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# Radiological comparison of tumour burden of lymphoma in HIV positive and HIV negative patients

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**AGA KHAN UNIVERSITY**

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# TITLE: RADIOLOGICAL COMPARISON OF TUMOUR BURDEN OF LYMPHOMA IN HIV POSITIVE AND HIV NEGATIVE PATIENTS

By

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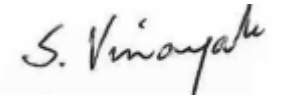

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# DEDICATION

To Gurmukh Singh Panesar for your invaluable encouragement and support throughout my journey, I dedicate this attestation of the inspiration you provide for me to always aim for the best

To my parents, the Kamaljit Singh Loyal, Narinderpal Kaur Loyal and Joginder Panesar and my brother Karanjit Singh Loyal for your support all through this journey. I dedicate this culmination of success and work to you.

## ABSTRACT

**Introduction:** Patients with Human Immunodeficiency Virus (HIV) are known to exhibit atypical pattern of lymphoma on imaging. There is paucity of literature on differences in tumour volume or burden of disease amongst HIV positive patients compared with HIV negative patients and how this correlates with clinicopathological parameters of aggressiveness and effects on prognosis.

**Objective**: The purpose of this study was to evaluate the tumour burden of non-Hodgkin's lymphoma in HIV positive patients compared with HIV negative and how this correlates with the clinicopathological parameters of aggressiveness and the overall clinical outcome.

**Methods:** This was a retrospective analytical cross-sectional study. All patients diagnosed with non-Hodgkin lymphoma from January 2011 to June 2021 were identified. These were then stratified into those with HIV and those without HIV and the tumour burden and site of disease on CT imaging calculated using the Lugano classification for lesion measurement. The international prognostic score, the histological type and Ki-67 index were recorded. Continuous variables were analyzed using the Kruskal Wallis test while the categorical variables were analyzed using the Fischer's Exact test. Logistic regression was performed to assess if HIV is independently associated with clinical outcome after controlling for extranodal disease.

**Results**: Out of the 92 patients with non-Hodgkin lymphoma, 47 were HIV positive while 45 were HIV negative with a median age of 45 years. The median sum of product diameters used to measure the tumour burden was 102.6 [51.7, 173.1] with no difference seen in the two groups. The extranodal disease was significantly higher in the HIV positive group (85.1%) while exclusive nodal disease was seen predominantly in the non-HIV group (66.7%) (p value <0.001). Although, there was no difference in the clinical IPI score and Ki-67 between the two groups, when comparing the IPI score with the volume of disease, the patients who had a higher burden of disease had poor prognosis and vice versa but this was only statistically significant for the non-HIV group (p value <0.001). Complete treatment response was higher in the non-HIV group 54.5% compared to 20.9% for the HIV group (p value <0.001). More HIV positive patients succumbed, 37.2% compared to the 4.5% for non-HIV patients (p value <0.001).

**Conclusion**: HIV related lymphoma remains a poorly understood subset of lymphoma. Imaging plays a critical role in staging of the HIV lymphoma. The significant imaging finding in HIV related lymphoma is presence of extranodal disease irrespective of the overall imaging burden. Furthermore, the clinical IPI score and Ki-67 which apply well for HIV-negative patients may not be apply for HIV related lymphoma.

**Recommendations**: We propose a separate clinical prognostication index for HIV related lymphoma that incorporates the stage of the disease and a higher weighting given to presence of extra nodal disease. Further studies are also needed to determine the initiation, type of HAART and the type of chemotherapy regimens and how this relates to occurrence and prognosis of HIV related lymphoma.

## LIST OF ABBREVIATION AND ACRONYMS

| | | |
|---|---|---|
| CODOX-M/IVAC | - | Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine |
| COO | - | Cells Of Origin |
| CT | - | Computed Tomography |
| ECOG | - | Eastern Cooperative Oncology Group |
| FDG | - | Fluorodeoxyglucose |
| HIV | - | Human Immuno-Deficiency Virus |
| IPI | - | International Prognostic Score |
| LDi | - | Long Axis Diameter |
| PET CT | - | Positron Emission Tomography – Computed Tomography |
| R-CHOP | - | Rituximab- cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone |
| SPD | - | Sum of Product Diameters |
| SDi | - | Short Axis Diameter |

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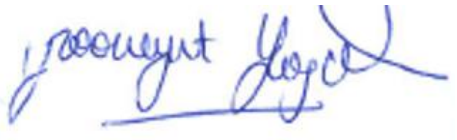
Thank you all

**DECLARATION**

*I declare this dissertation does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that to the best of my knowledge it does not contain any material previously published or written by another person except where due reference have been made in the text.*



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(Signature of candidate)

30th May, 2022

Date

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# CHAPTER 1: INTRODUCTION

## 1.1 BACKGROUND OF THE STUDY

Non-Hodgkin's lymphoma (NHL) accounts for approximately 3% of all cancers worldwide (2). Infection with human immunodeficiency virus (HIV) has been known to increase the risk of lymphoma by 5 to 15 fold (3). There are conflicting findings on the influence of HIV on the overall outcome of patients with lymphoma. Although, there are some studies showing no difference in the outcome of patients with lymphoma who have HIV compared to those who do not(4,5), others report an increase in the risk of cancer related deaths (6). This information is pertinent to Kenya where HIV prevalence rate is 4.7% with approximately 1.6 million people living with HIV, of which 69% of adults and 61% of children are on antiretroviral treatment (7). There are variable mortality outcomes for HIV related-lymphomas worldwide with wide ranges reported between 24.4 and 71.7% from the US and Europe(8). This could be due to differences in demographic or disease factors such as stage, antiretroviral use, access to healthcare and histological type (3).

### 1.1.1 Role of imaging in evaluation of lymphoma; Calculation of tumour burden, staging and evaluation of treatment response.

Imaging plays a critical role in the diagnosis, staging and evaluation of treatment response of lymphoma. Fluorodeoxyglucose positron emission tomography- computed tomography (FDG-PET CT) remains the gold standard but there is a provision for using CT where PET-CT is not available or for non-FDG avid tumours(9). Although there are several reports on the rare forms of lymphoma and the atypical imaging patterns of lymphoma in HIV which make imaging interpretation difficult(10), there is paucity of literature on disease burden of lymphoma in HIV patients and how this compares with HIV negative patients.

The tumour burden is the volume of tumour on imaging and for lymphoma definitive measurements are performed using the Lugano classification (11). The disease is first classified as measurable or non-measurable and further into nodal and extranodal. It is measurable if the long axis diameter is >1.5cm for nodal disease and >1.0cm for extra-nodal disease. Spleen is

defined as enlarged if it is >13cm. For measurable disease, up to 6 largest nodal/extra-nodal disease sites should be included which are representative of the different body regions/overall disease burden. Mediastinal and retroperitoneal disease should also be included if measurable. The tumour burden is measured in two dimensions i.e. the longest transverse diameter (LDi) and short axis diameter (SDi) and this is then summed up for all the measurable lesions giving a sum of product diameters (SPD)(9).

Most histological types of lymphoma are (18)F-fluorodeoxyglucose (FDG) avid and can be evaluated using PET-CT, with the exception of chronic lymphocytic leukaemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstorm's macroglobinemia, and marginal zone lymphomas. For lymphomas that are FDG avid, evaluation of tumour stage and response to treatment can be evaluated with PET/CT. Splenic involvement with PET-CT is defined as diffuse uptake, presence of a solitary mass, miliary lesions or nodules. In the liver, diffuse uptake, mass or nodules may be seen (9).

Staging of lymphoma is also clearly defined in the Lugano's classification according to the Modified Ann Arbor classification as follows: Stage I disease is defined as one node or group of adjacent nodes or single extra-nodal lesion without nodal involvement. Stage II disease is two or more nodal groups on the same side of the diaphragm or Stage I or II by nodal extent with limited, contiguous extra-nodal involvement. Stage III disease is defined as nodes on both sides of the diaphragm and nodes above the diaphragm with spleen involvement. Stage IV disease is additional non-contiguous extra-nodal involvement. In this staging, tonsils, Waldeyer's ring, and spleen are considered nodal tissue (11).

The treatment response of lymphoma can also be assessed with interim and end of treatment imaging by evaluating the tumour burden. If mid-therapy imaging is performed, then PET CT is superior to CT. Interpretation of an interim PET-CT scan requires careful consideration and a multidisciplinary approach to select the cases which merit a change in therapy based on interim PET result. Deauville criteria which is a 5-point scoring system is used in PET-CT imaging to evaluate 18-FDG uptake as follows: Score 1 is no uptake, Score 2 is defined as < mediastinal pool, Score 3 is defined as more than mediastinal pool but less than or equal to liver, score 4 is moderately > than liver at any site, score 5 is markedly >liver at any site and or/new sites of disease. Score x is new sites of disease that are unlikely to be lymphoma (9). The definitions for treatment response are grouped into complete response, partial response, stable disease,

and progressive disease as described in the Lugano classification(11) and also listed in the appendix 1.

As described in the Lugano classification, the treatment response depends on the tumour burden seen on imaging before and after treatment and is a way of quantitatively evaluating the response to treatment. It has been reported that the risk of relapse and death is also increased with a higher tumour burden on imaging (12,13). There is however no literature that has compared quantitatively the tumour burden on imaging between HIV positive and HIV negative patients. A previous study in a Kenyan population with lymphoma found that these patients had aggressive form of lymphoma that requires R-CHOP (Rituximab-cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone) regimen to achieve better prognosis (14). There is also dearth of literature on whether the response to treatment on imaging is different among HIV positive and HIV negative patients.

1.1.2. Clinical prognostication index

The clinical outcome of Non-Hodgkin's lymphoma is based on the International Prognostic Index (IPI). This score has several parameters which vary depending on the histological type of tumour. For diffuse large B cell lymphoma the parameters include age >60, elevated serum LDH, Stage III or IV disease, number of involved extra nodal sites >1, Eastern cooperative oncology group (ECOG) performance status. Based on the number of points scored by a patient, disease is classified as low risk, low-intermediate risk, high-intermediate risk and high risk which then helps in prognostication of patients, see summary in Figure below (15). There is however, little literature available as to how this may differ in patients who have HIV-related lymphoma and whether there is a correlate between the imaging burden of disease and the clinical predictor of outcome in patients with HIV compared to the non-HIV group.

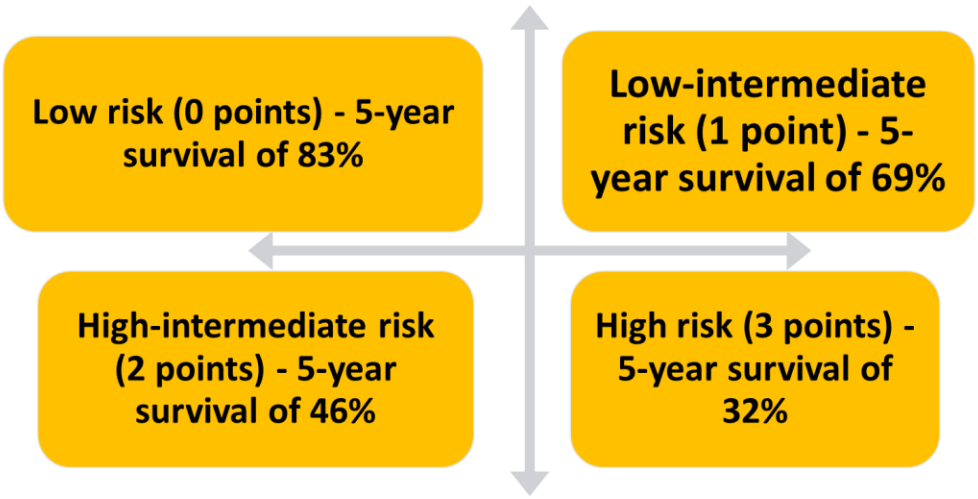


Figure 1: Clinical prognostication of Non-Hodgkin lymphoma.

It is not clear how HIV status integrates with the clinical prognostication index. Furthermore, there is paucity of information on how HIV status correlates with the tumour volume on imaging

1.1.3 Markers of histological aggressiveness

There are several studies done to establish histological parameters of aggressiveness of lymphoma including Ki-67 and others related to the molecular profiling including cells of origin (COO) and single hit versus double hit or triple hit. Ki-67 is a nuclear nonhistone protein, which is manufactured at the start of cellular proliferation and is expressed in all cell cycle phases except the G0 phase (1). It has thus been used in clinical practice as a marker to evaluate the proliferative activity of lymphoma. Its correlation with prognostication is contradictory and inconclusive with some studies showing no association or negative correlation (16). There is also little information on how Ki-67 correlates with the tumour burden on imaging and further investigation is necessary to clearly delineate the relationship between the two.

Regarding the cells of origin, there are three molecular subgroups being described including germinal centre B-cell type (GCB), activated B-cell (ABC) type, and the unclassifiable type (17). The GCB type DLBCL is known to have a better prognosis than the ABC-type (18,19). This affects treatment management especially in low resource settings where rituximab is not always available, and clinicians have to make do with conventional chemotherapy consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (CHOP) which translates to a poor prognosis with ABC and unclassified types. A study done in the local setting shows that DLBCL not only occurred in a younger subset of the population but that 59.4% had

the unfavorable non–GCB-cell type of DLCBL, highlighting a large group of patients who need rituximab added to their treatment (14). It is therefore pertinent to determine the COO in patients with DLBCL who may benefit from newer targeted therapeutic agents.

There is paucity of literature on correlation between the identified markers of tumour aggressiveness and the tumour volume on imaging as defined by the Lugano classification and how this differs between HIV positive and negative patients.

## 1.2 PROBLEM STATEMENT/JUSTIFICATION/SCIENTIFIC RATIONALE

The atypical disease pattern of lymphoma in HIV patients has been described qualitatively but there is paucity of literature on how HIV status affects tumour burden and prognosis. To the best of our knowledge, there is no publication comparing the tumour burden on imaging between HIV and non-HIV patients. The relationship between imaging findings in lymphoma and clinical predictors of outcome such as the Internal Prognostic Index; histological parameters such as the Ki-67; and virologic parameters such as the viral load/CD4 count in patients with HIV has also not been studied despite its implication on management and prognosis.

## 1.3 PURPOSE

- This study sought to evaluate the tumour burden of lymphoma in HIV positive patients compared with HIV negative patients.

## 1.4 RESEARCH QUESTION

Is there a difference in the tumour burden of lymphoma on imaging between HIV positive and HIV negative patients?

## 1.5 OBJECTIVES

### Primary objective

To compare the difference in tumour burden of lymphoma on imaging between HIV positive and HIV negative patients.

### Secondary objective

1. To evaluate for correlation between tumour burden on imaging with IPI score and histologically assessable disease aggressiveness.
2. To determine the association between tumour burden and response to treatment between the two arms.

## CHAPTER TWO: MATERIALS AND METHODS

### 2.1 STUDY DESIGN

This was a single centre retrospective cross-sectional analytical study conducted between January 2011 to June 2021. Data were obtained from retrospective review of patients' clinical records.

### 2.2 STUDY SETTING:

The study took place at the Aga Khan University Hospital, Nairobi a tertiary teaching and referral hospital in Kenya.

### 2.3 STUDY VARIABLES

The study variables were HIV status, imaging, and tumour factors as shown in Table 1. The age, LDH levels, CD 4 count, viral load, and tumour burden measured as sum of product diameters were continuous variables while the rest including nodal versus extranodal disease, histological aggressiveness, sex, HIV status and clinical outcome were categorical variables.

| HIV status related FACTORS | IMAGING FACTORS | TUMOUR FACTORS | PATIENT FACTORS | Clinical outcome |
|---|---|---|---|---|
| HIV status<br>CD4<br>Viral load | Tumour burden (sum of product diameters) on cross-sectional study on the initial imaging scan<br>Nodal versus Extra-nodal disease | LDH<br><br>Ki67, COO | Age of patient<br>Sex of patient<br>HIV status | Type of response |

Table 1: Study Variables

2.4 STUDY POPULATION:

Patients with lymphoma who had imaging performed at Aga Khan University Hospital Nairobi between 2011 to June 2021 were enrolled and divided into two groups based on their HIV status. This is because of ability to access images from Picture Archiving and Communication System (PACS) which was installed in 2011 in our radiology department. The inclusion and exclusion criteria are summarized in Table 2 below.

| **Inclusion Criteria** | **Exclusion criteria** |
|---|---|
| Imaging for lymphoma | Incomplete imaging or pathological records |
| HIV status is known | |
| Histopathology results are available | |

Table 2: Inclusion and Exclusion Criteria

2.5 STUDY PROCEDURES

Data was collected from records of patients diagnosed with lymphoma in Aga Khan University Hospital from January 2011 to June 2021 and met the inclusion criteria. The relevant clinical data, pathological data, and data following review of the imaging of study participants was obtained (Appendix 2). These data was entered into an Excel document and further analysis with SPSS (IBM statistics) version 20 software was done. The following steps summarize the data collection process (Figure 2):

1. A search was made in the medical records department of patients diagnosed with lymphoma during the study period. Only the patient identification numbers were collected. On CARE 2000, the HIV status of these patient was determined and only those whose status was known were enrolled.
2. Using the patient identification numbers another search was carried out in the Radiology department's PACS to identify patients who had imaging for staging purposes. The imaging burden of lymphoma was calculated using the Lugano classification system. It was also documented as to whether the patients had nodal versus extranodal disease. This was done on the initial pre-treatment scan either CT or PET/CT images. For patients who had a post treatment scan, the disease response was determined according to the Lugano classification as: complete response, partial response, stable disease, or progressive disease. Note was also made as to whether the patients were deceased or not.

3. Clinicopathological data were obtained from CARE 2000 (a health information system) and appropriate IPI index, histological type and marker of histological aggressiveness which included the Ki-67 or the COO status were recorded. The data included age, LDH level, tumour stage, ECOG score, number of extra nodal sites for non-Hodgkin's disease. This was then used to risk stratify the groups into high risk, medium risk and low risk group as was outlined in Table 2. For patients who were HIV positive, the viral load and CD4 count at the time of lymphoma diagnosis was also documented.
4. This data were then compiled and made available for analysis

The imaging tumour burden was measured using the Lugano classification and a sum of product diameters calculated for measurable data. The Ann harbor tumour stage was also evaluated for calculation of the prognostic index.

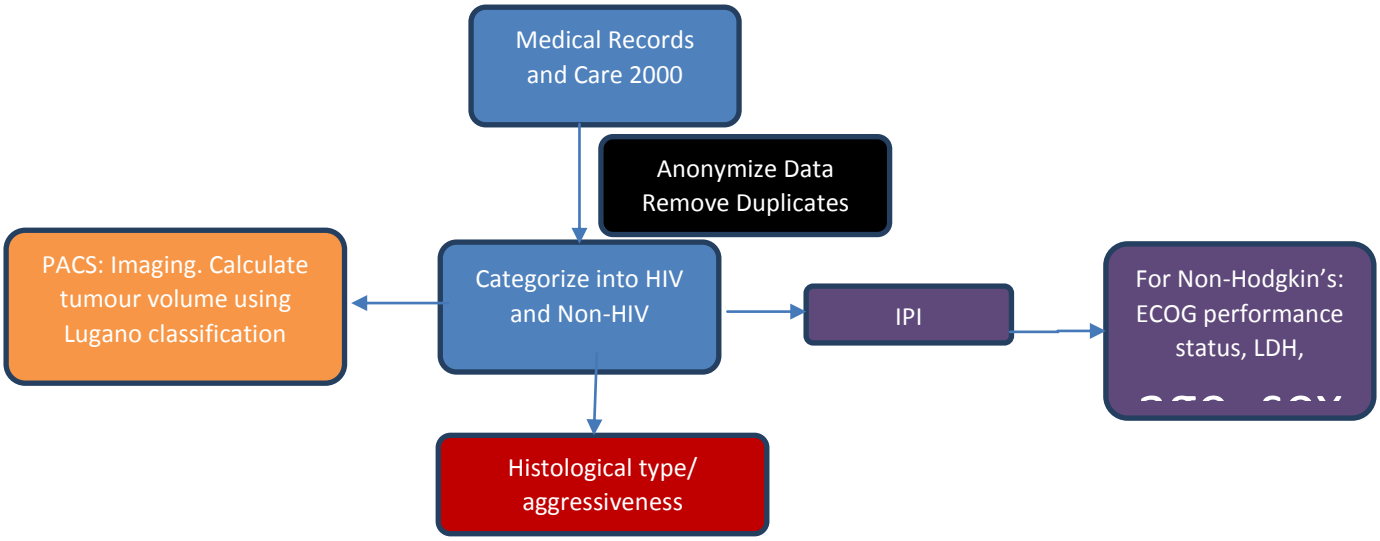


Figure 2: Data flow

## 2.6 SAMPLE SIZE ESTIMATION

The sample size was estimated using the equation for comparing the means for two groups (Figure 3):

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\mu_2 - \mu_1)^2}$$

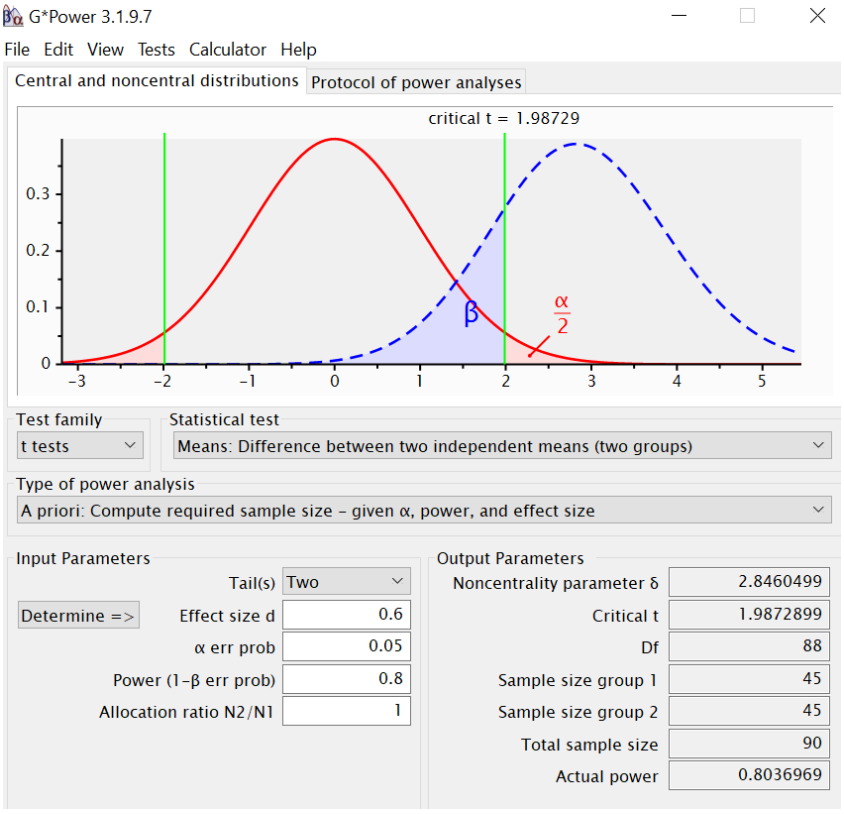


Figure 3: Sample size calculation tool

| Effect Size | Power | Sample size |
|---|---|---|
| **0.4** | **0.8** | **200 (100, 100)** |
| **0.5** | **0.8** | **128 (64/64)** |
| **0.6** | **0.95** | **148 (74/74)** |
| **0.6** | **0.90** | **120( 60/60)** |
| **0.6** | **0.8** | **90 (45/45)** |

Table 3: Sample size estimation

The G-power software version 3.1.9.7 was used (Figure 3). Due to paucity of data on the subject, a number of sample sizes for different powers were calculated and 90 (45 in each arm) was determined as the most appropriate sample size considering the financial and time constraints on this project (Table 3).

## 2.7 DATA MANAGEMENT

The data was collected and stored in a customized Microsoft Excel sheet which was kept on a password protected hard drive until the end of the study.

At the end of the study, once data analysis were completed, the data were handed over to the institution for archiving according to the Faculty of Health Sciences as per Section 4.1.6 (f) of the Faculty manual of research policies and procedures.

## 2.8 DATA ANALYSIS

Kruskal Wallis test was used to test for the differences in medians of the sum of product diameters for the tumour burden between the two groups. Correlation between the nodal and extranodal disease, IPI score, histological aggressiveness and clinical outcome for the HIV and non-HIV group was done using Fischer's Exact test. Logistic regression was performed to assess if HIV status is associated with the clinical outcome after controlling for extranodal disease. All statistical tests were based on a significance level cut-off of 0.05. Data analyses were conducted using IBM SPSS statistical software (Version 20).

## 2.9 ETHICAL CONSIDERATION

Application for waiver of consent was sought and granted from the Research and Ethics Committee at the Aga Khan University since the study was retrospective and there was no clinical intervention. It also did not have direct implication on ongoing patient management. Protocol approval number 2020/IERC-133(v1).

## CHAPTER 3: RESULTS

A total of 192 patients with Non-Hodgkin lymphoma were identified during the study period. A hundred patients were excluded due to lack of HIV status or lack of imaging studies in our PACS system. A total of 92 patients met the inclusion criteria and were included in the study.

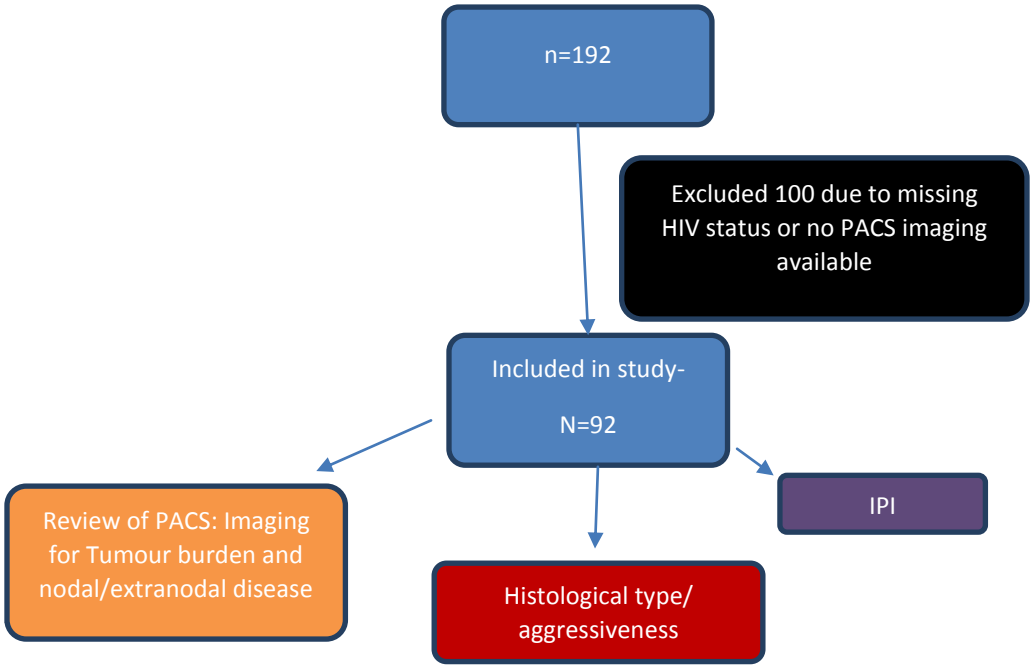


Figure 4: Patient flow diagram

### 3.1 BASELINE CHARACTERISTICS

Out of the 92 patients with non-Hodgkin lymphoma that were enrolled, 47 were HIV positive while 45 were HIV negative. The median age of patients was 45 years (interquartile range) with the median age for HIV patients being slightly lower compared to non-HIV patients which was 48 years but this was however not statistically significant. The majority were male patients comprising 69.6%. For the HIV positive patients, the median CD4 count was 147 [with interquartile range 67.0, 211.5] with a viral load of 19032.0 [interquartile range 34.0, 255193.0]. In terms of the ECOG status, the two groups were similar with majority (57.6%) having a good ECOG status of 0-2. Most patients (87%) presented with an elevated LDH status. The baseline characteristics are summarised in Table 4 below.

| Variables | | Total ( n = 92 ) | | HIV ( n = 47 ) | | Non-HIV ( n = 45 ) | | P Value |
|---|---|---|---|---|---|---|---|---|
| Age (Years) | | 45.0 | [36.5, 55.0] | 45.0 | [39.0, 53.0] | 48.0 | [32.0, 58.0] | 0.873 |
| Gender | Female | 28 | 30.4% | 10 | 21.3% | 18 | 40.0% | 0.070 |
| | Male | 64 | 69.6% | 37 | 78.7% | 27 | 60.0% | |
| ECOG | 0 to 2 | 53 | 57.6% | 27 | 57.4% | 26 | 57.8% | 1.000 |
| | 3 to 4 | 39 | 42.4% | 20 | 42.6% | 19 | 42.2% | |
| LDH | Elevated | 80 | 87.0% | 44 | 93.6% | 36 | 80.0% | 0.067 |
| | Normal | 12 | 13.0% | 3 | 6.4% | 9 | 20.0% | |

Table 4: Clinical characteristics of HIV versus Non-HIV patients with Lymphoma

3.2 IMAGING FINDINGS

As shown in the Table 5 below, the sum of product diameters which denotes the tumour burden was similar in the two groups. The median sum of product diameters was 102.6 [51.7, 173.1]. However, the extranodal disease was significantly higher in the HIV positive group (85.1%) while exclusive nodal disease was seen predominantly in the non-HIV group (66.7%).

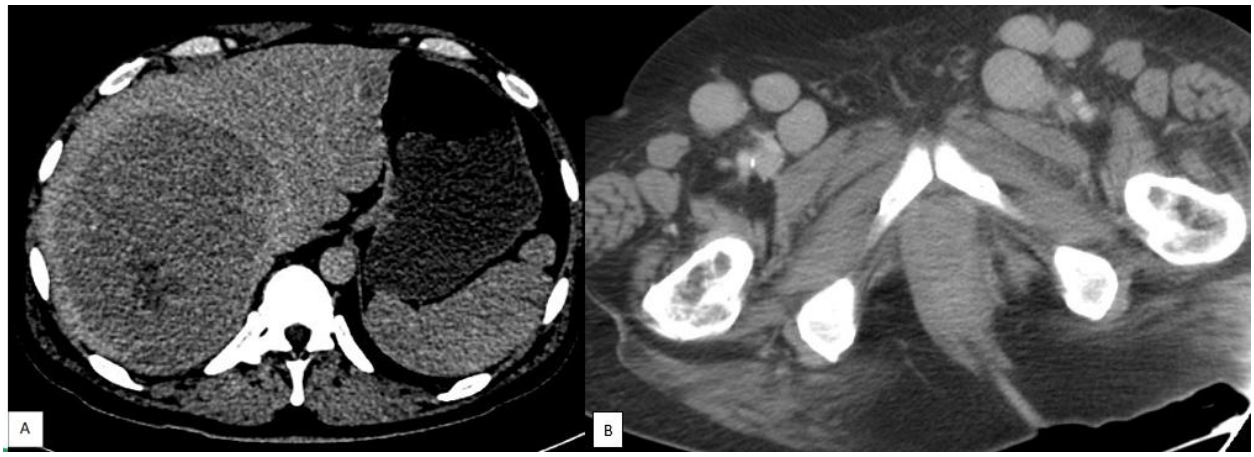


Figure 5 A, B: Disease on CT in HIV and Non-HIV. Figure 5A shows axial CT image of a HIV patient with extranodal disease in the liver while figure 5B is an axial CT image of a non-HIV patient with nodal disease in the bilateral inguinal regions.

Although not statistically significant, we observed a higher Ann Arbor stage of disease of lymphoma i.e. either stage III or IV in HIV positive patients (78.7%) compared to the HIV negative patients (66.7%).

| **Variables** | | **Total ( n = 92 )** | | **HIV ( n = 47 )** | | **Non-HIV ( n = 45 )** | **P Value** | |
|---|---|---|---|---|---|---|---|---|
| Product Diameters | | 102.6 | [51.7, 173.1] | 105.5 | [48.3, 202.4] | 100.8 | [64.8, 145.6] | 0.935 |
| Stage- | I-II | 25 | 27.2% | 10 | 21.3% | 15 | 33.3% | 0.244 |
| | III-IV | 67 | 72.8% | 37 | 78.7% | 30 | 66.7% | |
| Extranodal Stage IV | Yes | 55 | 59.8% | 40 | 85.1% | 15 | 33.3% | <0.001 |
| | No | 37 | 40.2% | 7 | 14.9% | 30 | 66.7% | |

Table 5: Imaging findings of HIV versus Non-HIV patients with Lymphoma

3.3 CLINICAL IPI SCORE

The clinical IPI score was classified into 4 categories including High and High intermediate which were grouped as High IPI score and low and low intermediate which were grouped as Low IPI score. There was no statistical difference in the IPI score between the HIV and non-HIV groups (see table 6). There was also no difference in the predicted 4 year survival rate between the two groups. However, when comparing the IPI score with the volume of disease (SPD), the patients who had a higher burden of disease had poor prognosis and vice versa but this was only statistically significant for the non-HIV group. Patients with a good prognosis had a mean tumour burden of 77.8 while those with poor prognosis had a mean tumour burden of 177.38 (Table 7).

| Clinic IPI | | Total ( n = 92 ) | | HIV ( n = 47 ) | | Non-HIV ( n = 45 ) | | P Value |
|---|---|---|---|---|---|---|---|---|
| IPI Score | 0 | 4 | 4.3% | 0 | 0.0% | 4 | 8.9% | 0.244 |
| | 1 | 13 | 14.1% | 5 | 10.6% | 8 | 17.8% | |
| | 2 | 27 | 29.3% | 17 | 36.2% | 10 | 22.2% | |
| | 3 | 25 | 27.2% | 13 | 27.7% | 12 | 26.7% | |
| | 4 | 18 | 19.6% | 10 | 21.3% | 8 | 17.8% | |
| | 5 | 5 | 5.4% | 2 | 4.3% | 3 | 6.7% | |
| Prognosis according to the R-IPI | Good | 45 | 48.9% | 23 | 48.9% | 22 | 48.9% | 0.133 |
| | Poor | 47 | 51.1% | 24 | 51.1% | 23 | 51.1% | |
| Predicted 4 year Progression Free Survival Rate | | 53.0 | [53.0, 80.0] | 53.0 | [53.0, 80.0] | 53.0 | [53.0, 80.0] | 0.687 |
| IPI Risk group prior to rituximab | High | 23 | 25.0% | 12 | 25.5% | 11 | 24.4% | 0.163 |
| | High-Intermediate | 24 | 26.1% | 12 | 25.5% | 12 | 26.7% | |
| | Low | 17 | 18.5% | 5 | 10.6% | 12 | 26.7% | |
| | Low-Intermediate | 28 | 30.4% | 18 | 38.3% | 10 | 22.2% | |
| Predicted 5 Year Survival Rate Prior to Rituximab | | 43.0 | [34.5, 51.0] | 43.0 | [26.0, 51.0] | 43.0 | [43.0, 73.0] | 0.474 |

Table 6: Comparing the clinical IPI score with HIV versus non-HIV patients

| | ***SPD(sum of product diameter)*** | | |
|---|---|---|---|
| | IPI | | |
| | Low | High | P value |
| ***NON HIV Patients-*** | 77.80 [65.89] | 177.38 [131.21] | <0.001 |
| ***HIV Patients*** | 103.19 [97.66] | 170.69 [142.24] | 0.070 |

Table 7: Comparing the SPD with the clinical IPI score between HIV and non-HIV patients.

3.4 HISTOLOGICAL AGGRESSIVENESS

The most common histological subtype of tumour was diffuse large B cell lymphoma in both groups, (85.1% for the HIV group and 71.1% for the non-HIV group). The other histological subtypes included Anaplastic large cell lymphoma, Burkitt's Lymphoma, T cell lymphoma. For a total of 72 patients, the histological aggressiveness was reported either in terms of the Ki-67 or the COO. Patients with a Ki-67 of 70% and above were categorized to have aggressive disease(1). Although not statistically significant, there were more patients with HIV (70.2%) had higher Ki-67 scores compared to the non-HIV patients (53.3%) as shown in the Table 9 below.

| | | **Total** | | **HIV** | | **Non-HIV** | | **P Value** |
|---|---|---|---|---|---|---|---|---|
| Subtype | DLBCL | 72 | 78.3% | 40 | 85.1% | 32 | 71.1% | 0.01 |
| | Others | 20 | 21.7% | 7 | 14.9% | 13 | 28.9% | |
| Ki-67 (n = 72) | High | 57 | 62.0% | 33 | 70.2% | 24 | 53.3% | 0.562 |
| | Low | 15 | 16.3% | 7 | 14.9% | 8 | 17.8% | |

Table 8: The subtype and histological aggressiveness of the lymphoma in the HIV versus non-HIV patients.

There was no association between the histological aggressiveness and the clinical IPI score in the two groups (Table 10).

| ***HIV Patients*** | | | | |
|---|---|---|---|---|
| | | Ki 67 | | |
| | | High | Low | P value |
| IPI | High | 19 (57.6%) | 2 (28.6%) | 0.226 |
| | Low | 14 (42.4%) | 5 (71.4%) | |

| ***NON HIV Patients*** | | | | |
|---|---|---|---|---|
| | | Ki 67 | | |
| | | High | Low | P value |
| IPI | High | 10 (41.7%) | 4 (50.0%) | 0.496 |
| | Low | 14 (58.3%) | 4 (50.0%) | |

Table 9: Histological aggressiveness and the clinical IPI score in the two groups

3.5 CLINICAL OUTCOME

Out of 92 patients, 87 patients had follow-up imaging. Complete treatment response was higher in the non-HIV group 54.5% compared to 20.9% for the HIV group. More HIV positive patients succumbed (37.2% compared to the 4.5% for non-HIV patients (Table 11). Out of the 16 patients that died in the HIV group, 11 had opportunistic infections at the time of death. Out of the two patients that succumbed in the non-HIV group, one succumbed due to cardiac arrest and the other patient succumbed due to an opportunistic infection.

| Clinical outcome (n = 87) | Total | | HIV | | Non-HIV | | P Value |
|---|---|---|---|---|---|---|---|
| | | | | | | | <0.001 |
| Complete Response | 33 | 37.9% | 9 | 20.9% | 24 | 54.5% | |
| Refractory disease | 36 | 41.5% | 18 | 41.9% | 18 | 40.9% | |
| Deceased | 18 | 20.7% | 16 | 37.2% | 2 | 4.5% | |

Table 10: The clinical outcome the HIV versus non-HIV patients

Logistic regression was performed and controlling for extranodal disease, the odds for having complete response was low for patients with HIV and the odd of patients dying were higher. The odds of HIV patients having extranodal disease was also high (Table 12).

| Dependent Variable = HIV Status | | | | |
|---|---|---|---|---|
| | Odd Ratio | 95% C.I.for EXP(B) | | P value |
| | | Lower | Upper | |
| Complete Response | 0.268 | 0.08 | 0.903 | 0.034 |
| Deceased | 7.141 | 1.162 | 43.882 | 0.034 |
| Extranodal (Yes) | 13.118 | 3.918 | 43.928 | <0.001 |

Table 11: Logistic regression

## CHAPTER 4: DISCUSSION

Patients with HIV are known to have an increased predisposition to developing lymphoma and lymphoma is the most common AIDS related cancer. At the onset of the HIV epidemic, there were reports of lymphoma being 100 times more prevalent in HIV patients, but this has since decreased since the advent of anti-retroviral drugs. However, the risk remains threefold higher compared to the non-HIV population (20).

The most common non-Hodgkin lymphomas reported in the HIV population group are B-cell lymphomas. Although, there was a limitation of selection bias, this is in tandem with the present study where 78.3% of the patients had DLBCL Other histological types observed in this study in the two groups were anaplastic large cell lymphomas, Burkitt's lymphoma, small cell lymphocytic lymphoma and T cell lymphoma. Contrary to previous literature where AIDS related lymphoma has been shown to be associated with the more aggressive histological subtypes, we observed no difference in the two subgroups. These results are similar to other studies that have shown black population not only present at a younger age, but may be associated with more aggressive disease with most patients having more symptomatic disease, more B symptoms and higher ECOG status >2 (21,22, 23). This may also explain why we found no difference between the tumour burden as measured by the sum of product diameters between the HIV and the non-HIV groups.

Extranodal disease was significantly higher in the HIV group compared to the non-HIV group. This is similar to previous reports by Nganga et al 2020 which demonstrated HIV patients present with atypical imaging patterns in the extranodal disease sites. Although, the exact mechanism of this is unknown, there are studies that have demonstrated HIV virus has transforming properties resulting in B- cell immortalisation, dysregulation

of *MYC*, and activation of EBV(24). Certain HIV gene products such as Tat have oncogenic properties and may interfere with cell cycle control by interaction with other regulatory proteins such as Rb2/p130 and plays a role in pathogenesis of HIV Burkitt lymphoma (25,26). Other indirect mechanisms for HIV oncogenesis which may also influence the subtype of HIV lymphoma include duration and degree of immunosuppression, induction of cytokines leading to B-cell proliferation, and opportunistic infections with oncogenic herpesviruses such as EBV and HHV8(27).

The clinical IPI score has been extensively validated for prognostication of patients with lymphoma. There was no statistically significant difference in the age at presentation of the two patient groups, with the median age in the HIV being 45 years while in non-HIV it is 48 years. This translates to a younger population being diagnosed with non-Hodgkin's lymphoma in the current population. These results are in similar to past studies done from the region which show an early age of onset of lymphoma in Africans compared to the West(28). The LDH levels were high in most of the patients which is in tandem with other studies that have found that genetic make-up and ethnic differences may explain why African Americans have a significantly lower age of onset, elevated LDH levels, and more B symptoms compared to the white population(21). Although Flowers et al. described most African Americans with lymphoma as having a higher ECOG status of >2 the ECOG status for most of the patients in the current study was between 0-2. This has led to questions whether the clinical IPI score needs to be revisited in the local setting. Furthermore, the utility of clinical IPI score in the setting of HIV remains questionable. There has also been work to develop new IPI scores for HIV related lymphoma, however these remains controversial. While there are studies that

have identified a number of prognostication factors including older age >60, advanced stage, low serum albumin and treatment with ART as relevant prognostic factors, these are few and a consensus is yet to be arrived(29,30). Barta et al suggested a separate IPI score for HIV patients which should include a HIV score including CD4 count, viral load and prior AIDs, number of sites of extranodal disease in addition to the parameters included in the original IPI score. This appears a plausible approach as we observed HIV patients with a greater burden of extranodal disease had a worse prognosis. Similar to prior studies, we did not find an association between the clinical IPI score and the histological aggressiveness(31). The Ki-67 index is also a subjective index and may not be the ideal marker of histological aggressiveness.

The median CD4 count was 147 [with interquartile range 67.0, 211.5] with a viral load of 19032.0 [interquartile range 34.0, 255193.0] which compared closely to a study by Bart et al where the median CD4 was 173 and viral load of 23,801(32).

The mortality rate in patients with HIV related lymphoma was higher compared to the Non-HIV group. Although, this study was not designed to ascertain the cause of mortality but it was observed that the patients had opportunistic infections at the time of death. This differs from previous study, the main cause of death was progressive or relapsed disease(32). This may be due to the patients in the current study having poorly controlled HIV infection with a median CD4 count of 147 with a viral load of 19032.0. Although, there is paucity of literature in this field, there are a few studies that have observed a similar trend with some recommending incorporating the stage of HIV into prognostication(29). A study by Spin et al 2004, found the 3-year overall survival was 37% among patients with HIV-NHL and 74% among HIV-negative patients with NHL(23). This has therefore led to recommendation of optimization of the HIV disease

prior to chemotherapy regimen initiation with some advocating for cotrimoxazole prophylaxis for all patients irrespective of their CD4 count(33). The latter is done in the current setting as part of the National Guidelines for management of HIV. The cut-off for institution of immunoprophylaxis has not yet been established but there are studies which have recommended prophylaxis for patients with low CD4 counts and patients with profound neutropenia(30).

In view of the poor prognosis in patients with HIV related lymphoma, studies have suggested modifying the chemotherapy regimen in this subgroup with some advocating for cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) with addition of rituximab rather than the conventional R-CHOP(34). Although larger studies are neededto validate such regimens in the current setting, the preliminary findings from the present study does not support this since the leading cause of mortality was opportunistic infections rather than progressive or recurrent disease.

# CHAPTER 5: CONCLUSION

HIV related lymphoma remains a poorly understood subset of lymphoma and imaging plays a critical role in staging of the disease. Although there was no difference in tumor burden between HIV positive and HIV negative patients, the significant imaging finding in HIV related lymphoma was presence of extra-nodal disease irrespective of the overall imaging burden. Furthermore, the clinical IPI score and histological markers of aggressiveness which apply well for HIV-negative patients may not apply for HIV related lymphoma.

## CHAPTER 6: RECOMMENDATIONS

We propose a separate clinical prognostication index for HIV related lymphoma that incorporates the stage of the disease and a higher weighting given to presence of extra nodal disease. Further studies are also needed to determine the initiation, type of HAART and the type of chemotherapy regimens and how this relates to occurrence and prognosis of HIV related lymphoma.

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# APPENDICES

## APPENDIX 1: DEFINITION OF TREATMENT RESPONSE AS PER LUGANO CLASSIFICATION

*Complete response/complete metabolic response*

On CT imaging, disease response to treatment can be classified as complete radiological response which is target nodes or nodal masses regressed to < or = 15mm in the long axis, extrandodal lesions have disappeared, no residual non-target disease, no new lesions or disease due to lymphoma and spleen is normal sized. On PET-CT, this is termed as complete metabolic response and is defined as Deauville score 1, 2 or 3 in nodal or extranodal sites with or without a residual response.

*Partial remission/Partial response/partial metabolic response*

Partial response is defined as: for multiple lesions, > or = 50% decrease in SPD of up to six target measurable nodes and extranodal sites. For a single lesion is > or =50% decrease in the PPD. Partial metabolic response on PET CT is score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size.

*Stable disease*

On CT, <50% decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites with no criteria for progressive disease are met. PET-CT this appears as no metabolic response with score of 4 or 5 with no obvious change in FDG uptake. No metabolic response on PET CT is defined as Score of 4 or 5 with no obvious change in FDG uptake.

*Progressive disease*

This may be based on a single dominant lesion; progressive disease is assigned with at least one of the following:

1. New or increased adenopathy; an individual node must be abnormal with: (a) LDi > 1.5 cm and (b) PPD increase by > 50% from nadir and (c) LDi or SDi increase from nadir; the increase in LDi or SDi from nadir (the smallest recorded measurement) must be >0.5 cm for lesions < or = 2 cm and > 1.0 cm for lesions > 2 cm.

2. Splenic volume increase: (a) With prior splenomegaly: increase in length by > 50% of its prior increase beyond baseline; for example, splenic length increases from 15 cm (2 cm above baseline splenomegaly of 13 cm) to >16 cm (>3 cm above baseline) (b) Without prior splenomegaly: length increase by at least 2 cm (c) New or recurrent splenomegaly

3. New or larger non-measured lesions

4. Recurrent previously resolved lesions

5. New extra nodal lesion > 1 cm in any axis (new lesions > 1 cm in any axis are included if these are "unequivocally attributable" to lymphoma).

6. A new node > 1.5 cm in any axis

On PET-CT progressive disease is defined as score 4 or 5 in any lesion with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma.

**APPENDIX 2: DATA COLLECTION TOOL**

| ***DATA ITEM*** | ***DATA ENTY*** |
|---|---|
| ***PATIENT INDENTIFICATION*** | |
| ***PATIENT AGE/SEX*** | |
| ***HIV STATUS*** | If positive: CD4:<br>Viral load: |
| ***MEASURABLE DISEASE: NODAL + EXTRA NODAL*** | **PD1+PD2+PD3+PD4+PD5+PD6** |
| ***SUM OF PRODDUCT DIAMETERS*** | |
| ***HISTOLOGIC SUBTYPE:***<br>*Non-Hodgkin (Diffuse Large B cell lymphoma, Peripheral T cell lymphoma, Burkitt's Lymphoma, Follicular lymphoma* | |

| | |
|---|---|
| *etc.)*<br><br>*Hodgkin's lymphoma* | |
| ***IPI score*** | Low risk, Intermediate risk, High Risk |
| ***TREATMENT OUTCOME*** | Complete response, Partial response, Stable disease, Progressive disease. |