It is a rare, often rapidly growing lymphoma that can be found in the blood, lymph nodes, skin or multiple areas of the body (20). In the 1980's, the association of ATLL and Human T-cell Lymphotropic virus (HTLV-1) was documented (21, 22). Infections with HTLV-1 are endemic in several regions of the world including south western Japan (Kyushu), the Caribbean basin, and Central Africa. ATLL is an uncommon diagnosis in Western countries and is seen more commonly in Japan where it accounts for one in four lymphomas. The virus is transmitted by blood transfusion, sexual intercourse, breast feeding and sharing of needles. Typical clinical features are constitutional symptoms, marked lymphocytosis, hepatosplenomegaly, and cutaneous involvement. The diagnosis of ATLL is based upon morphology, immunophenotyping and serology. Light microscopy shows the classical "flower cells" which represent activated lymphocytes with indented nuclei. Immunohistochemically ATLL lymphocytes are CD3 positive, CD4 positive, CD8 negative, CD7 negative, CD25 positive and HLA-DR positive (13, 20).

The diagnostic criteria for ATLL formulated in 1991, are as follows:

1. Histological and cytological malignancy with CD2 positive, CD3 positive, and CD4 positive T-cells.
2. Abnormal T lymphocytes in peripheral blood (PB) except for lymphoma type.
3. Presence of antibody to HTLV-1 (20).

With regard to cutaneous disease, HTLV-1 pro viral sequences can assist in the diagnosis (23).

Four different clinical subtypes of the ATLL are recognised, including smouldering, leukemic (acute and chronic) and the lymphomatous variety (see table 1.4 below) (13, 20).

Table 1.4: ATLL: Classification and characteristics (Adapted from Shimoyama M) (20)

Type n (%)	Smouldering, 45 (5.5)	Chronic, 152 (18.6)	Lymphoma, 156 (19.1)	Acute, 465 (56.8)
Abnormal T-Cells	>5% in PB, normal lymphocyte level	>5% in PB, lymphocytosis	<1% in PB, no lymphocytosis	Both leukaemia and tumour
Laboratory features	No hypercalcemia, LDH >1.5 × normal	No hypercalcemia LDH >2 × normal	Some hypercalcemia LDH >2 × normal	50% hypercalcemia LDH >3 × normal
LAD	None	Present	Present	Present
Organs Involved	Rare, skin and lungs	Liver, spleen, skin and lungs	+/−	Present
Two-year survival	77.7%	52.4%	21.3%	16.7%
Four-year survival	62.85%	26.9%	5.7%	5%

LAD- Lymphadenopathy; PB-Peripheral Blood

Management depends on the subtype: one can apply conservative management in the smouldering and chronic subtype of ATLL, while the aggressive subtypes are treated like other T-cell lymphomas. Specific therapy includes CHOP, CHOEP, dose adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) and hyper CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), with the poorest survival being in the acute leukaemic subtype (13, 14, 20).

1.4.1.5. Extranodal Natural Killer T-cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type (NK/T-NT) is a rare, rapidly growing, aggressive type of Non-Hodgkin lymphoma (23). It is more common in Asia, Central America and South America. The average age at diagnosis is 60 years. Epstein-Barr virus (EBV) is involved in the process of lymphomagenesis. This extranodal lymphoma usually affects areas in the nose, the nasal passages, paranasal sinuses and upper part of the throat. Patients can present with nasal obstruction, epistaxis, facial or periorbital swelling. The disease may be rapidly progressive within a few months. Several biopsies may be required to confirm the diagnosis. The morphology shows a range of cells from

small mature lymphocytes to large transformed cells. Immunochemistry shows T-cell positivity for CD2, CD3, and CD45RO. CD56 positivity supports a NK cell origin and TIA-1 (T-cell restricted intracellular antigen) suggests a cytotoxic T- lymphocyte cell origin (23).

Patients with extranodal NK-cell/T-cell NHL are staged according to the Ann-Arbor staging system, which is summarised below (24).

Stage I (E) - a single nodal or extranodal site

Stage II (E) - multiple nodal sites ipsilateral to the diaphragm or a single extranodal site with ipsilateral nodal involvement

State III (E) - lymph nodes above and below the diaphragm with or without extranodal disease

Stage IV- diffuse or disseminated disease with more than one extranodal site involved.

Treatment options include chemotherapy and radiation therapy. Chemotherapy regimens include CHOP, CHOP-like regimens, COP-BLAM-V (cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine) and ProMACE/CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate and prednisone). Radiation therapy dosages range from 22Gy to 65Gy, and combination therapy (chemotherapy and radiotherapy) is considered if patients fail to respond to chemotherapy only (13, 23).

1.4.1.6. Hepatosplenic T-cell Lymphoma

Hepatosplenic T- cell lymphoma (HSTCL) is a rare type of T-cell Lymphoma and accounts for approximately 1.4 percent of all known peripheral T-cell lymphomas. It has a very aggressive clinical course and a poor clinical outcome. The disease can occur at any age but is more common in young males during their teenage years and young adulthood. HSTCL is associated with various forms of

immunosuppression ranging from the treatment of malignancy, to inflammatory conditions or organ transplantation (14, 25, 26).

Malignant T-cells characteristically proliferate in the sinuses of the liver, sinuses and red pulp of the spleen and the sinuses of the bone marrow. Patients present with hepatosplenomegaly, jaundice, cytopenias, constitutional symptoms and minimal lymphadenopathy.

The diagnosis of HSTCL is usually based upon tissue obtained at liver biopsy or splenectomy. Infiltrates comprise of lymphocytes of small to medium size with a pale cytoplasm. There is no viral association. Immunophenotyping of the T lymphocytes show the cells to be CD2 positive, CD3 positive, gamma delta TCR positive, CD4 negative, CD5 negative, CD8 negative and ± CD 56 positive (14, 25). Isochrome of the long arm of chromosome 7 (i(7)q10) is a recurrent genetic abnormality encountered in HSTCL either in isolation or in association with other abnormalities such as trisomy 8, with the combination of these 2 abnormalities being highly indicative of HSTCL (26).

There is no consensus on a standard treatment regimen. The disease is aggressive and most therapies are disappointing and have limited efficacy. Combination therapies consist of CHOP, CHOP- like regimens, ICE (ifosfamide, carboplatin, etoposide) and IVAC (ifosfamide, etoposide, high dose cytarabine). Successful use of allogeneic stem cell transplants (SCT) may be associated with long term remission and potential cure (14, 25).

1.4.1.7. Enteropathy associated T-cell Lymphoma

Enteropathy Associated T-cell Lymphoma (EATL) is a rare type of extranodal peripheral T-cell lymphoma. It is an intestinal tumour of intraepithelial T-lymphocytes. EATL is an aggressive disease associated with gluten sensitive enteropathy (celiac disease). There is a higher frequency in areas with a high prevalence of celiac disease like Northern Europe. There is a variant, type 2 EATL which is rare and occurs sporadically in areas where celiac disease is rare, such as in Asia (2, 14, 27). In

the 2016 WHO classification, EATL now only refers to type 1 cases and all type 2 cases were renamed as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (2). Enteropathy associated T-cell lymphoma (EATL) is a disease of adulthood affecting individuals in their 50's. The disease typically affects the gastrointestinal tract with few extraintestinal sites including the lymph nodes. Clinical presentation includes diarrhoea, abdominal pain, weight loss and 'B' symptoms. Twenty five percent of the patients upon diagnosis can present with small bowel perforation or obstruction. Patients many have concomitant iron deficiency anemia. In the small intestine, the disease typically affects the jejunum or ileum on enteroscopy, with findings of circumferential ulcers which may be restricted to the jejunum or can occur throughout the small bowel. These ulcers frequently perforate spontaneously. Histology reveals a collection of lymphocytes with rounded nuclei and a single nucleolus, together with significant pleomorphism of the malignant lymphocytes. Immunophenotypic analysis shows CD3 expression cytoplasmically but no expression of CD3 on the surface of the cell, CD4 negativity, CD8 negativity and CD103 positivity. E-cadherin ligand is expressed by muscosal lymphocytes. The clonal Intraepithelial lymphocytes (IEL's) may express cytotoxic T-cell associated proteins, T-cell restricted Intracellular Antigen (TIA-1) granzyme B and perforin. Anaplastic cells may coexpress CD30 and small to medium cells can express CD56 (14, 27, 28).

Once the diagnosis of EATL is made, further work up and staging consists of a full physical examination, an abdominal, chest and pelvic CT scan as well as blood analysis and a BMAT. PET scans are used for bowel involvement and as a screening modality for high-risk individuals or for post- treatment monitoring. Surgical resection of the lymphoma does not prove to be curative. Anthracycline based chemotherapeutic agents like CHOP, VAMP (vincristine, doxorubicin, high-dose methotrexate, and prednisolone) and PEACE-BOM (prednisolone, etoposide, doxorubicin,

cyclophosphamide, bleomycin, vincristine, and high-dose methotrexate), are most commonly used. Poor outcomes in this disease are mostly due to severe malnutrition and surgical complications. The use of stem cell transplantation in EATL is limited to a few patients and the benefits remain unclear (14, 27).

1.5. Clinical Features of T-cell Lymphoma

The most common clinical features found in the T-cell lymphomas include constitutional symptoms (such as fever, night sweats and weight loss), fatigue, generalised lymphadenopathy, hepatosplenomegaly, and skin involvement (29). Each type of PTCL has unique clinical features, which has been discussed in the preceding literature review.

The ECOG performance status is an attempt to quantify the general well-being of the patient and activities of daily life (see table 1.5 below) (30).

Table 1.5: Eastern Cooperative Oncology Group - measure of functional status

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

1.6. Diagnosis and Staging of Peripheral T-cell Lymphoma

There are several challenges in the diagnosis of T-cell lymphoma due to the presence of defined laboratory features as well subtyping the lymphoma according to the diagnostic criteria for each subtype. Careful clinicopathological correlation is vital in each individual patient (29).

It is essential to perform a full physical examination, blood analysis which includes a full blood count, differential count, urea and electrolytes, liver function tests, calcium, magnesium, phosphate, uric acid, LDH, HTLV-1, HIV testing and flow cytometry. For a definitive diagnosis, a lymph node biopsy or other tissue biopsies must be performed. A chest X-ray, neck, chest, abdomen, and pelvic CT scan, MRI scan where indicated as well as Bone Marrow aspirate and trephine (BMAT) is required for completion of the staging, to determine the extent of spread of the disease and add to prognostication of the disease. A CT scan alone may be insufficient in establishing the diagnosis. Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scans have proven to be very useful in the diagnosis as well as management. FDG-PET scans are particularly useful in identifying extranodal disease. Immunophenotyping and T-cell rearrangement studies are performed on the specimens, in order to further subtype the lymphoma (29).

The Ann-Arbor classification system was established (with particular reference to HL) in order to differentiate patients who are more suited for chemotherapy and those who are more suited for radiotherapy. The Cotswold Modification of the Ann-Arbor system is a further extension to the Ann-Arbor staging system, adding “bulk” disease (subscript ‘X’) as an adverse prognostic factor (24). Table 1.6 below shows the Cotswold modification of the Ann-Arbor classification system (31).

Table 1.6: Ann Arbor staging system (Cotswold Modification)

STAGE	**CHARACTERISTICS**
I	Involvement of one lymph node region or lymphoid structure
II	Two or more lymph node regions on same side of the diaphragm
III	Lymph nodes on both sides of the diaphragm
IV	Involvement of extranodal sites
MODIFICATIONS	
A	No symptoms
B	Fever, night sweats, weight loss >10% in 6 months
X	Bulky disease (greater than one third widening of the mediastinum or >10cm diameter of nodal mass)
E	Involvement of single, contiguous, or extranodal site

Although these staging systems were developed for HL patients, they are also used in the staging of NHL, including T-cell lymphomas.

1.7. Management of T-cell Lymphoma

There is currently no agreement on standard frontline treatment or an approach to managing PTCL. The goal of initial therapy is long term remission or cure. Most patients receive CHOP as first line treatment and thereafter consolidation in first remission, ± autologous SCT. Patients have shown better outcomes with this treatment scheme, although survival rates remain unfavourable. Alternatives to the CHOP backbone are the addition of agents such as etoposide (CHOEP) or alemtuzumab (an anti-CD 52 monoclonal antibody). In refractory/relapsed cases, treatment is aimed at allogeneic SCT, where the patient is deemed fit (29). Novel treatments and better combination regimens require further clinical trials in order to progress beyond CHOP as a first line for PTCL (13, 14, 29).

Response criteria for NHL are detailed in Appendix D (32). A number of prognostic indices have been described, such as the prognostic Index for T-cell lymphoma (PIT) which was developed by the 'Intergruppo Italiano Linfomi' for patients with PTCL. The PIT is based on age, performance status, serum lactate dehydrogenase (LDH) levels and bone marrow (BM) involvement (See table 1.7) (33).

1.8. HIV and T-cell Lymphoma

The association between T-cell lymphoma and HIV is uncommon. However, there has been an increase in the USA of these lymphomas among AIDS patients when compared to the general population (34). The varieties of T-cell lymphomas seen in HIV individuals include: PTCL, CTCL, ATLL, ALCL, and Angiocentric T-cell lymphoma. The risk of developing T-cell lymphoma in the setting of HIV increased by 15-40-fold when compared to the general population (34, 35, 36).

PTCL in the setting of HIV has a highly aggressive clinical course and diagnosis requires exclusion of EBV and HHV-8 as part of the workup. HIV associated PTCL has a poor prognosis and survival. Standard treatment regimens appear to be inadequate, and may be associated with increased toxicity. There may also be a higher incidence of CNS involvement (36).

However, due to insufficient evidence (based on small numbers of patients) there is a need for more prospective studies in patients with PTCL and HIV in order to provide further insight into this association (36).

1.9. TB and T-cell Lymphoma

The co-existence of TB and NHL is not uncommon. The signs and symptoms of both diseases are similar and therefore the diagnosis of either disease may be confused, delayed or misdiagnosed.

Moreover, both diseases may co-exist, especially in the setting of underlying immunosuppression (HIV/AIDS). Caseating or necrotising granulomatous lesions which are characteristic of TB, may also be found in NHL. If initial treatment failure occurs in either NHL or TB, one should have a high index of suspicion of simultaneous occurrence of both diseases, especially in countries like South Africa where TB is endemic. In addition, concomitant chemotherapy may worsen the clinical course of existing TB, especially if the TB is untreated (37, 38).

FDG-PET-CT can be used as a diagnostic tool in inflammatory or infectious diseases because of the increased FDG uptake. However, this may occur as a 'false-positive' in the context of underlying lymphoma. In such cases, biopsy remains the most sensitive and specific diagnostic procedure. Similarly, proof of TB still remains the presence of acid-fast bacilli in biopsy or culture or GeneXpert positivity (37, 38, 39).

1.10. Cutaneous T-cell Lymphoma (CTCL) (Extra-Nodal)

Cutaneous T-cell lymphomas (CTCL) include among other conditions, Mycosis Fungoides (MF), Sezary Syndrome (SS): and CD30 positive lymphoproliferative disorders (see table 1.1 and 1.2). A summarised classification of these entities appears below:

A) Mycosis Fungoides (MF):

1. Folliculotropic MF
2. Pagetoid Reticulosis
3. Granulomatosis Slack skin

B) Sezary Syndrome (SS)

C) CD30 + lymphoproliferative disease:

1. Anaplastic large cell lymphoma
2. Lymphomatoid papulosis

The most common type of the CTCL is Mycosis Fungoides (MF) and comprises almost 50% of all primary CTCLs. MF is a rare condition, with an incidence of approximately 0.3/ 100 000. It affects adults at a median age of 55 to 60 years. The male to female ratio is 2:1 (40, 41). The causative factors in the development of MF are not known. Genetic, environmental and immunological factors have been postulated. The clinical progression is from patch to plaque stage and finally to the nodular and tumoral stage. The disease may have a prolonged clinical course before a definitive diagnosis is made. On average, it may take 4 to 6 years, from initial presentation of the skin lesions, up to the diagnosis of MF. Many patients present with symptoms of eczema or parapsoriasis for years before a definitive diagnosis is made (40, 41). MF comprises a range of clinical presentations varying from early patch stage, characterized by the presence of variably sized erythematous, fine scaly lesions, or clinical variants (hypopigmentation, poikiloderma, atrophy, telangiectasia), progressing to more infiltrated lesions to form the plaque stage, and finally patients may develop nodules or tumours. Extra cutaneous disease is more common in erythroderma and tumour stage disease and rare in patients with limited patch or plaque stage disease. The draining lymph node is the first extra cutaneous site involved and this may be followed by visceral involvement. A skin punch biopsy is used to confirm the diagnosis. The characteristic histopathological features include: lymphocytes with cerebriform nuclei and a haloed appearance that displays epidermotropism. In the patch or plaque stage, band-like infiltrates in the papillary dermis populate the dermoepidermal junction. The presence of intra-epidermal clusters of malignant lymphocytes (Pautrier microabscesses) in the absence of spongiosis is characteristic. Pautrier microabscesses are pathognomonic for MF but are only seen in 25% of cases (40, 41). Transformation to a diffuse large cell lymphoma that may be either CD30 negative or CD30 positive, is associated with a poor prognosis. Immunohistochemical markers in MF shows the

following phenotype: CD3 positive, CD4 positive, CD45RO positive and CD8 negative. Clonal T-cell receptor gene rearrangements are detected in most cases (40, 41).

The staging system is based on the TNMB (tumor, node, metastases, blood) classification scheme which is specific to MF and SS (42). A complete physical examination, skin biopsy and relevant blood investigations are required. T- Cell Receptor (TCR) gene rearrangement analysis of the peripheral blood has shown conflicting results and depends on the sensitivity of the technique employed. A CT scan of the chest and abdomen is necessary where extra-cutaneous disease is suspected. A bone marrow aspirate and trephine should be performed as part of the routine staging process. The stage of disease together with the general condition and age of the patient will determine the treatment modality. In general, three different types of treatment may be considered:

1) Skin targeted therapies (topical corticosteroids, cytotoxic agents, and phototherapy - Psoralen and UVA (PUVA) and radiotherapy - including total skin electron beam therapy (TSEBT)).

2) Systemic chemotherapy

3) Biologic response modifiers – (interferon alpha and other cytokines), retinoids (bexarotene) and receptor targeted cytotoxic fusion proteins (e.g. denileukin diftitox) (40, 41,43).

The variants or subtypes of MF include Folliculotropic, Pagetoid Reticulosis and Granulomatous slack skin disease. These entities have distinctive clinicopathological features, and therefore have been included as distinct subtypes of MF in the WHO-EORTC classification scheme (44). In folliculotropic MF there is preferential involvement of the head and neck region by folliculotropic T-cell infiltrates. The clinical presentation is that of follicular papules, acneform lesions, indurated plaques and occasionally tumours. The lesions are often associated with alopecia and infiltrated plaques in the eyebrow region. The dermal perifollicular localization of the infiltrates requires more aggressive local radiotherapy or TSEBT and sustained complete remissions are rare.

Pagetoid reticulosis is a rare variant of MF. It presents clinically as a solitary psoriasiform or hyperkeratotic patch or plaque, usually on an extremity, and is slowly progressive. Extracutaneous disease is rare. Treatment modalities include radiotherapy or surgical excision.

Granulomatous slack skin is also a rare subtype of MF, characterised by folds of lax skin and a granulomatous infiltrate with clonal T cells. There is a predilection for the axillae and groin areas. Patients have an indolent course. Radiotherapy may be effective, but clinical experience is limited. Rapid recurrence after surgical excision has been reported (44).

Sezary syndrome (SS) is a rare, aggressive leukaemic variant of MF. It is defined by the triad of erythroderma, lymphadenopathy, and the presence of neoplastic T cells (Sezary cells) in the skin, lymph nodes or peripheral blood. Prognosis is generally poor with most patients succumbing from infectious complications, rather than from progressive disease. Being a leukaemic variant, systemic treatment is required. PUVA or potent topical steroids may be used as adjuvant therapy. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities (including chemotherapy), is the treatment of choice in SS (7, 43).

Primary cutaneous CD30+ lymphoproliferative disorders represent the second most common group of CTCL, accounting for approximately 25% of CTCLs. This group includes primary cutaneous anaplastic large cell lymphoma (cALCL), Lymphomatoid Papulosis (LyP) and borderline cases (7, 45).

In cALCL, the majority of cells express the CD30 antigen with no evidence of another CTCL. This tumour occurs in adults and rarely in children with a male to female ratio of 1.5-2:1. It presents clinically with reddish to brownish nodules and tumours occurring on the trunk, often with ulceration. There may be lymph node involvement in 10-30% of patients. Seventy five percent of these patients are CD30 positive but clinico-pathological correlation is necessary to ensure an accurate diagnosis.

Radiotherapy is preferred for localised disease or solitary lesions. In cases of disseminated disease, chemotherapy should be considered. The prognosis of CD30 positive cALCL is more favourable than extra-cutaneous ALCL (7, 45).

Lymphomatoid Papulosis (LyP) is a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease. The lesions involve the trunk, can be seen in various stages of evolution and can regress spontaneously. Histologically, it closely resembles a malignant lymphoma. Narrow band UVB, PUVA and radiotherapy can be effective but may not alter the natural course of the disease (7, 45).

Rare variants of CTCL include the following: subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous CD4 positive pleomorphic T-cell lymphoma, Extra-Nodal Natural Killer/T- cell Lymphoma Nasal Type, Adult T-cell leukaemia/lymphoma, primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma, cutaneous gamma / delta T-cell lymphoma and primary cutaneous peripheral T-cell lymphoma, unspecified (45).

1.10.1. Pathogenesis of Cutaneous T-cell Lymphoma

The cause of CTCLs remains unknown. Although there have been studies that have reported the association between infectious and chemical agents and CTCLs, no studies have been conducted to prove causation (7, 40, 41, 43). MF has been reported to occur in patients following an organ transplantation, however, the mechanism of this association remains unclear (7). Immunohistochemistry-based studies that focus on the tumour microenvironment have recently reported that dendritic cells that are actively recruited in the tumour environment by tumour-derived chemokines, have a role to play a role in the pathogenesis of CTCLs. Apart from the role of dendritic cells in contributing to the suppression of anti-tumour immunity, the tumour microenvironment also plays a role in the pathogenesis of CTCLs (46). In addition, macro-environmental factors such as

infections are also postulated to be involved in the pathogenesis of CTCLs. CTCLs can be characterized by a significant loss in T-cell receptor diversity that is similar to that observed in HIV (7). Under normal conditions, T-cells undergo a controlled process of cell activation and cell death facilitated by extrinsic death receptors such as Fas (CD95). However, studies on the molecular pathogenesis of CTCLs have revealed cell death receptors to be diminished in patients presenting with CTCL including other defects in factors associated with cell cycle processes (7).

1.10.2. Classification of Cutaneous T-cell lymphoma

Staging of a CTCL patient requires an assessment of skin, blood and lymph nodes by a multi-disciplinary team of oncologists and dermatologists. The World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classifies CTCLs into two categories, viz., those with indolent characteristics and those with aggressive features. CTCLs with indolent characteristics include: mycosis fungoides and its subtypes, primary cutaneous CD4+T-cell lymphoma, and primary cutaneous CD30+T-cell lymphoma. CTCLs with aggressive behavior include the following: Sezary syndrome, primary cutaneous peripheral T-cell lymphoma, extra-nodal NK/T-cell lymphoma, adult T—cell lymphoma and cutaneous gamma/delta-positive T-cell lymphoma (2, 7, 42, 47).

Despite MF and SS being types of NHL, a different staging approach is used for this group of lymphomas (see Table 1.7). Table 1.8 below shows the revised staging of MF and SS based on the International Society for Cutaneous Lymphoma (ISCL) (42). The staging is described as follows:

Table 1.7: Staging of Cutaneous T-cell Non-Hodgkin Lymphoma

STAGE	SUMMARY
Stage IA	Patch or plaque-like skin disease involving less than 10% of skin surface area (T1 skin disease)
Stage IB	Patch/plaque-like skin disease involving 10% or more of the skin surface area (T2 skin disease)
Stage IIB disease	Tumors are present (T3 skin lesions)
Stage III disease	Generalized erythroderma is present
Stage IVA1 disease	Erythroderma and significant blood involvement occur
Stage IVA2 disease	Lymph node biopsy result shows total effacement by atypical cells (LN4 node)
Stage IVB disease	Visceral involvement (e.g., liver, lung, bone marrow) occurs

Table 1.8: Revised staging of MF and SS based on the ISCL

STAGE	T	N	M	B
IA	1	0	0	0 or 1
IB	2	0	0	0 or 1
II	1 or 2	1 or 2	0	0 or 1
IIB	3	0 to 2	0	0 or 1
III	4	0 to 2	0	0 or 1
IIIA	4	0 to 2	0	0
IIIB	4	0 to 2	0	1
IVA1	1 to 4	0 to 2	0	2
IVA2	1 to 4	3	0	0-2
IVB	1 to 4	0 to 3	1	0-2

MF=Mycosis Fungoides; SS=Sezary syndrome; ISCL=International Society for Cutaneous Lymphoma

T=tumor, N=node, M=metastasis, B=blood

1.10.3. Clinical presentation of Cutaneous T-cell lymphoma

Mycosis Fungoides (MF) comprises a range of clinical presentations. Many patients present with symptoms of eczema or parapsoriasis for years before a definitive diagnosis is made (40). Classic MF can be divided into 3 stages, viz., patch -which are non-specific dermal patches found in the lower trunk of the body, plaques- which are scaly infiltrative plaques that may resemble eczema or parapsoriasis and tumours- which are prone to ulceration. The patch stage of classic MF consists of asymmetric scaly patches that commonly affect the buttocks, extremities and breasts. The patch stage of MF normally lasts for months or a few years before progression to the plaque stage. In the plaque stage, patients present with scaly, sharply demarcated plaques that are reddish to brown in colour. The plaque stage is similar to the patch stage of MF histologically, however, the plaque stage has a dense band in the upper dermis that is composed of lymphocytes. The tumour stage of MF is characterized by a large reddish-brown smooth nodule that is prone to ulceration (40, 41, 43).

1.10.4. Diagnosis of Cutaneous T-cell Lymphoma

The two most common sub-types of CTCLs are MF and SS. The average time from symptom onset to diagnosis has been reported variably to be between 3-4 years (40). Diagnosis can be missed in elderly patients who frequently complain of itchy, dry skin due to advanced age. The early diagnosis of MF is a challenge clinically and histologically because it can resemble other inflammatory dermatoses and not all histological features of MF are always present (47, 48, 49). Table 1.10 below was developed as a guideline for the diagnosis of MF (47, 49). The algorithm was developed by the International Society for Cutaneous Lymphoma (ISCL) and includes molecular, biological, histological and immunologic criteria in a scoring system that is to be used in the diagnosis of early MF (47, 49). Complete physical examination is essential with attention to skin and lymph nodes. The

following tests are required for the diagnosis of MF: Full blood count, liver function tests, uric acid, LDH, HIV testing, peripheral blood smear review, flow cytometry (40). In cases of suspicious lymph nodes, lymph node biopsies should be performed. Chest X-ray, neck/chest/abdomen/pelvis CT or whole-body PET/ CT, can assist in diagnosis and staging. In selected cases, BMAT may be recommended. General guidelines suggest that early stage disease (stage IA-IIA) is limited to the skin and does not require such an extensive work up. For stage IIB disease or more advanced disease, there is greater systemic involvement and the above investigations are essential in determining prognosis and treatment options (40, 42, 47).

Table 1.9: Algorithm for the diagnosis of MF developed by the ISCL

Criteria	**Major (2 points)**	**Minor (1 point)**
Clinical		
Persistent and/or progressive patches and plaques plus	Any 2	Any 1
(1) Non–sun-exposed location		
(2) Size/shape variation		
(3) Poikiloderma		
Histopathologic		
Superficial lymphoid infiltrate plus	Both	Either
(1) Epidermotropism without spongiosis		
(2) Lymphoid atypia*		
Molecular/biologic: clonal TCR gene rearrangement	NA†	Present
Immunopathologic		
(1) CD2,3,5 less than 50% of T cells	NA†	Any 1
(2) CD7 less than 10% of T cells		
(3) Epidermal discordance from expression of CD2,3,5 or CD7 on dermal T cells		

MF=Mycosis Fungoides; ISCL=International Society for Cutaneous Lymphoma

Four points are required for the diagnosis of MF, based on any combination of points from the clinical, histopathologic, molecular and immunopathologic criteria.

Sezary Syndrome should be considered in any erythrodermic patient. Diagnosis requires skin biopsy, blood tests, lymph node biopsy, and TCR gene rearrangement tests (43). For the diagnosis of SS, one or more of the following criteria should be met: an absolute Sezary cell count of at least 1000 cells/µl,

identification of T-cell clones in the peripheral blood, revealed by flow cytometry and immunophenotypic abnormalities or loss of one or more of the following antigens: CD2, CD3, CD4 and CD5 based on the ISCL criteria for SS diagnosis (40, 42, 47). In addition to the ISCL criteria for SS diagnosis, the World Health Organization (WHO) classification requires generalized lymphadenopathy, erythroderma and clonally related T-cells (Sezary cells) to be present in the skin, lymph nodes and blood for a SS diagnosis. The ISCL also recommends that on rare occasions when SS is preceded by a history of MF, patients with MF but without erythroderma, may meet the criteria for SS (40, 42, 47, 49).

1.10.5. Treatment of Cutaneous T-cell lymphoma

The treatment of MF and SS is dependent on the extent of the disease and the presence of defined prognostic factors. Treatment for early stage CTCLs includes topical therapies with or without interferon alpha (IFN-α) or oral agents, whereas advanced-stage disease is treated with chemotherapy and novel agents (43). Table 1.11 below provides a summary of the treatments used for patients with MF and SS (43).

Table 1.10: Summary of the available treatments for patients with MF and SS

Therapy type	Treatment
A) Early stage (stage IA-IIA) Topical/skin-directed therapy	 Steroids Phototherapy, Nitrogen mustard, Bexarotene, Local radiation, TSEBT
B) Refractory early stage MF (stage IA-IIA) Combination therapy	 PUVA or NBUVB and IFNα (low dose) PUVA or NBUVB and Bexarotene (low-dose)
C) Advanced MF/SS (stage IIB-IVB) i) Skin directed therapy	 TSEBT

ii)	Immunomodulators	Interferons (IFNα and IFNγ) Retinoid/rexinoid (bexarotene) ECP
iii)	Biologic/targeted therapies	Alemtuzumab HDAC (e.g. romidepsin and vorinostat) Antifolates (e.g.methotrexate and pralatrexate)
iv)	Combined therapy	IFNα and phototherapy IFNα and retinoids /rexinoids Retinoid and phototherapy ECP and IFNα ECP and retinoids/rexinoids
v)	Systemic chemotherapy Single-agent chemotherapy Multiagent Chemotherapy	Pegylated doxorubicin Purine/pyrimidine analogues (e.g. gemcitabine) CHOP and CHOP-like chemotherapy
vi)	Stem cell transplant (SCT)	Autologous SCT Allogeneic SCT Nonmyeloblative allogeneic
vii)	Investigational therapy	Lenalidomide Bortezomib CCR4 antibody TLR agonists Interleukins Anti-PD-1 agents Protein kinase C inhibitors Phosphoinositide 3-kinase inhibitors Brentuximab vedotin

CHOP -cyclophosphamide, doxorubicin, vincristine and prednisone; ECP- extracorporeal photopheresis; HDAC- histonedeactetylase inhibitors IFNα- interferon-alpha; IFNγ- interferon-gamma; MF-Mycosis Fungoides; NBUVB- narrowband ultraviolet B light phototherapy; PD-1- Programmed-Death-1; PUVA-psoralen plus ultraviolet A light phototherapy; SS-Sezary syndrome; SCT- Stem Cell Transplant; TLR- Toll-like receptor; TSEBT-total skin electron beam therapy

Common therapies used in patients with skin limited disease (stage IA-IIA) include, topical steroids which are most commonly used to treat early MF and are an adjunct to other topical and systemic

therapies in all stages. Topical nitrogen mustard has a similar efficacy in early stage MF and maintenance therapy may be required in order for patients to remain in complete remission. Total Skin Electron Beam Therapy (TSEBT) at a dose (30Gy) is effective in refractory/relapsed extensive plaque and tumor MF. Low dose radiation therapy may be useful in selected patients (43).

In patients with advanced disease, TSEBT is a means of administering ionising radiation to the entire surface of the skin with deeper penetration than nitrogen mustard and phototherapy. TSEBT is used for rapidly progressing or refractory disease with extensive plaque (T2) and tumour (T3) involvement. Single agent systemic therapy like bexarotene is often used as a skin directed therapy in cases of advanced disease. Immunomodulators include interferons as well as retinoids which are commonly used as first line monotherapy in advanced MF. Vorinostat and romidepsin are histone deactetylase inhibitors (HDAC), which may be effective as single agents in treating skin, nodal, and blood disease. In erythrodermic MF/SS, alemtuzumab is effective in depleting the central memory T-cell subset. The treatment of refractory or advanced stage MF is generally chemotherapy. Allogeneic SCT is reserved for advanced stage disease and may have curative potential in MF (43).

At CHBAH, we are limited as to the availability of a number of treatments. Treatments available that are routinely used in skin limited disease are topical and systemic steroids, phototherapy such as NBUVB, and TSEBT and local radiation therapy. Retinoids are occasionally used as skin directed therapies. Systemic chemotherapy is available and includes CHOP and CHOP-like therapies (CHOEP), as well as nucleoside analogues such as fludarabine. Alemtuzumab, an anti-CD52 monoclonal antibody is now also available. SCT is reserved for refractory cases, where feasible.

2.0. CHAPTER TWO: PATIENTS AND METHODS

2.1. Study Design

This is a retrospective study of all adult patients seen at the Clinical Hematology Unit, Department of Medicine, CHBAH from January 2004 – December 2015 with mature T-cell and Natural killer cell NHL. The patient files and outpatient records were reviewed.

2.2. Study Population

A total of 52 patients were evaluable for review during this study period. The study population was non-uniform (with a variety of different subtypes of lymphoma). The inclusion criteria and exclusion criteria were as follows:

a) Inclusion criteria

   i) Adult patients ≥18 years of age

   ii) Histological evidence of mature T-cell or NK-cell NHL

b) Exclusion criteria

   i) Lymphomas other than mature T-cell or NK-cell NHL

   ii) Inadequate data available for review

2.3. Methods and Procedures

The data were collected using a data collection sheet as shown in Appendix A. Permission to review all files/records of the patients was obtained from the CEO of the Hospital, the Head of the Department of Medicine and the Head of the Clinical Hematology Unit, Department of Medicine at CHBAH. Patients were identified using a study number with the name and hospital number kept on a separate password protected file. Demographic and clinical features including cutaneous

manifestations were documented. In addition, relevant blood investigations and radiological findings were recorded as was treatment and response to treatment, for all the patients studied.

2.4. Sampling

T-cell an NK-cell lymphoma are rare conditions hence the sampling strategies used for the present study was 'convenience sampling' meaning that all patient records meeting the study inclusion criteria during the specified time period for data collection were evaluated.

2.5. Data Management

Information from the patient's files was captured in a Microsoft Excel spread sheet database. The data management procedure entailed cleaning the data by checking for missing data, duplicates and errors in recording. This process was rechecked manually to verify that the data was recorded correctly.

2.6. Data Analysis

Data were analyzed using STATA version 14.1. In order to conduct the descriptive analysis of demographics, clinical presentation, staging and prognostic factors of the patients, frequency tables were computed for categorical variables such as gender and ethnicity. For continuous variables such as lymphocyte count and age, the Shapiro Wilk test for normality was used to check for the distribution of the data at a significance level of 5% ($p<0.05$). For data that were normally distributed, means±SD were calculated and for data that were skewed, medians (IQR) were used. To describe and compare the impact of HIV on the presentation of the clinical features and clinical outcomes, a chi-squared test was used at the 5% significance level ($p<0.05$).

Kaplan-Meier curves were used to determine whether prognostic variables affected the survival of lymphoma patients.

3.0. CHAPTER THREE: RESULTS

3.1. Demographics

A total number of 52 patients with T-cell and NK-cell lymphoma were reviewed for this study. The median age was 46 years with a range of 21 – 82 years.

Table 3.11: Gender distribution

Gender	Frequency	%
Female	30	57.69%
Male	22	42.31%
Total	52	100.00

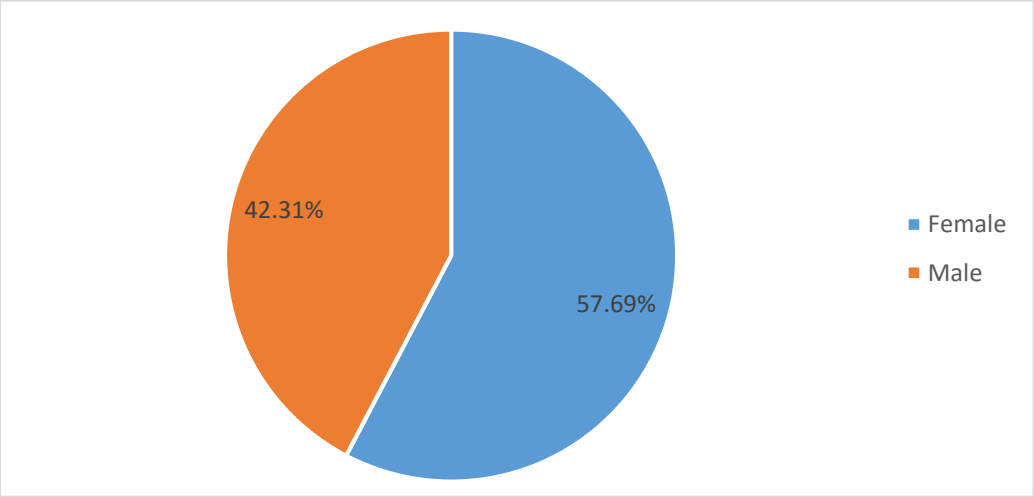


Figure 3.1: Gender distribution

Table 3.11 and Figure 3.1 show the gender distribution. There were 30 females and 22 males recruited for the study with a female to male ratio of 1.4:1

Table 3.2: Distribution of patients by ethnicity

	Frequency	%
Black	49	94.23
Asian	1	1.92
Coloured	2	3.85
Total	52	100.00

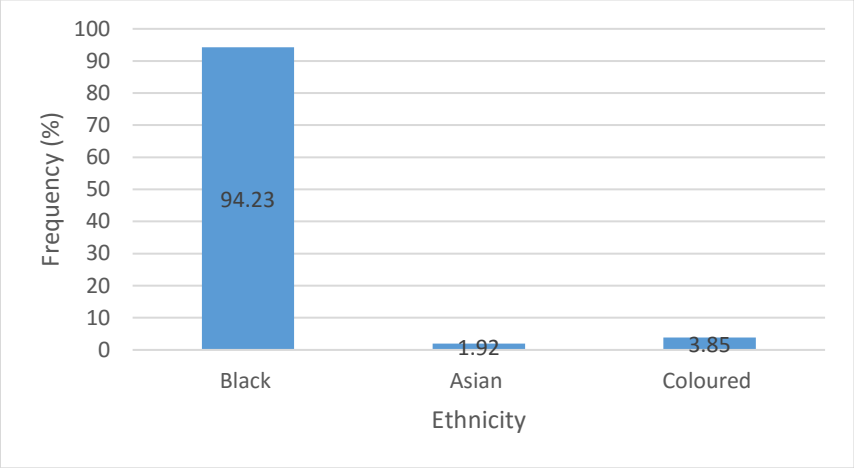


Figure 3.2: Distribution of patients by ethnicity

Table 3.2 and Figure 3.2 show the distribution of patients by ethnicity. The majority of the study patients were black (94.23 %) and less than 6% of the patients belonged to other ethnic groups. This is in keeping with the demographics of the patients seen at CHBAH.

Table 3.3: ECOG performance status

ECOG performance status	Frequency	%
1.0	31	59.61
2.0	14	26.92
3.0	3	5.77
4.0	2	3.85
Unknown	2	3.85
Total	52	100.00

EC0G =Eastern Cooperative Oncology Group

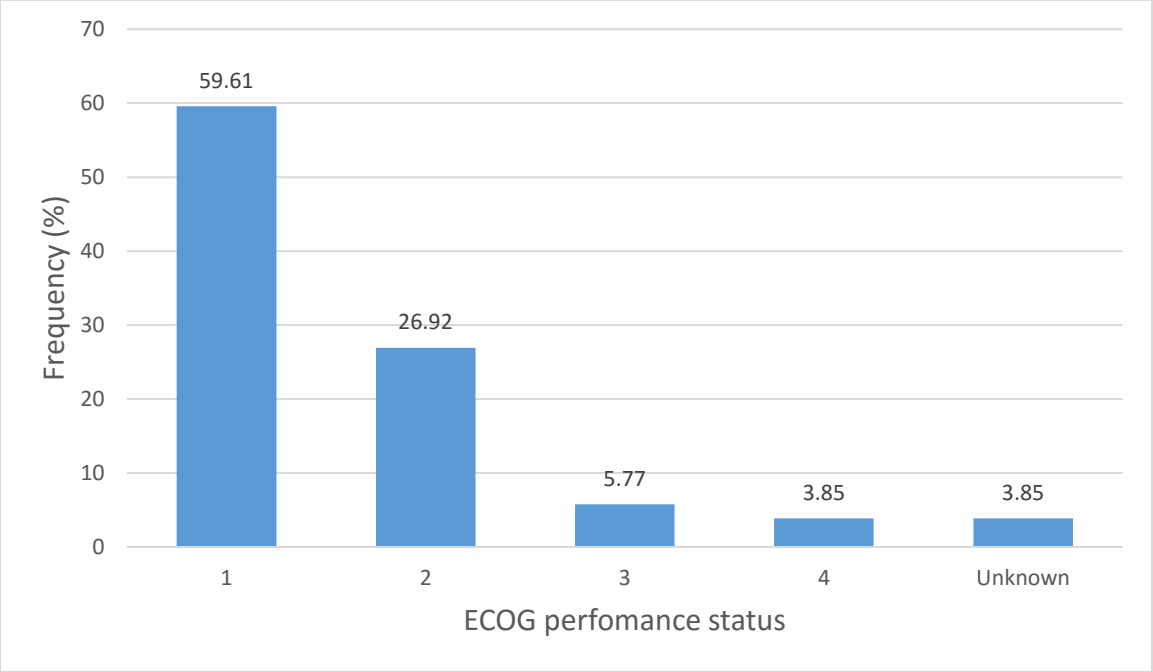


Figure 3.3: ECOG performance status

The ECOG (Eastern Cooperative Oncology Group) performance status of the patients is depicted in Table 3.3 and Figure 3.3. As noted, the majority of the patients (86.5%) had a favorable performance status of 1 or 2 at presentation.

3.2 Comorbidities

Table 3.4: Distribution of patients by comorbidity, excluding HIV and TB

Comorbidity	Frequency	%
Yes	21	40.38
No	31	59.62
Total	52	100.00

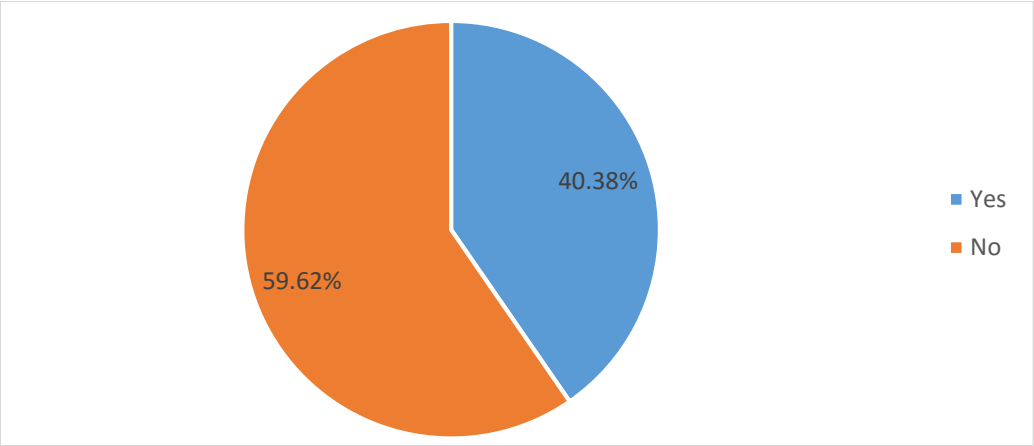


Figure 3.4: Distribution of patients by comorbidity, excluding HIV and TB

Table 3.4 and Figure 3.4 shows that of the 52 patients recruited in the study, 40.38% had comorbidities other than TB or HIV. The three most common comorbidities were: hypertension 45%, diabetes 30%, and epilepsy 20%. Other comorbidities included: cardiac failure, pericardial effusion,

schizophrenia, thoracic myelopathy, mixed mitral valve disease, pulmonary hypertension, sarcoidosis, hepatitis B, hepatitis C, Norwegian scabies, multinodular goiter, impaired hearing, blindness, neuropathy, Baker's cyst, syphilis, cytomegalovirus, benign prostatic hyperplasia, dementia and cranial nerve palsies.

Table 3.5: TB in association with T-cell/NK-cell Lymphoma

TB	Frequency	%
yes	9	17.31
no	43	82.69
Total	52	100.00

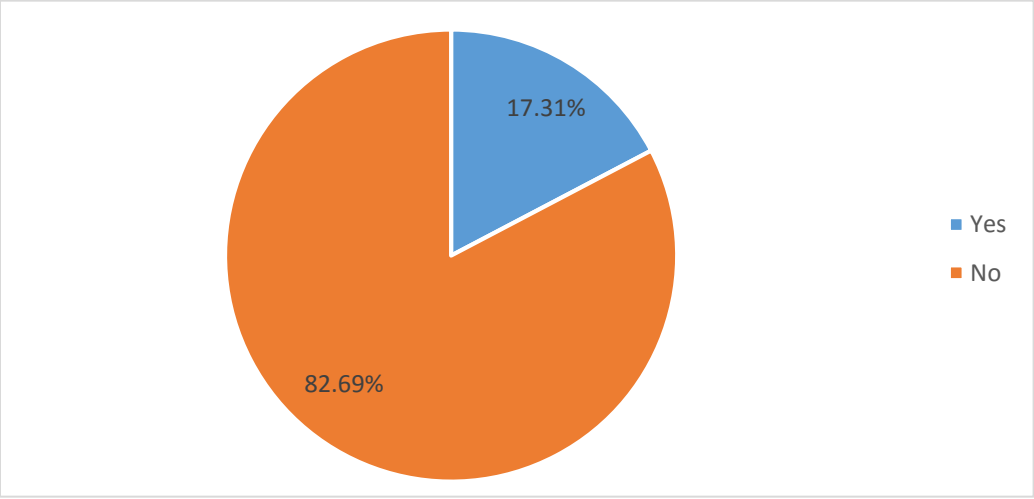


Figure 3.5: TB in association with T-cell Lymphoma

Of the 52 patients studied, 17.31% had TB. This is shown in Table 3.5 and Figure 3.5.

Table 3.6: Diagnosis of TB

Diagnosis of TB	Frequency	%
Prior to lymphoma diagnosis	4	44.44
During lymphoma diagnosis	5	55.56
Total	9	100.00

Table 3.6 shows the distribution of the 9 patients who had TB, and the association of TB in relation to the time of the diagnosis of T-cell Lymphoma. 44.44% of the patients with TB had their TB diagnosis prior to the lymphoma diagnosis.

Table 3.7: Distribution of patients by HIV status

HIV status	Frequency	%
Positive	11	21.15
Negative	41	78.85
Total	52	100.00

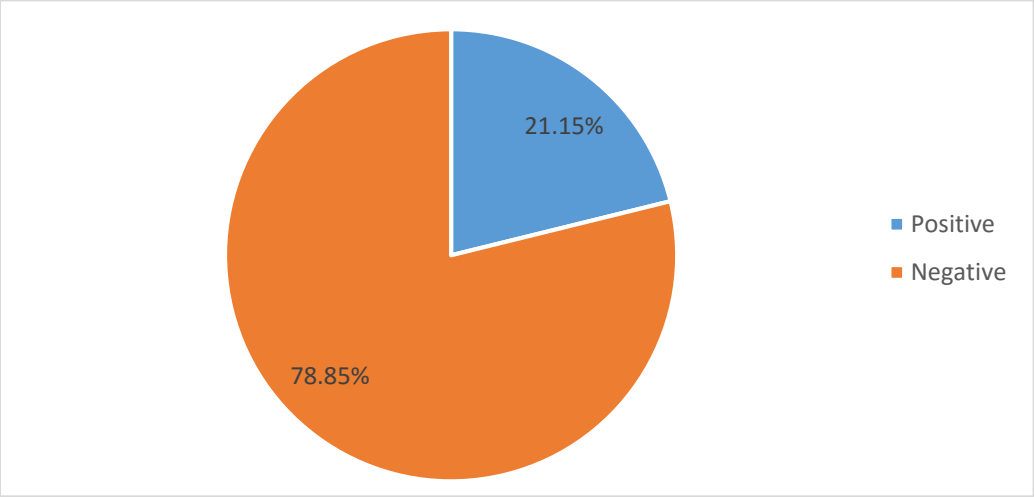


Figure 3.6: Distribution of patients by HIV status

Table 3.7 and Figure 3.6 show the distribution of patients by HIV status. Of the 52 patients studied, 11 (21.15%) were HIV sero-positive.

Table 3.8: Distribution of patients by combination antiretroviral therapy (cART)

On ART	Frequency	%
yes	6	55%
no	3	27%
unknown	2	18%
Total	9	100.00

Table 3.8 and Figure 3.7 show that out of the 9 HIV sero-positive patients who were on cART, (55%) were on combination antiretroviral therapy (cART) at the time of their lymphoma diagnosis.

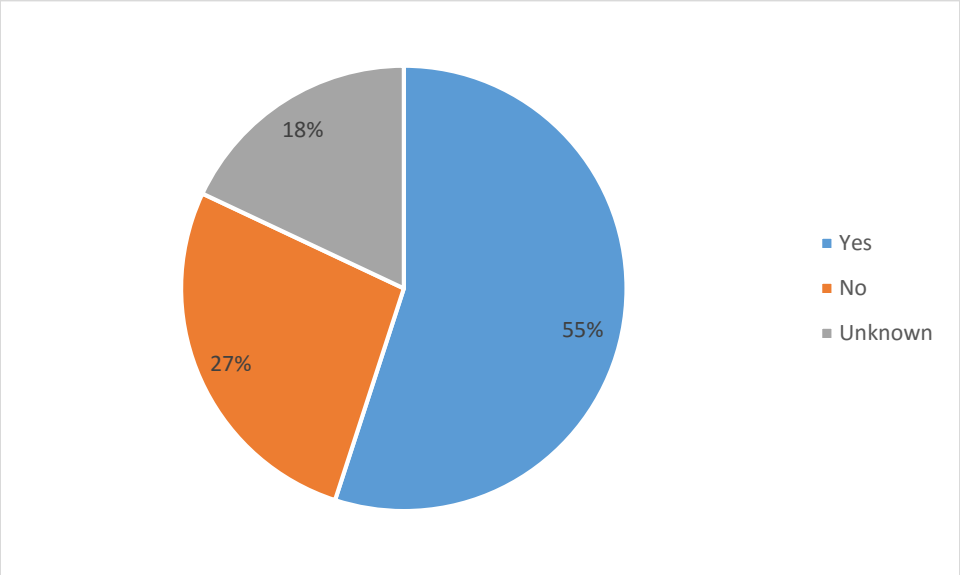


Figure 3.7: Distribution of patients on cART

3.3 Clinical features

Of the 52 patients in the study, the most common clinical features encountered at presentation are shown in Table 3.9 below.

Table 3.9: Clinical features

Clinical features	Frequency	%
Cutaneous involvement	38	73.07
B symptoms	34	65.38
Hepatomegaly	21	40.38
Bone marrow involvement	19	38.78
Lymphadenopathy	15	28.85
Splenomegaly	14	26.92

Cutaneous involvement was the most common clinical feature seen. This is not unexpected, given the T-cell/NK-cell nature of the lymphomas studied. Other clinical features noted in Table 3.9 are those regularly encountered in patients presenting with lymphoproliferative disorders, such as 'B' symptoms, lymphadenopathy, hepatosplenomegaly and bone marrow involvement.

3.4 Subtypes of T-cell and NK-cell Non-Hodgkin lymphoma

Table 3.10: Subtypes of T-cell and NK-cell NHL

Subtype		**N**	**%**
Non-cutaneous (N=33)	PTCL, NOS	13	39.39
	ALCL	8	24.24
	ATLL	5	15.15
	HSTCL	3	9.09
	TPLL	2	6.06
	AITL	1	3.03
	T-cell lymph unclassified	1	3.03
Cutaneous (N=19)	MF	15	78.95
	SS	4	21.05

PTCL,NOS ─ Peripheral T-cell lymphoma not otherwise specified

ALCL -Anaplastic large cell lymphoma

ATLL – Adult T-cell leukemia lymphoma

HSTCL -Hepatosplenic T-cell lymphoma

TPLL – T-cell prolymphocytic leukemia

AITL -Angioimmunoblastic T-cell lymphoma

MF – Mycosis Fungoides

SS- Sezary Syndrome

Of the subtypes of T-cell and NK-cell NHL, the non-cutaneous varieties or peripheral T-cell lymphoma (PTCL) was seen in 63% (33/52) patients, while the cutaneous variety or cutaneous T-cell lymphoma (CTCL) was seen in 37% (19/52). Various aspects of the PTCL and CTCL are depicted in Tables 3.11, 3.12 and 3.13.

3.5 Comparison between the Cutaneous and Peripheral T-cell lymphomas

Table 3.11: Comparison of the Cutaneous and Peripheral T-cell lymphomas

Variable	Categories	Group			P-value	Test
		Cutaneous (n=19)	Peripheral (n=33)	Total (n=52)		
Age	Median (Range)	52 (30 - 82)	33 (21 - 70)	46 (21 - 82)	0.138	Mann-Whitney U Test
Gender	Female	12 (63.2%)	18 (54.5%)	30 (57.7%)	.576	Chi-square
	Male	7 (36.8%)	15 (45.5%)	22 (42.3%)		
Ethnicity	Black	17 (89.5%)	32 (97%)	49 (94.2%)	.374	Chi-square
	Asian	1 (5.3%)	0 (0%)	1 (1.9%)		
	Coloured	1 (5.3%)	1 (3%)	2 (3.8%)		
ECOG PS 0-4	n=	18	32	50		Chi-square
	1	16 (88.9%)	15 (46.9%)	31 (62%)	.030	
	2	2 (11.1%)	12 (37.5%)	14 (28%)		
	3	0 (0%)	3 (9.4%)	3 (6%)		
	4	0 (0%)	2 (6.3%)	2 (4%)		
B symptoms	Yes	3 (15.8%)	31 (93.9%)	34 (65.4%)	.000	Chi-square
Skin Involvement	Yes	19 (100%)	19 (57.6%)	38 (73.1%)	.001	Chi-square
Hepatomegaly	Yes	4 (21.1%)	17 (51.5%)	21 (40.4%)	.042	Chi-square
Splenomegaly	Yes	2 (10.5%)	12 (36.4%)	14 (26.9%)	.055	Chi-square
	n=	19	30	49		

Bone Marrow involvement	Yes	7 (36.8%)	12 (40%)	19 (38.8%)	1.000	Chi-square
	No	12 (63.2%)	18 (60%)	30 (61.2%)		

Table 3.12: Comparison of laboratory features between Cutaneous and Peripheral T-cell NHL

Variable	Categories	Group			P-value	Test
		Cutaneous (n=19)	Peripheral (n=33)	Total (n=52)		
Hb	n=	18	33	51		Chi-square
	Normal	9 (50%)	12 (36.4%)	21 (41.2%)	.197	
	Grade 0 (Borderline anaemia)	6 (33.3%)	7 (21.2%)	13 (25.5%)		
	Grade I (Mild anaemia)	2 (11.1%)	8 (24.2%)	10 (19.6%)		
	Grade II (Moderate anaemia)	0 (0%)	3 (9.1%)	3 (5.9%)		
	Grade III (Severe anaemia)	1 (5.6%)	0 (0%)	1 (2%)		
	Grade IV (Very severe/ life threatening anaemia)	0 (0%)	3 (9.1%)	3 (5.9%)		
WCC	n=	18	33	51		Chi-square
	Normal	9 (50%)	14 (42.4%)	23 (45.1%)	.220	
	Leukopenia	0 (0%)	5 (15.2%)	5 (9.8%)		
	Leucocytosis	9 (50%)	14 (42.4%)	23 (45.1%)		
Platelets	n=	18	32	50	.306	Chi-square
	Normal (150 - 400)	11 (61.1%)	18 (56.3%)	29 (58%)		
	Clinical Thrombocytopenia (<100)	0 (0%)	6 (18.8%)	6 (12%)		
	Borderline Thrombocytopenia (100 - 150)	2 (11.1%)	3 (9.4%)	5 (10%)		
	Borderline Thrombocytosis (400 - 450)	2 (11.1%)	1 (3.1%)	3 (6%)		
	Thrombocytosis (>450)	3 (16.7%)	4 (12.5%)	7 (14%)		
Neutrophils	n=	17	26	43	.997	Chi-square
	Normal	7 (41.2%)	11 (42.3%)	18 (41.9%)		
	Neutropenia	2 (11.8%)	3 (11.5%)	5 (11.6%)		
	neutrophilia	8 (47.1%)	12 (46.2%)	20 (46.5%)		
Lymphocytes	n=	17	25	42	.305	Chi-square
	Normal	11 (64.7%)	12 (48%)	23 (54.8%)		
	Lymphopenia	3 (17.6%)	3 (12%)	6 (14.3%)		
	Lymphocytosis	3 (17.6%)	10 (40%)	13 (31%)		
Monocytes	n=	16	25	41	.322	Chi-square
	Normal	8 (50%)	8 (32%)	16 (39%)		

	Low monocytes	0 (0%)	2 (8%)	2 (4.9%)		
	Elevated monocytes	8 (50%)	15 (60%)	23 (56.1%)		
Basophils	n=	15	16	31		Chi-square
	Normal	0 (0%)	5 (31.3%)	5 (16.1%)	.043	
	Raised Basophils	15 (100%)	11 (68.8%)	26 (83.9%)		
Eosinophils	n=	16	18	34		Chi-square
	Normal	6 (37.5%)	13 (72.2%)	19 (55.9%)	.082	
	Raised Eosinophils	10 (62.5%)	5 (27.8%)	15 (44.1%)		
Total Bilirubin	n=	13	27	40		Chi-square
	Normal	13 (100%)	19 (70.4%)	32 (80%)	.037	
	Raised Total Bilirubin	0 (0%)	8 (29.6%)	8 (20%)		
Albumin	n=	18	27	45		Chi-square
	Normal	13 (72.2%)	16 (59.3%)	29 (64.4%)	.527	
	Low Albumin	5 (27.8%)	11 (40.7%)	16 (35.6%)		
AST	n=	18	28	46		Chi-square
	Normal	17 (94.4%)	16 (57.1%)	33 (71.7%)	.007	
	Raised AST	1 (5.6%)	12 (42.9%)	13 (28.3%)		
ALT	n=	18	28	46		Chi-square
	Normal	15 (83.3%)	20 (71.4%)	35 (76.1%)	.486	
	Raised ALT	3 (16.7%)	8 (28.6%)	11 (23.9%)		
ALP	n=	18	28	46		Chi-square
	Normal ALP	13 (72.2%)	12 (42.9%)	25 (54.3%)	.039	
	Low ALP	2 (11.1%)	1 (3.6%)	3 (6.5%)		
	Raised ALP	3 (16.7%)	15 (53.6%)	18 (39.1%)		
LDH	n=	14	26	40		Chi-square
	Normal	1 (7.1%)	0 (0%)	1 (2.5%)	.350	
	Elevated LDH	13 (92.9%)	26 (100%)	39 (97.5%)		
Calcium	n=	16	31	47		Chi-square
	Normal	15 (93.8%)	23 (74.2%)	38 (80.9%)	.199	
	Low calcium	1 (6.3%)	3 (9.7%)	4 (8.5%)		
	High calcium	0 (0%)	5 (16.1%)	5 (10.6%)		
Uric acid	n=	14	24	38		Chi-square
	Normal Uric acid	8 (57.1%)	13 (54.2%)	21 (55.3%)	.741	
	Low Uric acid	0 (0%)	1 (4.2%)	1 (2.6%)		
	Elevated Uric acid	6 (42.9%)	10 (41.7%)	16 (42.1%)		
Beta-2 microglobulin	n=	5	16	21		
	Elevated Beta 2 microglobulin	5 (100%)	16 (100%)	21 (100%)	-	Chi-square

Table 3.13: Comparison of Cutaneous and Peripheral T-cell NHL - HIV, TB and Outcome

Variable	Categories	Group			P-value	Test
		Cutaneous (n=19)	Peripheral (n=33)	Total (n=52)		

HIV	n=	19	33	52		Chi-square
	Positive	1 (5.3%)	10 (30.3%)	11 (21.2%)	.040	
	Negative	18 (94.7%)	23 (69.7%)	41 (78.8%)		
TB	n=	19	33	52		Chi-square
	Yes	0 (0%)	9 (27.3%)	9 (17.3%)	.018	
	No	19 (100%)	24 (72.7%)	43 (82.7%)		
Ann-Arbor stage		0	33	33		
	Stage 1B	0 (0%)	1 (3%)	1 (3%)	-	Chi-square
	Stage 1BE	0 (0%)	1 (3%)	1 (3%)		
	Stage 1E	0 (0%)	1 (3%)	1 (3%)		
	Stage 2A	0 (0%)	1 (3%)	1 (3%)		
	Stage 2B	0 (0%)	2 (6.1%)	2 (6.1%)		
	Stage 2E	0 (0%)	1 (3%)	1 (3%)		
	Stage 3B	0 (0%)	1 (3%)	1 (3%)		
	Stage 4	0 (0%)	1 (3%)	1 (3%)		
	Stage 4A	0 (0%)	1 (3%)	1 (3%)		
	Stage 4B	0 (0%)	23 (69.7%)	23 (69.7%)		
TNMB Classification		19	0	19		
	Stage 1B	4 (21.1%)	0 (0%)	4 (21.1%)	-	Chi-square
	Stage 2A	4 (21.1%)	0 (0%)	4 (21.1%)		
	Stage 2B	3 (15.8%)	0 (0%)	3 (15.8%)		
	Stage 3	1 (5.3%)	0 (0%)	1 (5.3%)		
	Stage 4	1 (5.3%)	0 (0%)	1 (5.3%)		
	Stage 4A1	1 (5.3%)	0 (0%)	1 (5.3%)		
	Stage 4A2	2 (10.5%)	0 (0%)	2 (10.5%)		
	Stage 4B	3 (15.8%)	0 (0%)	3 (15.8%)		
Initial Response		15	32	47		Chi-square
	CR = Complete response 100% improvement	2 (13.3%)	3 (9.4%)	5 (10.6%)	.010	
	PR = Partial Response> 50% improvement	10 (66.7%)	7 (21.9%)	17 (36.2%)		
	< PR = less than partial response	0 (0%)	9 (28.1%)	9 (19.1%)		
	In-evaluable (< 2 cycles of chemotherapy and died before)	3 (20%)	13 (40.6%)	16 (34%)		
Response at last visit		18	32	50		Chi-square
	PR = Partial Response> 50% improvement	8 (44.4%)	6 (18.8%)	14 (28%)	.298	
	< PR = less than partial response	4 (22.2%)	7 (21.9%)	11 (22%)		
	No response	0 (0%)	2 (6.3%)	2 (4%)		
	PD = Progression of disease	1 (5.6%)	2 (6.3%)	3 (6%)		

	In-evaluable (< 2 cycles of chemotherapy and died before)	5 (27.8%)	15 (46.9%)	20 (40%)		
Outcome		19	33	52		Chi-square
	Alive	4 (21.1%)	3 (9.1%)	7 (13.5%)	.152	
	Dead	9 (47.4%)	25 (75.8%)	34 (65.4%)		
	Lost to follow-up	5 (26.3%)	5 (15.2%)	10 (19.2%)		
	Transferred	1 (5.3%)	0 (0%)	1 (1.9%)		
Possible reasons for death		9	25	34		Chi-square
	Progression of disease	4 (44.4%)	9 (36%)	13 (38.2%)	.124	
	Infection	1 (11.1%)	8 (32%)	9 (26.5%)		
	Organ failure	0 (0%)	3 (12%)	3 (8.8%)		
	Other	1 (11.1%)	4 (16%)	5 (14.7%)		
	Unknown	3 (33.3%)	1 (4%)	4 (11.8%)		

3.6 Comparison of results by HIV status

In addition, among the patients that had Peripheral T-cell lymphoma, a number of variables were assessed to compare the HIV sero-positive against the HIV sero-negative patients. The results of the comparison are shown in table 3.14.

Table 3.14: Comparison of HIV sero-positive and HIV sero-negative Peripheral T-cell lymphoma patients

Variable	Categories	Group			P-value	Test
		HIV Positive (n=10)	HIV Negative (n=23)	Total (n=33)		
Total		10 (30.3%)	23 (69.7%)	33 (100%)	0.024	
Age	Median (Range)	39.5 (25 - 51)	42 (21- 70)	46 (21- 70)	0.221	Mann-Whitney U Test
Gender	Female	7 (70%)	11 (47.8%)	18 (54.5%)	.283	Chi-square
	Male	3 (30%)	12 (52.2%)	15 (45.5%)		
ECOG PS 0-4	1	5 (50%)	10 (43.5%)	15 (45.5%)	.053	Chi-square
	2	2 (20%)	10 (43.5%)	12 (36.4%)		
	3	3 (30%)	0 (0%)	3 (9.1%)		
	4	0 (0%)	2 (8.7%)	2 (6.1%)		
	Unknown	0 (0%)	1 (4.3%)	1 (3%)		
Lymph-adenopathy	Yes	4 (36.4%)	11 (26.8%)	15 (28.8%)	.709	Chi-square
	No	7 (63.6%)	30 (73.2%)	37 (71.2%)		
	Yes	5 (45.5%)	33 (80.5%)	38 (73.1%)	.0495	

Cutaneous Involvement	No	6 (54.5%)	8 (19.5%)	14 (26.9%)		Chi-square
Bone marrow involvement	n=	9	40	49		Chi-square
	Yes	3 (33.3%)	16 (40%)	19 (38.8%)	1.000	
	No	6 (66.7%)	24 (60%)	30 (61.2%)		
Hb	n=	11	40	51		Chi-square
	Normal	2 (20%)	10 (43.5%)	12 (36.4%)	.061	
	Grade 0 (Borderline anaemia)	1 (10%)	6 (26.1%)	7 (21.2%)		
	Grade I (Mild anaemia)	3 (30%)	5 (21.7%)	8 (24.2%)		
	Grade II (Moderate anaemia)	3 (30%)	0 (0%)	3 (9.1%)		
	Grade IV (Very severe/life threatening anaemia)	1 (10%)	2 (8.7%)	3 (9.1%)		
WCC		11	40	51		Chi-square
	Normal	5 (45.5%)	18 (45%)	23 (45.1%)	.996	
	Leukopenia	1 (9.1%)	4 (10%)	5 (9.8%)		
	Leukocytosis	5 (45.5%)	18 (45%)	23 (45.1%)		
Platelets		18	32	50	.055	
	Normal (150 - 400)	11 (61.1%)	18 (56.3%)	29 (58%)		Chi-square
	Clinical Thrombocytopenia (<100)	0 (0%)	6 (18.8%)	6 (12%)		
	Borderline Thrombocytopenia (100 - 150)	2 (11.1%)	3 (9.4%)	5 (10%)		
	Borderline Thrombocytosis (400 - 450)	2 (11.1%)	1 (3.1%)	3 (6%)		
	Thrombocytosis (>450)	3 (16.7%)	4 (12.5%)	7 (14%)		
Lymphocytes		7	18	25		Chi-square
	Lymphopenia	1 (14.3%)	2 (11.1%)	3 (12%)	.000	
	Normal	4 (57.1%)	8 (44.4%)	12 (48%)		
	Lymphocytosis	2 (28.6%)	8 (44.4%)	10 (40%)		
Hepatomegaly		10	23	33		Chi-square
	Yes	3 (30%)	14 (60.9%)	17 (51.5%)	.141	
	No	7 (70%)	9 (39.1%)	16 (48.5%)		
Splenomegaly		10	23	33		Chi-square
	Yes	1 (10%)	11 (47.8%)	12 (36.4%)	.054	
	No	9 (90%)	12 (52.2%)	21 (63.6%)		
TB		11	41	52		

	Yes	5 (45.5%)	4 (9.8%)	9 (17.3%)	.014	Chi-square
	No	6 (54.5%)	37 (90.2%)	43 (82.7%)		
Ann-Arbor stage		10	23	33		Chi-square
	Stage 1B	1 (10%)	0 (0%)	1 (3%)	.106	
	Stage 1BE	0 (0%)	1 (4.3%)	1 (3%)		
	Stage 1E	0 (0%)	1 (4.3%)	1 (3%)		
	Stage 2A	0 (0%)	1 (4.3%)	1 (3%)		
	Stage 2B	2 (20%)	0 (0%)	2 (6.1%)		
	Stage 2E	0 (0%)	1 (4.3%)	1 (3%)		
	Stage 3B	0 (0%)	1 (4.3%)	1 (3%)		
	Stage 4	1 (10%)	0 (0%)	1 (3%)		
	Stage 4A	1 (10%)	0 (0%)	1 (3%)		
	Stage 4B	5 (50%)	18 (78.3%)	23 (69.7%)		
Initial Response		10	37	47		Chi-square
	CR = Complete response 100% improvement	3 (30%)	2 (5.4%)	5 (10.6%)	.039	
	PR = Partial Response> 50% improvement	1 (10%)	16 (43.2%)	17 (36.2%)		
	< PR = less than partial response	1 (10%)	8 (21.6%)	9 (19.1%)		
	In-evaluable (< 2 cycles of chemotherapy and died before)	5 (50%)	11 (29.7%)	16 (34%)		
Response at last visit		10	40	50		Chi-square
	PR = Partial Response> 50% improvement	3 (30%)	11 (27.5%)	14 (28%)	.803	
	< PR = less than partial response	3 (30%)	8 (20%)	11 (22%)		
	No response	0 (0%)	2 (5%)	2 (4%)		
	PD = Progression of disease	0 (0%)	3 (7.5%)	3 (6%)		
	Inevaluable (< 2 cycles of chemotherapy and died before)	4 (40%)	16 (40%)	20 (40%)		
Outcome		10	23	33		Chi-square
	Alive	3 (30%)	0 (0%)	3 (9.1%)	.000	
	Dead	5 (50%)	20 (87%)	25 (75.8%)		
	LFU	2 (20%)	3 (13%)	5 (15.2%)		
		6	28	34		Chi-square

Possible reasons for death	Progression of disease	2 (33.3%)	11 (39.3%)	13 (38.2%)	.405	
	Infection	3 (50%)	6 (21.4%)	9 (26.5%)		
	Organ failure	1 (16.7%)	2 (7.1%)	3 (8.8%)		
	Other	0 (0%)	5 (17.9%)	5 (14.7%)		
	Unknown	0 (0%)	4 (14.3%)	4 (11.8%)		

3.7 Kaplan Meier survival curves

Table 3.15 and Figure 3.8 depict the overall survival of the study population. The curve for the overall survival of lymphoma patients shows that the probability of survival gradually declines with time. The median overall survival is 14 months, with a 95% CI of 3.421-24.579 months.

Table 3.15: Means and Medians for Overall Survival

Means and Medians for Survival Time							
Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Upper Bound			Lower Bound	Upper Bound
36.528	8.906	19.072	53.985	14.000	5.398	3.421	24.579
a. Estimation is limited to the largest survival time if it is censored.							

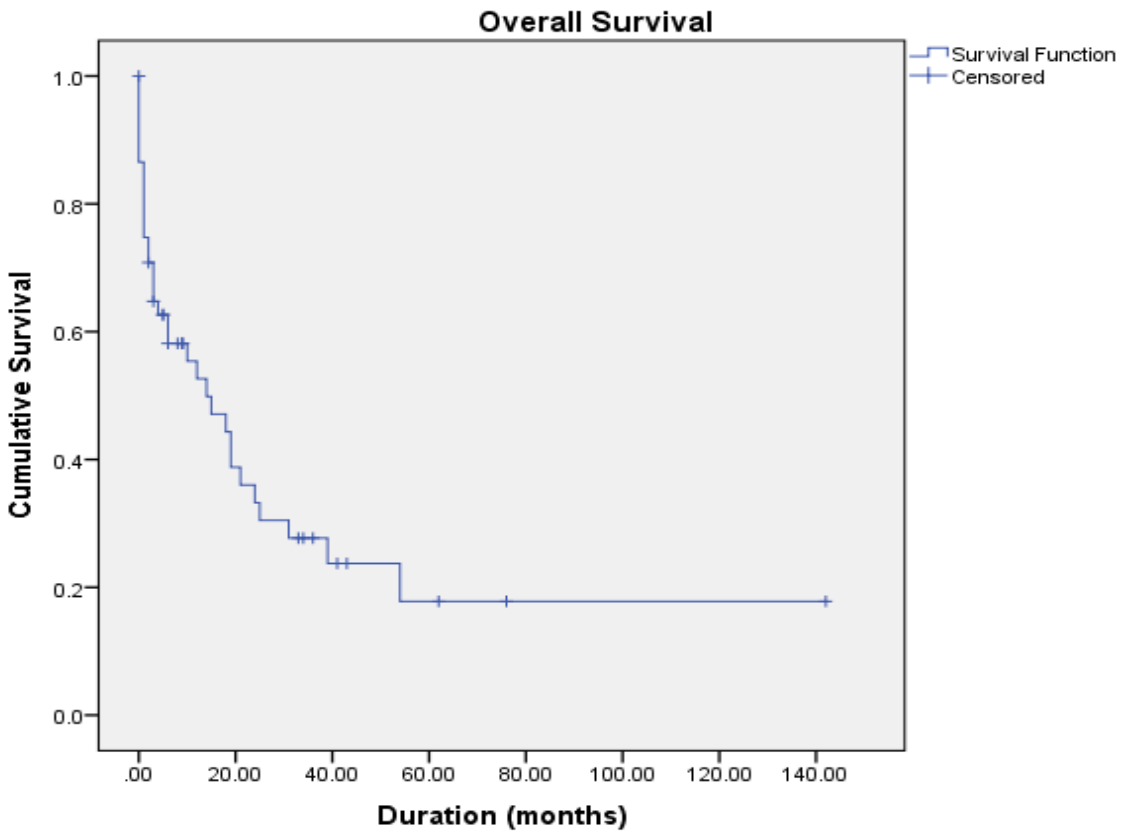


Figure 3.8 Kaplan Meier overall survival curve

Table 3.16: Means and Medians for Overall Survival by disease stage

Means and Medians for Survival Time								
Stage	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Stage 1 - 2	41.924	9.425	23.451	60.398	54.000	24.970	5.058	102.942
Stage 3 - 4	26.045	8.258	9.860	42.230	4.000	3.743	.000	11.337
Overall	36.528	8.906	19.072	53.985	14.000	5.398	3.421	24.579
a. Estimation is limited to the largest survival time if it is censored.								

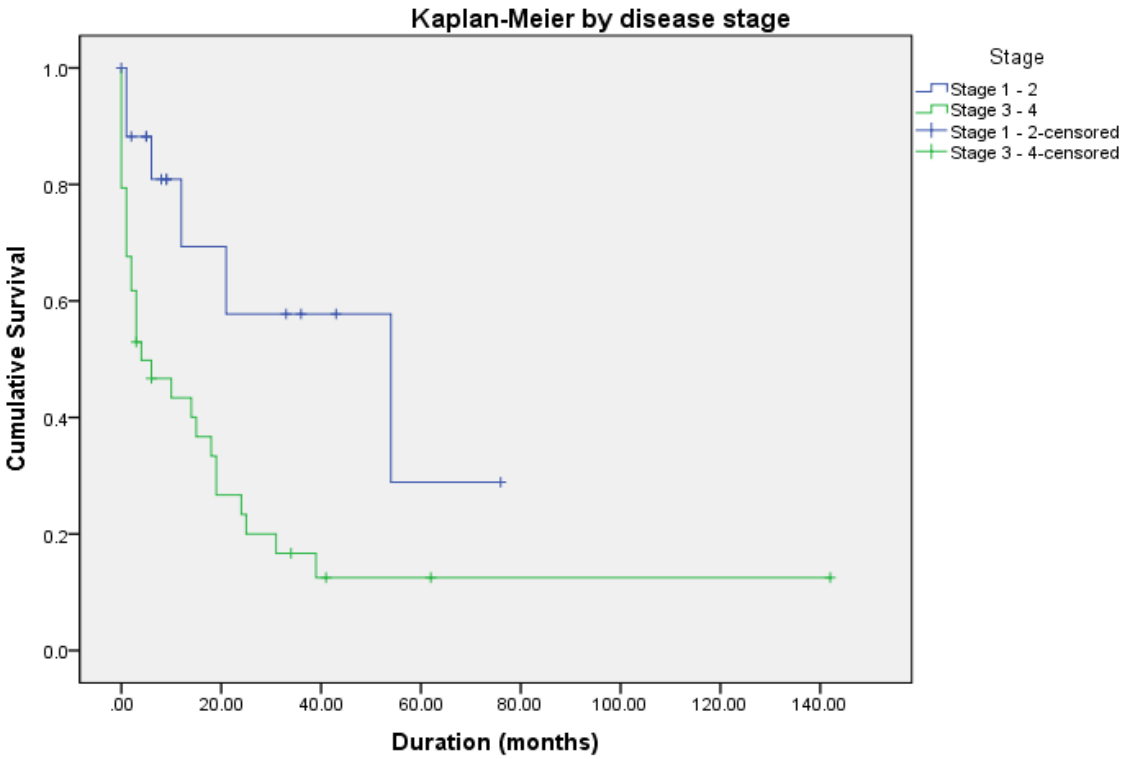


Figure 3.9 Kaplan Meier survival curve by disease stage

Furthermore, survival was looked at, based on disease stage. Early stage lymphoma patients appear to have better survival than late stage lymphoma patients. Patients in disease stage 3-4 (median survival time= 4 months; 95% CI = 0 - 11.337 months) died sooner than patients in disease stage 1-2 (median survival time= 54 months; 95% CI (5.058 - 102.942 months) (see Table 3.19 and Figure 3.9).

Table 3.17: Means and Medians for Overall Survival by age group

Means and Medians for Survival Time								
Age	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
≤ 46 years	36.249	11.560	13.591	58.907	10.000	6.021	.000	21.800
> 46 years	23.793	5.005	13.983	33.604	19.000	5.613	7.998	30.002
Overall	36.528	8.906	19.072	53.985	14.000	5.398	3.421	24.579
a. Estimation is limited to the largest survival time if it is censored.								

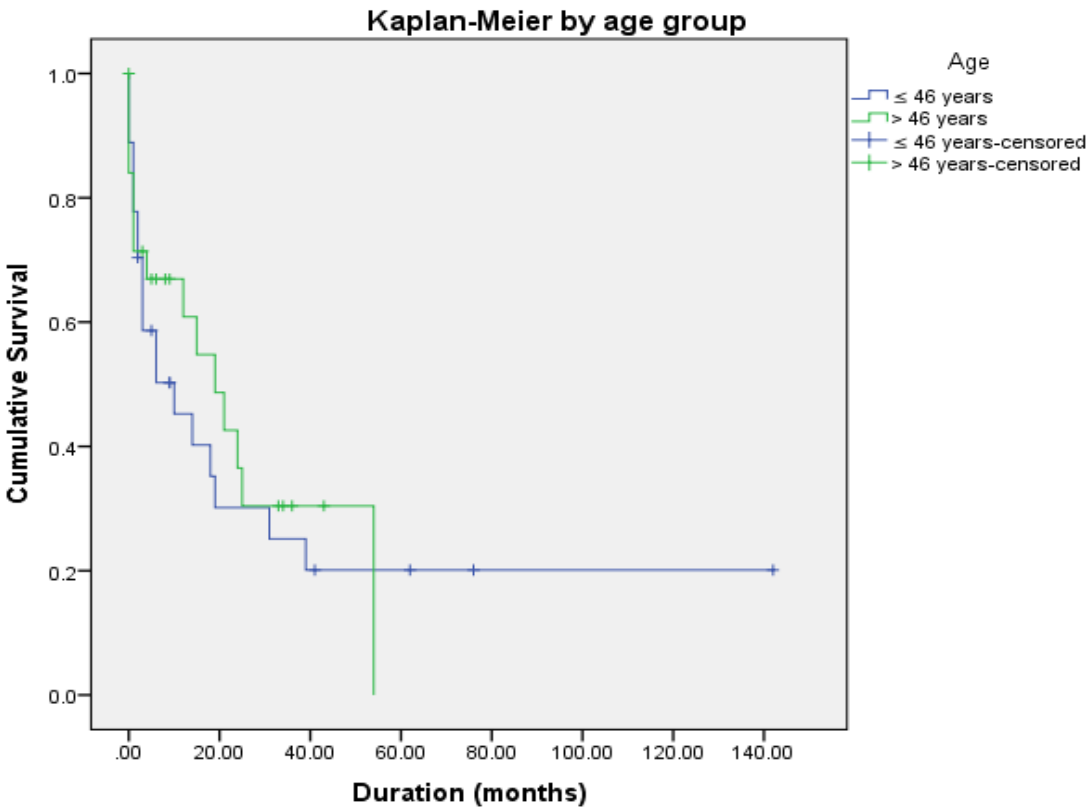


Figure 3.10 Kaplan Meier survival curve by age group

Patients were divided into two age groups based on the median age of 46 years. Figure 3.10 shows an overlap between the two curves showing that there was no significant difference in the survival probability of patients based on their age group.

Table 3.18: Means and Medians for Overall Survival by HIV Status

Means and Medians for Survival Time								
HIV	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Positive	61.782	21.132	20.364	103.200	39.000	24.535	.000	87.089
Negative	19.027	3.529	12.111	25.944	12.000	5.352	1.510	22.490
Overall	36.528	8.906	19.072	53.985	14.000	5.398	3.421	24.579

a. Estimation is limited to the largest survival time if it is censored.

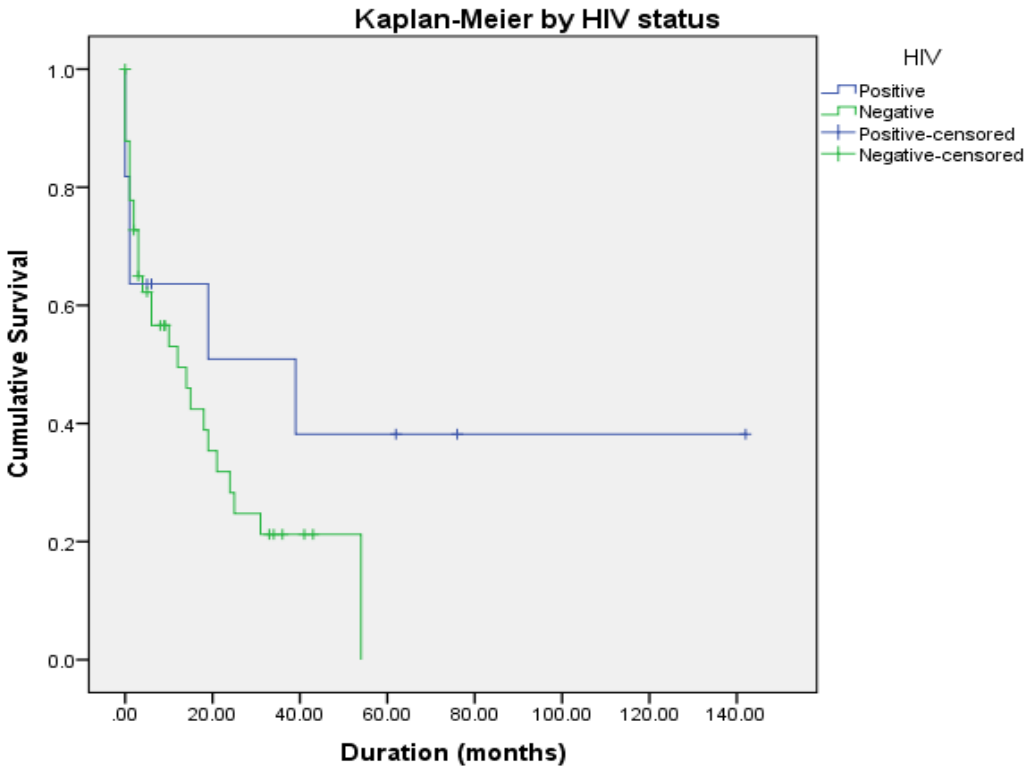


Figure 3.11 Kaplan Meier survival curve by HIV status

In Table 3.18 and Figure 3.11 it is clearly shown that HIV sero-negative lymphoma patients (median survival time= 12 months; 95% CI =1.510 – 22.490 months) had a lower probability of survival in comparison to HIV positive lymphoma patients (median survival time= 39 months; 95% CI = 0 – 87.089 months). However, the number of patients in the sero-positive group was small, making the results less meaningful.

Finally, survival curves were looked at in relation to cutaneous versus non-cutaneous (peripheral) T-cell lymphomas. Table 3.19 and Figure 3.12 show that lymphoma patients in the Peripheral T-cell lymphoma group (median survival time= 6 months; 95% CI =0 – 13.070 months) had a lower probability of survival in comparison to patients in the cutaneous group (median survival time= 39 months; 95% CI = 19.773 – 58.227 months). This is not unexpected, as the cutaneous lymphomas,

tend to run an indolent course. This is particularly true of the most common variety of cutaneous T-cell lymphoma, which is Mycosis Fungoides.

Table 3.19: Means and Medians for Overall Survival by patient group

Means and Medians for Survival Time								
Group	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Cutaneous	31.861	5.745	20.601	43.121	39.000	9.809	19.773	58.227
Peripheral	29.082	9.630	10.208	47.957	6.000	3.607	.000	13.070
Overall	36.528	8.906	19.072	53.985	14.000	5.398	3.421	24.579

a. Estimation is limited to the largest survival time if it is censored.

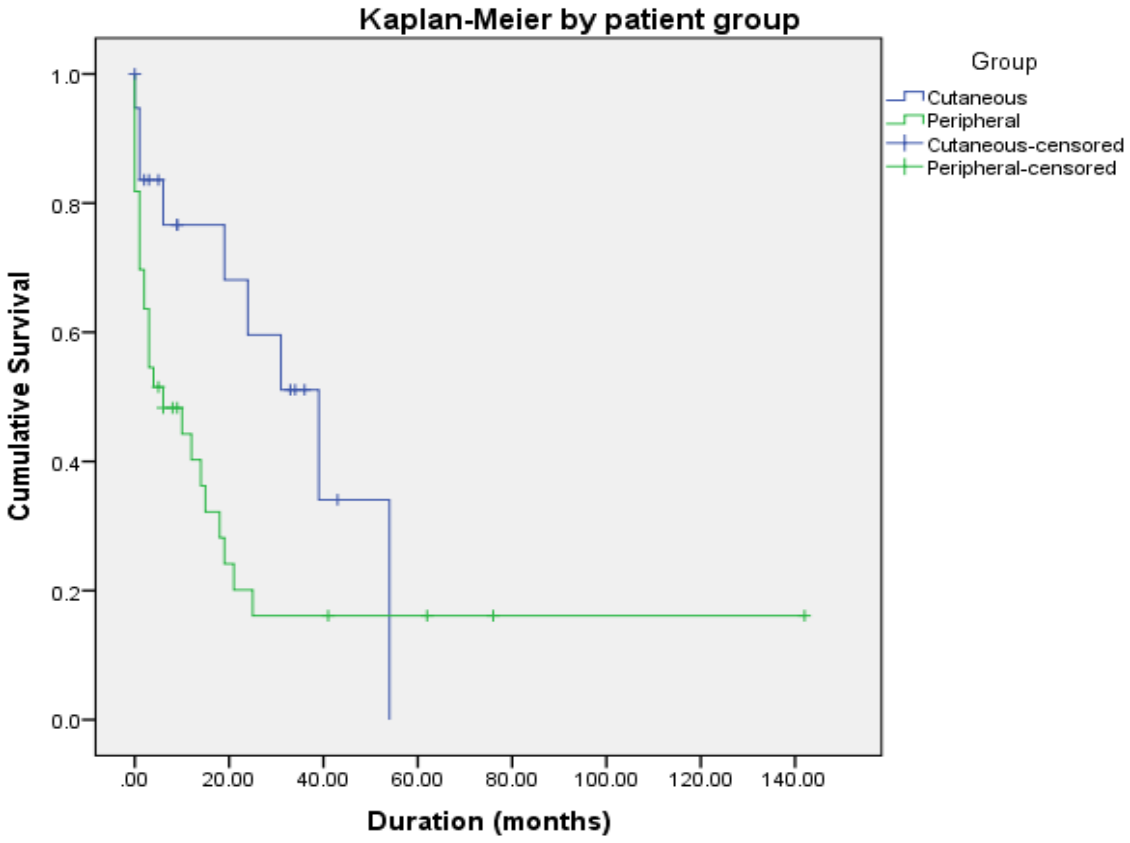


Figure 3.12 Kaplan Meier survival curve by patient group

4.0. CHAPTER FOUR: DISCUSSION

Non-Hodgkin lymphoma (NHL) is the most common haematological malignancy encountered in adults and constitutes a heterogeneous group of clonal neoplasms of B-cell, T-cell and natural killer (NK) cell origin (1, 2). Based on the recently updated World Health Organisation (WHO) classification, 5 major categories of mature lymphoid neoplasms are identified (1, 2). These include: Mature B-cell neoplasms, Mature T-cell and Natural Killer (NK)–cell neoplasms, Hodgkin Lymphoma (HL), Post transplantation lymphoproliferative disorders (PTLDS) and Histiocytic and dendritic cell neoplasms (1, 2).

Of the two main categories of lymphoma, Hodgkin Lymphoma (HL) constitutes approximately 20% of all lymphoid neoplasms, whereas Non-Hodgkin Lymphoma (NHL) comprises approximately 80% of all lymphoid neoplasms. Furthermore, of the NHL, 80-95% are of B-cell origin and 10-15% are of T-cell/Natural killer (NK-cell) derivation (1, 2, 3).

T-cell/NK-cell lymphoma is further classified into precursor types such as NK-cell/T-cell lymphoblastic lymphoma/leukaemia and peripheral or mature T-cell lymphoma. Where the T-cell/NK-cell lymphomas arise primarily from the lymph nodes, they are referred to as nodal or peripheral, whereas those that affect mainly the skin are referred to as cutaneous types (1, 4, 5).

The current study was performed in order to specifically review the entity of ‘peripheral or mature T-cell and NK-cell lymphomas’ and does not include the precursor T-cell lymphomas and B-cell lymphomas.

4.1. Patient demographics

A total of 67 newly diagnosed patients with T-cell and NK-cell lymphoid neoplasms were seen at the adult Clinical Haematology Unit, Department of Medicine, Chris Hani Baragwanath Academic

Hospital (CHBAH), during the period 01/01/2004 to 01/01/2015 (12 years). Of these patients, 52 were available for review in this study, while the other 15 patients were excluded, primarily because they had a diagnosis of a precursor T-cell/NK-cell disorder such as acute T-cell lymphoblastic leukaemia/lymphoma, rather than a peripheral or mature T-cell/NK-cell lymphoid neoplasm.

During the same 12 year period, a total of 862 patients were seen with newly diagnosed B-cell lymphoid neoplasms (lymphoma). This number excludes patients with chronic lymphocytic leukaemia, plasma cell disorders and conditions such as Castleman's disease. Based on these numbers, the T-cell and NK-cell lymphoid neoplasms constitute only 7.2% of the NHL patients, while the B-cell lymphoid neoplasms account for the vast majority of patients (92.8%) with NHL seen at CHBAH. The percentage of T-cell/NK-cell lymphoid neoplasms seen at CHBAH is lower than the generally quoted figure of 10-15% in the literature (50, 51). However, it is well recognized that there is a geographical variation in the incidence of these neoplasms, with the largest proportion of T-cell lymphoid neoplasms being reported from the Far East and the Asian Continent (50).

Of the 52 patients included in the study, ninety four percent were of black ethnicity, in keeping with the ethnic demographic encountered at CHBAH. There were 30 females (58%) and 22 males (42%), with a female to male ratio of 1.4:1. The median age was 46 years, with a range of 21-82 years. This is more marked in the peripheral T-cell lymphoma (PTCL) group (median age – 33 years), compared to the cutaneous T-cell lymphoma (CTCL) group (median age 33 years) (see Table 3.11). The lower median age at presentation and the female preponderance are different from that which is encountered in the literature (5, 6). A possible explanation regarding the younger age is that it may just be a reflection of the younger age structure of the population that we have in Africa (including South Africa), compared to other parts of the world. However, it is more difficult to explain the gender difference. HIV, which is more common in females, does not appear to have a significant impact on

the T-cell/NK-cell lymphoid neoplasms, as compared to the B-cell neoplasms (38). Furthermore, this impression is confirmed by the lower HIV sero-positivity rate in this study of 21.15%.

4.2. Clinical manifestations

Of the 52 patients seen in this study, cutaneous involvement (73%), was the most common clinical feature encountered. This was evident in 100% of the patients with the cutaneous T-cell lymphomas (CTCL), and 58% of the patients with the peripheral T-cell lymphomas (PTCL) (p=0.001). This is not unexpected, given the T-cell/NK-cell nature of the disease, which has a predilection for the skin, based on the higher percentage of T-cells encountered in the skin. Other clinical features seen were those that are regularly encountered in patients with lymphoma, including 'B' symptoms (65%), hepatomegaly (40%), bone marrow involvement (39%), lymphadenopathy (29%) and splenomegaly (27%) (see Table 3.9).

A favourable ECOG performance status (PS) of ≤ 2 was noted in the vast majority of patients in this study (86.5%), with 89% of the CTCL patients having a PS of 1 (p=0.03) (see Table 3.11).

Advanced stage disease (stage III/IV), based on the Ann-Arbor staging system was present in 50% of the patients with PTCL, while advanced stage disease using the TNMB classification was evident in 42% of patients with CTCL (see Table 3.13). This is similar to other studies in patients with PTCL (52).

4.3. Laboratory Results

Regarding the blood results, anaemia was present in 59% of the study population, while thrombocytopenia and leucopaenia were evident in 42% and 10% of the patients, respectively.

Elevated levels of beta-2 microglobulin, LDH, uric acid and calcium were noted in 100%, 97.5%, 42.1%, and 11% of the patients, respectively (see Table 3.12).

Of the 52 patients in the study, approximately two thirds had a PTCL (33/52 -63%), while approximately one third of the patients had a CTCL (19/52 – 37%). The histological subtypes of the PTCL and CTCL are shown in Table 3.10. The three most common subtypes of the PTCL's seen in the study were, i) PTCL,NOS (39%); ii) ALCL (24%) and ATLL (15%). Based on the findings of the International T cell Lymphoma Project, the most common varieties of PTCL were: PTCL, NOS (25.9%); AITL (18.5%); ALCL (12.1%); NK-TCL (10.4%) and ATLL (9.6%) (52). Compared to these findings, our patients had a higher percentage of PTCL, NOS, ALCL and ATLL, but much lower numbers of patients with AITL and NK-TCL. Regarding the CTCL's, MF was seen in approximately three quarters of the patients (79%), while Sezary syndrome was present in remainder of the patients (21%) (see Table 3.4).

4.4. Comorbid diseases

Comorbid diseases, including HIV and TB were also encountered in this study population. Forty percent of the patients in this study had comorbidities other than HIV and TB, such as hypertension, diabetes, epilepsy, schizophrenia, cardiac failure, pericardial effusion, thoracic myelopathy, mixed mitral valve disease, pulmonary hypertension etc. (see Table 3.4). These comorbidities were likely to be coincidental and not directly related to the T-cell/NK-cell lymphoid neoplasm.

4.5. HIV and Tuberculosis

HIV sero-positivity was noted in 11 patients (21%), while the remaining 41 patients (79%) were HIV sero-negative. The association is most likely coincidental. HIV sero-positivity was statistically more

significantly encountered in the PTCL group (10 patients), compared to the patients with CTCL (1 patient) (p=0.040). A comparison was made between the HIV sero-positive and HIV sero-negative group of PTCL patients (see Table 3.14). Due to small numbers, no definite conclusions were drawn, In the HIV sero-positive group, the median age was lower, there was a higher female to male ratio and TB was more commonly encountered, compared to the HIV sero-negative group. Strangely and unexpectedly, the outcome appears to be better in the HIV sero-positive group of patients compared to the HIV sero-negative group.

Tuberculosis was present in 17% of the patients in this study. TB was only seen in the PTCL group, where there was a higher proportion of patients with HIV. However, there is a high likelihood that in many of the patients, the association is coincidental, given the high prevalence rate of TB in the background general population.

4.6. Treatment

Treatment consisted of both supportive and specific therapy. In the PTCL group, combination chemotherapy was the mainstay of specific therapy. CHOP (cyclophosphamide, hydroxydaunorubicin/adriamycin, oncovin/vincristine, prednisone) was the most commonly used chemotherapy regimen.

With regard to the CTCL patients, skin directed therapies including PUVA (psoralens and ultraviolet light and Total Body Electron Beam Irradiation) formed the mainstay of treatment, where the disease was localized to the skin, while chemotherapy was used for patients with visceral involvement (more advanced disease) and those with Sezary syndrome. Overall, the response rates were statistically significantly better in patients with PTCL compared to CTCL (p=0.010) (see Table 3.13). The median overall survival for the study population was 14 months (see Figure 3.8). The median overall survival

was much better for patients with CTCL (39 months), compared to patients with PTCL (6 months) (see Figure 3.12). This is not unexpected, as the cutaneous lymphomas tend to run an indolent course. This is particularly true of the most common variety of cutaneous T-cell lymphoma, which is Mycosis Fungoides.

4.7. Study Limitations

Due to the retrospective nature of the study, there were a number of limitations. These include:

- Incomplete demographic and clinical data from patient files
- Incomplete and missing blood results, imaging and histology results in the patient files
- Poor compliance and lost to follow up of patients
- Incomplete documentation and information on treatment, follow up and response to treatment in some patient files

Lack of the above information does impact on accurate assessment of treatment response, disease-free survival and overall survival. Moreover, the documentation of short and long-term toxicities of treatment may not be adequately reflected.

5.0 CHAPTER FIVE: CONCLUSION

The T-cell/NK-cell lymphoid neoplasms account for only 7% of the lymphoid neoplasms seen in adults at CHBAH, as compared to the 10-15% quoted in the literature. At CHBAH, patients present at a younger age, with a female predominance. The majority of the patients with the mature/peripheral T-cell/NK-cell lymphoid neoplasms have a PTCL (63%), while the CTCL are present in 37% of the patients. The subtypes of PTCL are similar to that described in the literature, with a noticeable paucity of the AITL and NK-TCL subtypes. PTCL when compared to CTCL, are statistically significantly different in that they present with lesser patients with an ECOG PS of 1 and 2 (p=0.030), have more 'B' symptoms (94% vs 16%; p=0.00), less cutaneous involvement (58% vs 100%; p=0.01), more frequent hepatomegaly (52% vs 21%; p=0.042), a higher association with HIV (30% vs 5%; p=0.04), poorer response to treatment and a poorer outcome (lower median survival rate of 6 months, compared to 39 months).

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APPENDIX A: Normal blood parameters

BLOOD PARAMETERS	**NORMAL VALUES**
Hemoglobin (g/dl)	Females: 12-16 Males: 14-18
Platelets ($x10^9$/l)	150-400
White blood cells ($x10^9$/l)	4-11
Neutrophil count ($x10^9$/l)	2-7.5
Lymphocyte count ($x10^9$/l)	1-4
Albumin (g/l)	35-50
Globulin (g/l)	25-30
Total bilirubin (μmol/L)	0-21
Direct bilirubin(μmol/L)	0-6
Indirect bilirubin(μmol/L)	0-15
AST (IU/L)	5-40
ALT(IU/L)	5-40
Alkaline Phosphate(IU/L)	40-120
Lactate Dehydrogenase (IU/L)	100-200
Calcium (mmol/L)	2.05-2.56
Magnesium (mmol/L)	0.65-1.1
Uric Acid (mmol/L)	0.2-0.45 /0.15-0.35
Beta-2-microglobulin (mg/L)	0.7-1.8

APPENDIX B: Data collection sheet

DATA COLLECTION SHEET

Patient study number: _____

Area/Town/City/Country of birth: _____

Where living currently: _____

Occupation(s) past and present – list dominant occupations or environmental exposures, where applicable:

_____

_____

Age: _____

Gender: Male ❑ Female: ❑

Patient ethnic origin:

African ❑ Asian ❑ White ❑ Coloured ❑ Other ❑ Specify _____

ECOG performance status: 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑

Comorbid disease, (other than HIV or TB): Yes ❑ No ❑

If yes specify name and duration of disease: _____

_____

Family history of any disease: Yes ❑ No ❑

If yes specify: _____

History of TB: Yes ❑ No ❑

If yes, specify when was the diagnosis made? _____

How was TB diagnosed?_____

Start date and duration of treatment: _____

Regimen used: _____

HIV status- Positive=P Negative=N P ❑ N ❑ Unknown ❑

When was diagnosis made: _____

Was cART used? _____

If yes, date of initiation of treatment: _____

Drugs and doses (regimen/s used): _____

Clinical features: Pyrexia ❑ Pallor ❑ Petechiae❑ Jaundice ❑

Specify details of above: _____

_____

_____

_____

Other ❑ _____

Skin features on presentation: Patch ❑ Plaque ❑ Tumour❑ Erythroderma❑

Poikiloderma❑ Other ❑ Specify: _____

Specify order and duration of skin lesions: _____

_____

Lymphadenopathy at presentation: Yes ❑ No ❑

If yes specify site, size, symmetry and other relevant characteristics: _____

_____

Hepatomegaly: Yes ❑ No ❑

Splenomegaly: Yes ❑ No ❑

If yes, give details: _____

Blood investigations: (see Appendix B)

Skin biopsy findings: Site, histological sub-type, special stains (immunohistochemistry), conclusion:

_____

_____

_____

_____

FNA / Lymph node biopsy results: _____

_____

Radiological findings:

CXR _____

_____

Sonar _____

_____

CT scan _____

_____

PET scan _____

_____

MRI scan _____

_____

Bone marrow aspirate and trephine involvement: Yes ❑ No ❑

If yes, mention the findings: _____

_____

_____

Ann Arbor stage of lymphoma: _____

_____

Clinical staging of Mycosis Fungoides (MF):

1 A ❑ 2A ❑ 3 ❑ 4 A 1 ❑

1 B ❑ 2B ❑ 4 A 2 ❑

4 B ❑

Initial therapy:

Topical agents: _____

Topical steroids: Yes ❑ No ❑ Topical chemotherapeutics: Yes ❑ No ❑

Specify (duration and clinical response): _____

Phototherapy:

UVB: Yes ❑ No ❑ PUVA: Yes ❑ No ❑

Specify (duration and clinical response): _____

Radiotherapy:

Total skin electron beam irradiation (TSEB): Yes ❑ No ❑

Specify (duration and clinical response): _____

Adjunctive chemotherapy: Yes ❑ No ❑

If yes, date of first treatment _____

Date of completion of treatment _____

Number of cycles of chemotherapy given _____

Details of regimen _____

Response to initial treatment:

Complete response ❑ Partial response ❑ No response ❑

Any subsequent therapy _____

Complications:

Chemotherapy related _____

Radiotherapy related _____

Infection related _____

Other _____

Outcome:

Dead ❑ Alive ❑ Lost to follow-up ❑

Date of last observation: _____

What was the status of the lymphoma (in terms of response) at the date of last observation

_____

_____

Survival:

Overall survival _____ Disease free survival _____

_____

Any other relevant information: _____

APPENDIX C: Histology form

HISTOLOGY FORM

Date: _____ Specimen number: _____

Site of biopsy: _____

Findings:

1. **Morphology** (click all those that apply. Underline the dominant cell population)

Size of cells:	Small	☐	Intermediate	☐	Large	☐
Pattern of infiltration:	Focal/nodular	☐	Interstitial	☐	Diffuse	☐
'Starry-sky' appearance:	Yes	☐	No	☐		
Pautrier microabscesses	Yes	☐	No	☐		
Epidermotropism	Yes	☐	No	☐		

Any other pertinent/special findings: _____

_____

2. Markers

CD 20:	Positive:	☐	Negative:	☐	Not done	☐	B cell markers
CD 10:	Positive:	☐	Negative:	☐	Not done	☐	
CD 79a	Positive:	☐	Negative:	☐	Not done	☐	
CD 3:	Positive:	☐	Negative:	☐	Not done	☐	T cell markers
CD 4	Positive:	☐	Negative:	☐	Not done	☐	
CD 8	Positive:	☐	Negative:	☐	Not done	☐	
CD 2:	Positive:	☐	Negative:	☐	Not done	☐	
CD 5:	Positive:	☐	Negative:	☐	Not done	☐	
CD 7:	Positive:	☐	Negative:	☐	Not done	☐	HL,MCL,T cell
CD 30:	Positive:	☐	Negative:	☐	Not done	☐	
CD 15:	Positive:	☐	Negative:	☐	Not done	☐	

Other: _____

Ki-67:	Positive:		Negative:		Not done						
Ki-67 % positivity	<60%		60-80%		80-90%						
		>90%			>95%			100%			

3. Other changes

Granulomatous infiltration:	Yes		No	
Caseous necrosis:	Yes		No	
AFB were relevant:	Positive		Negative	
Any other changes of relevance:	Yes		No	

If yes provide details: _____

4. Results of FISH, PCR, Cytogenetics performed on the biopsy specimen. Please detail:

_____

_____

_____

5. Conclusion

_____

_____

_____

Pathological diagnosis

A.	Primary Cutaneous T cell lymphoma:	Yes	☐	No	☐
	i) Mycosis Fungoides	Yes	☐	No	☐
	ii) Sezary Syndrome	Yes	☐	No	☐
	iii) Other	Yes	☐	No	☐
B.	Peripheral T cell lymphoma, NOS:	Yes	☐	No	☐
C.	Anaplastic large cell lymphoma:	Yes	☐	No	☐
	i) ALK- Positive	Yes	☐	No	☐
	ii) ALK - Negative	Yes	☐	No	☐
	iii) Primary Cutaneous	Yes	☐	No	☐
D.	Other:	Yes	☐	No	☐

APPENDIX D: Revised response criteria for Malignant Lymphoma, 2007

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

APPENDIX E: Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr A Omar
School of Clinical Medicine
Department of Medicine
Division of Dermatology
Medical School

E-mail: drayeshaomar@gmail.com

CC: Supervisor: Professor M Patel <Moosa.Patel@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 29/10/2018

REF: *R14/49*

PROTOCOL NO: **M1809108** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Mature T-cell and N/K-cell neoplasms at Chris Hani Baragwanath Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

APPENDIX F: Ethics approval continued

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr A Omar

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1809108

NAME: (Principal Investigator)	Dr A Omar
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Dermatology Medical School University
PROJECT TITLE:	Mature T-cell and N/K-cell neoplasms at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Renewal of M131117
SUPERVISOR:	Professor M Patel
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore reports and re-certification will be due early in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX G: Turn-it in report

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Ttp://www.bbraun.com
Division of Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg
Chris Hani Road, Diepkloof, Soweto. Tel: +27 11 9339377, Fax: +27 11 9339449, email: moosa.patel@wits.ac.za

26 June 2019

The Chair

Postgraduate Studies Committee

Faculty of Health Sciences

University of the Witwatersrand

Re: Turn-it-in report: Dr Ayesha Omar – MMed: 'Mature T-cell and Natural Killer Cell Lymphoma at Chris Hani Baragwanath Academic Hospital (CHBAH0)'. Student number: 9800561T

As the supervisor, I have reviewed the Turn-it-in report of Dr Omar's MMed dissertation. The report identifies an overall similarity index of 3% and 10% with regard to publications. This is well within the acceptable limits of similarity. Much of this similarity relates to standardized factual information, including definitions and classifications. The other information which bears a similarity has been appropriately referenced.

Thank you

Yours sincerely



Moosa Patel MBChB, FCP(SA), MMed(Wits), FRCP(Lond.), PhD(Wits)

Professor and Head of Clinical Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital and the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa