

**CLINICAL PROFILE AND HISTOLOGICAL CHARACTERISTICS OF HEAD AND  
NECK LYMPHOMAS IN PATIENTS SEEN AT TWO REFERRAL CENTRES IN  
NAIROBI, KENYA**

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## DECLARATION

This is my original work and has not been presented for a degree or any award in any other institution to the best of my knowledge. I have acknowledged and properly referenced other people's work in this study as requirements of the University of Nairobi.

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## **DEDICATION**

This work is dedicated to my wife, Zethu, my two children (Simamukele & Basanda) who allowed me to pursue this course. They released me to further my studies in a far country & endured the inconvenience during my absence.

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## **ABBREVIATIONS**

ABC: Activated B cell – like DLBCL

AIDS: Acquired Immunity deficiency syndrome

ADC: AIDS defining cancers

BL: Burkitt's lymphoma

CNLS: Central nervous system lymphomas

CT scan: computed tomography scan

DLBCL: Diffuse large B cell Lymphoma

DNA: Deoxyribonucleic acid

EBV: Epstein Barr Virus

FNA: Fine needle Aspirate

G1/S phase: Gap1/ synthesis interphase

GCB: Germinal centre B

H&E: Haematoxylin & Eosin stain

HBV: Hepatitis B virus

HCV: Hepatitis C virus

H. pylori: Helicobacter pylori

HIV: Human Immunity Deficiency Virus

HHV8: Human herpes virus 8

HL Hodgkin's lymphoma

IgH: immunoglobulin H

IHC: Immunohistochemistry

IQR: interquartile range

KNH: Kenyatta National Hospital

KNH-UON ERC: Kenyatta National Hospital and University of Nairobi Research

Ethics Committee

KS: Kaposi sarcoma

MALT: Mucosa-Associated lymphoid tissue

MCL: Mantle cell lymphoma

MRI: Magnetic Resonance Imaging

NADC: None AIDS defining cancers

NF- $\kappa$ B pathway: Nuclear factor- kappa B pathway

NHL: Non-Hodgkin's lymphoma

RS cells: Reed Sternberg cells

SD: standard deviation

SLL: Small lymphocytic lymphoma

SPSS: Statistical Package for Social Sciences

UoN: University of Nairobi

UNDH: University of Nairobi Dental Hospital

US: Ultrasound

WHO: World Health Organization

## **ABSTRACT**

### **Background**

Head and neck malignancies continue to be a challenge to patients due to the associated morbidity and mortality. The most common malignancies in the head and neck are squamous cell carcinomas, lymphomas and others. Lymphomas are lymphoproliferative neoplasms which are classified as Hodgkin's and Non-Hodgkin. They may either be nodal or extra nodal lymphomas. Extra nodal lymphomas are mainly the NHL and account for 5% all head and neck neoplasms. They may present with painless swellings which may be non-ulcerated. In addition these lesions may invade the local structures resulting in obstruction of oral and nasal passages. The common presenting complaints include facial asymmetry, dysphagia, dysphonia, nasal obstruction, blindness, proptosis and epiphora amongst others. This study was to determine the common types of head and neck lymphomas, their location, clinical and histopathological characteristics, and compare these with studies done elsewhere

**Objective:** To describe the clinical characteristics and histological types of lymphomas manifesting in the head and neck among patients presenting for treatment at Kenyatta National Referral and Teaching Hospital (KNH) and University of Nairobi Dental Hospital (UNDH).

**Materials and methods:** This study was a retrospective, cross-sectional descriptive study carried out on patients with lymphomas of the head and neck. It was conducted at KNH and UNDH registry with data from patient records between January 2010 and May 2019, duration of 8 years and 5 months. The patient files with histopathology and immunohistochemistry or both were included in the study. A pre-designed data collection tool (Appendix 1) was used to record patient information obtained from the records. The data was then coded and entered into the statistical package for social sciences (SPSS) software version 25 for analysis. The study was approved by KNH/UON- ERC on 02 October 2018 with study number P432/06/2018.

**Results:** A total of 82 patients with head and neck lymphomas presented in the two centres and met the inclusion criteria. The age distribution ranged between 3 and 77 years with mean age of 26.5 (SD =19), while the median age was 18.5 years. There were 57 (69.5%) males and 25 (30.5%) females with male to female ratio of 2.3: 1. 52% of the lymphomas were seen in the first and second decades. Out of the 82 patients, a total of sixty patients knew their HIV status with 51 being negative and nine being positive. There ratio of HL to NHL was

1.4:1. Classic HL was prevalent in both the paediatric and adult populations. BL were more prevalent NHL in children whilst DLBCL was more common in adults and tended to increase with age. HIV infection and types of lymphomas showed statistical significant difference of  $p= 0.033$ .

Head and neck lymphomas were located on the neck, mandible, maxilla, Waldeyer's ring, nose 3.7%) and orbit. The mean duration of head and neck lymphomas at presentation was 12.5 (SD= 16.4) months and median of 6 months. The clinical signs and symptoms were painless swelling, teeth mobility, dysphagia, dysphonia blindness, proptosis, epiphora, nasal obstruction and discharge. The B symptoms reported in this study were weight loss, fever and drenching night sweats.

### **Conclusion**

1. The head and neck lymphomas showed male predominance in both children and adults.
2. Head and neck lymphomas showed a wide range of clinical presentation which includes painless rapidly expanding swellings with no ulceration and B symptoms.
3. There were more HL compared to NHL in this study.
4. BL in children and DLBCL in adults were the commonest NHL.
5. There was low uptake of immunohistochemistry (IHC) for diagnosis of lymphomas which has negative impact on treatment and prognosis of disease.
6. The outcome of this study compares well with studies done elsewhere in the world

### **Recommendations**

1. The use of immunohistochemistry as definite diagnosis lymphoma typing is imperative to improve treatment outcomes.
2. Larger sample size studies to interrogate HIV trends and types of lymphomas may be necessary.
3. Introduction of synoptic reporting for lymphomas to capture full biological details for cancer registries.

**Limitations:** The study was retrospective and information was source from patient records of which some vital information may have been missing, such as lymphomas size at presentation, HIV status, imaging reports to enhance lymphoma staging.

# CHAPTER 1: INTRODUCTION

## 1.1 Background

Head and neck neoplasms continue to be a challenge as they cause morbidity and mortality to affected patients. The morbidity associated with these neoplasms include impaired mastication, breathing, swallowing, phonation, hearing and aesthetic problems. The most prevalent head and neck neoplasms are squamous cell carcinomas (90-95%), lymphomas (5-10%) and others (5%). Lymphomas manifesting in the head and neck are diagnosed mainly from histopathology/ immunohistochemistry as they have similar clinical signs and symptoms to squamous cell carcinoma. They are either primary or metastatic neoplasm. They arise from lymphoid tissues in the lymph nodes or in extra-nodal sites such as gastro intestinal tract, chest, head and neck. Lymphomas of the head and neck are classified as Hodgkin (HL) and Non Hodgkin lymphomas (NHL) <sup>1,2</sup>.

Lymphomas of the head and neck presents as cervical lymphadenopathy, painless rapidly expanding swellings in the oropharyngeal region, nose/ paranasal sinuses, orbit and ears. These swellings may be ulcerated, associated with pain, bleed or cause obstruction. Most of these neoplasms are located in the oropharyngeal region (Waldeyer's ring) especially in the adult population <sup>3,4,5</sup>. The NHL types are common and account for about 30% of head and neck neoplasms and tend to increase with age <sup>6</sup>. Lymphomas are the third most common neoplasm globally and occur in both sexes with a male to female ratio of 1.4:1, and mean age of 59.54 years<sup>7,8</sup>. The prevalence of NHL tends to increase with age and may be associated with immune suppression <sup>2,4</sup>. HL tends to occur comparatively in younger patients than adults and has bimodal age distribution with first peak in third and fourth decades, and the second peak in those above 50 years of age<sup>1</sup>. Head and neck lymphomas account for approximately 10-15% of paediatric neoplasms in developed countries with Diffuse Large B cell lymphoma being the most common type <sup>9,10</sup>. In the Sub Saharan Africa, the most common types are Burkitt's (endemic type) and Diffuse Large B cell (DLBCL), Natural Killer T (NK/T) cell lymphomas. These lesions tend to exhibit an aggressive nature and are highly associated with immunosuppression such as HIV infection <sup>11,12</sup>.

Burkitt's lymphomas (BL) are common paediatric neoplasms which exhibit aggressive behaviour affecting the oral cavity and surrounding tissues and tend to be associated with HIV infection especially in Sub-Saharan Africa <sup>11</sup>. In contrast, DLBCL are the most common types of lymphomas in other parts of the world and are commonly associated with the Epstein Barr virus infection (EBV). These lymphomas may present as rapidly growing masses which may invade the jaws resulting in tooth mobility <sup>13</sup>.

The treatment of lymphomas includes chemotherapy, radiation therapy, immunotherapy, radio immunotherapy depending on the histological subtypes. Chemotherapy is the main mode of treatment for lymphomas. Modern therapeutic regimens are able to offer fairly good prognoses and satisfactory responses to treatment. The use of stem cell transplantation and surgical interventions may be viable options in the management of recurrent or large lesions <sup>5, 10</sup>.

Studies on the pattern of lymphomas in the head and neck region have been predominantly in developed countries and have shown wide geographic variations in clinical presentation. The studies done in Sub-Saharan Africa were on head malignancies or isolated lymphomas such as BL. An audit done at the University of Nairobi for oral diseases estimates that the prevalence of head and neck lymphomas constitutes 6.05% of all the head and neck neoplasms at a Kenyan site <sup>14</sup>. The study, however, did not give elaborate details of clinical presentation, location, characteristics and histological types of these lymphomas. Butt, et al reported NHL (13%) and BL (3%) to have been the common head and neck lymphomas in HIV infected patients <sup>12</sup>.

Thus, this study will focus on profiling the common head and neck lymphomas based on clinical features and histologic types in two facilities in Nairobi, Kenya.

## **1.2 LITERATURE REVIEW**

### ***1.2.1 Introduction***

Lymphomas are a spectrum of malignant lymphoid-proliferative disorders which may affect various parts of the body. They are classified as nodal or extranodal forms and may present as primary or metastatic lesions with about 5% of them manifesting in the head and neck<sup>1, 2, 7, 15, 16</sup>. Primary extranodal lymphomas arise in tissues other than lymph nodes, spleen or bone marrow. Examples of these include gastro-intestinal tracts, head neck and chest. The head and neck is the second most frequently afflicted extra-nodal site after gastro-intestinal site<sup>1, 2, 3</sup>. Lymphomas are classified according to their histomorphology as HL or NHL, the latter being the most common<sup>1, 2</sup>. HL tends to occur in younger populations compared to NHL which increase with age<sup>2</sup>.

### ***1.2.2. Epidemiology***

Lymphomas are the third most common neoplasm globally and occur in both sexes with a male to female ratio at 1.4:1 and a mean age of 59.54 years<sup>7, 8</sup>. However, Picard et al reported a median age of 68 years in French population<sup>17</sup>. Chi et al reported an incidence of male to female ratio of 1.32: 1 in Taiwanese population<sup>18</sup>. Walter et al and others noted that there was an increasing incidence of NHL especially in the developed countries that may be attributed to the increase in life expectancy<sup>2, 4, 6</sup>. Studies done by Tamwine, et al and Huh reported the incidence of HL to be lower than that of NHL and a tendency to decrease with age<sup>19, 20</sup>. HL has bimodal age distribution with first peak in third and fourth decades, and the second peak above 50 years of age<sup>1, 19</sup>. Lloyd and McHugh reported that lymphomas manifesting in the head and neck accounted for 10-15% of paediatric neoplasms in developed countries<sup>9</sup>. Extra-nodal HL has an incidence of 2—4 cases/100 000 people annually and is more common in the younger age groups<sup>1</sup>. Lymphomas formed part studies on of the head and neck neoplasms in Kenya<sup>12, 14</sup>.

### ***1.2.3 Lymphomagenesis***

The etiology of lymphomas is largely unknown but believed to be an interplay between genetic susceptibility and environmental factors. The genetic susceptibility may be due to DNA modification occurring as somatic hyper-mutation or class switch recombination which results from gene mutations, deletions or insertions and translocations<sup>21, 22, 23</sup>. Some



environmental factors which have been implicated in lymphomagenesis include chemotherapy drugs such as azathioprine and cyclosporine as well as irradiation. Infections associated with lymphomagenesis may be viral such as the EBV, HIV, human herpes virus 8 (HHV8), hepatitis B (HBV), hepatitis C (HCV) and Simian virus 40 (SV40). Bacterial infections include: *Mycobacterium tuberculosis*, *Helicobacter pylori* and *Chlamydia psittaci*. Fungal and protozoal infections are mostly seen in the late stages of some cases. Other contributing factors to lymphomagenesis include acquired or congenital immune deficiencies. Acquired immune deficiencies include post-transplant patients on immunosuppressant and HIV infection and AIDS. Congenital immune suppression may be seen in conditions like Klinefelter's syndrome, Ataxia-telangiectasia and Chediak-Higashi syndrome. Autoimmune disorders associated with lymphomagenesis are Rheumatoid arthritis, coeliac disease, Systemic lupus erythematosus and Sjogren's syndrome<sup>10, 13, 15, 17, 18</sup>. Corti et al. (2014) and Opie (2012) observed that HIV infection increases the risk of NHL up to 200 times more than in the immune competent population<sup>20, 21</sup>.

Lymphomagenesis is more common in the B cell lineage and occurs at different stages of cell differentiation. Most lymphomas arise in the germinal centre of secondary lymphoid tissues such as lymph nodes, spleen or tonsils. These B cells are rapidly dividing and as such are prone to somatic hyper-mutation and cross-switch recombination of their genes which increase the chromosomal rearrangements, resulting in genetic modifications<sup>22</sup>. Most of these genetic modifications may be eliminated by tumour suppressor genes and apoptosis in normal cell cycle. The presence of environmental factors such as ionizing radiation, EBV, HIV, Sjogren's syndrome, amongst others has been shown to magnify the DNA aberrations thus inducing selective growth advantage of the malignant clone whilst suppressing apoptosis. Genetic aberrations target genes with essential functions such as MYC, BCL2 and BCL6 resulting in translocations associated with dysregulation of the expression of oncogenes that control cell proliferation, survival and differentiation. Lymphomagenesis may also be caused by irregular activity of the NF- $\kappa$ B signal pathway which controls expression of genes expressed in survival, growth, stress response, inflammation, and apoptosis<sup>22, 23, 24, 25</sup>.

#### ***1.2.4 HIV/AIDS defining cancers***

These are spectrum of human immune system deficiencies which exposes the individual to life threatening opportunistic infections, neurologic disorders and unusual malignancies. People living with HIV infection and AIDS tend to have lower CD4+ T cells which are

important immune cells, thus become prone to malignancies. These HIV infections and AIDS associated malignancies are classified as either AIDS defining (ADC) or non AIDS defining cancers (NADC). The ADCs are strongly associated with Kaposi sarcoma, high grade NHL mainly BL and DLBCL, Central Nervous System (CNS) lymphomas and cervical squamous cell carcinoma. The aggressive types NHL such BL and DLBCL tends to be associated with HIV infections. The NADCs are HL, head and neck carcinomas, anal, prostate, hepatocellular carcinomas and gastric adenocarcinomas<sup>24, 25, 26, 27</sup>.

A number of theories have been postulated in the pathogenesis of these carcinomas namely the immune suppression which exposes the body to viral, bacterial and fungal infections. Most head and neck cancers are associated with HHV-8 (KS) and EBV (BL, DLBCL, primary CNS lymphomas). HIV infection may cause persistent antigenic stimulation which results in lymphomagenesis in the presence of other viruses and bacteria. The burst theory states that there is elevation of pro-inflammatory cytokines such as interleukins 6, 10, 12, 13, vascular endothelial growth factors, Kaposi sarcoma growth factors amongst others. These cytokines promote carcinogenic cell activation, proliferation and survival<sup>24, 25, 26</sup>.

### ***1.2.5 Classification and histological features of lymphomas***

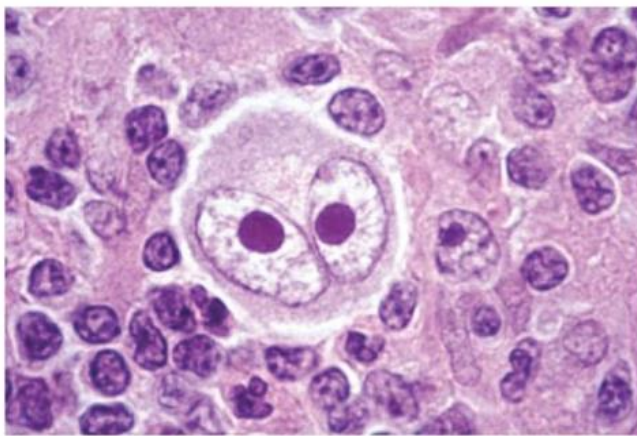
There are several classifications of lymphomas in literature and the updated 2016 WHO classification of haematological malignancies was adapted for this study (Appendix 2)<sup>28</sup>. Lymphomas are classified as HL and NHL types based on histological appearance. The HL account for about 10% whilst NHL are more abundant accounting for up to 90% of lymphomas<sup>2</sup>. Examples of NHL arising from B cell populations include mantle cell (from naïve B cells), follicular, nodal marginal zone, and extra- nodal marginal zone lymphoma of mucosa associated lymphoid tissues (MALT), DLBCL and BL<sup>24, 25</sup>.

#### ***1.2.5.1 Hodgkin's lymphoma***

HL arise from B lymphocyte cells and have characteristic RS cells with three variants, namely classic RS, lacunar cell (Fig. 2) and popcorn cell<sup>5</sup>. They are classified as either classic or Nodular lymphocyte predominant types with similar lymphomagenesis. Classical HL has the following subtypes; nodular sclerosis, lymphocyte- rich, mixed cellularity and lymphocyte depleted HL<sup>5, 19, 28, 30, 31</sup>. The nodular lymphocyte predominant subtype accounts for 5% of all HL. Lymphomagenesis of HL is an interplay between genetic and

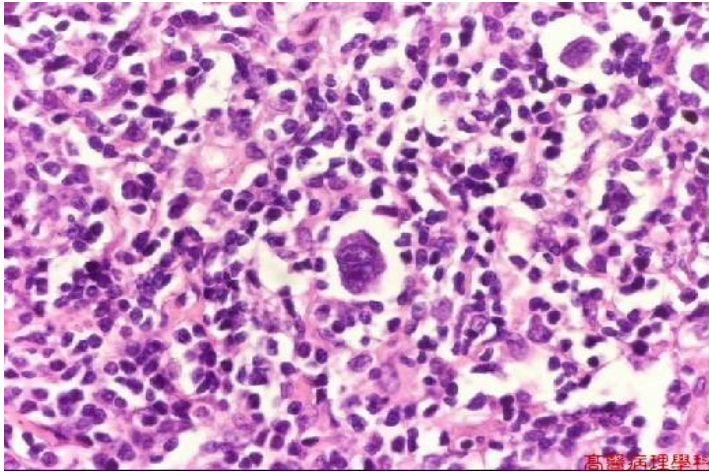
environmental factors giving rise to characteristic Reed Sternberg (RS) cells (Fig. 1) which are mature clonal B cells that have lost their mature B phenotype<sup>6, 23</sup>. These RS cells are large neoplastic cells found in an inflammatory background in H and E stains. These cells have escaped from apoptosis and have undergone transcriptional reprogramming thus developing survival mechanisms through the dysregulation of several signal pathways that control cell cycle. NOTCH and NF-κB signal pathways being the common ones which promote proliferation and protect cells from apoptosis<sup>5, 21, 23</sup>. HL are predominantly intra-nodal, commonly found in lymph nodes and spleen, may disseminate to the liver and other sites<sup>1</sup>. The classic HL are positive for CD15, CD30 and negative for CD20<sup>31, 32, 33</sup>.

- A. The classic variants have a moderate number of RS cells with a mixed cellularity background of infiltrates such as eosinophils, plasma cells, lymphocytes and atypical mononuclear cells (Fig. 1). They have an abundant finely granular or homogenous cytoplasm. This variant is common in the mixed cellularity type of HL<sup>9</sup>. The mixed cellularity variants have a moderate number of RS cells in mixed background infiltrate<sup>18, 19</sup>.



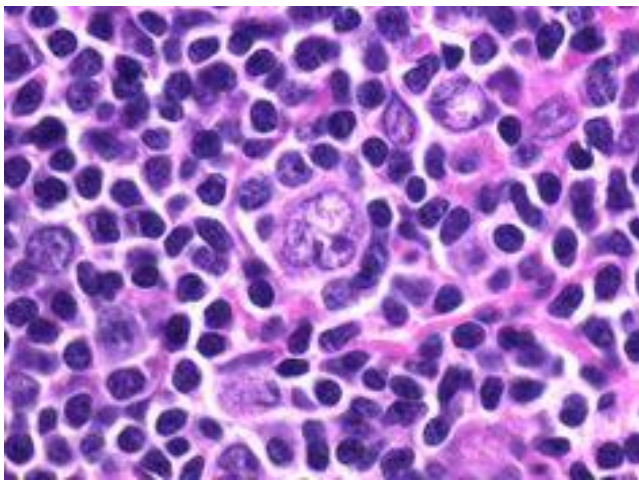
**Figure 1 Reed-Sternberg cell has large binucleated or multinucleated clear nuclei resembling owl eyes with an eosinophilic nucleoli surrounded by a thick nuclear membrane. It also has abundant finely granular or homogenous cytoplasm<sup>34</sup>.**

- B. The lacunar RS cell variant has large single multi lobulated nucleus with multiple small nucleoli surrounded by small lymphocytes. This eosinophilic cytoplasm is retracted around the nucleus creating an empty space known as lacunar and is surrounded by dense fibrous tissue. They are found in classic nodular sclerosis type of HL<sup>19, 27</sup>.



**Figure 2** *Lacunar cells in a mixed inflammatory background* ([www.pthology-home.com](http://www.pthology-home.com)).

C. The popcorn RS cell variant has few RS cells and many B cells with fine sclerosis (Fig. 3). The small cells have a lobulated nucleus with small nucleolus in a lymphocyte rich background, an example of the classic lymphocyte- rich type of HL. The nodular lymphocyte predominant HL has predominantly lymphocytic cells with or without RS cells and inflammatory cells in their background. They are positive for CD20 and B cell antigens but negative for CD15 and DC30<sup>32</sup>.



**Figure 3** *Nodular lymphocyte-predominant HL with a large multi-lobulated, folded nucleus surrounded by small lymphocytes* ([www.webpathology.com](http://www.webpathology.com), 2017).

D. The classic lymphocyte –depleted type has numerous RS cells and extensive fibrosis in a background of eosinophils, lymphocytes and macrophages. It is the most aggressive type of HL<sup>5,23</sup>.

### ***1.2.5.2 Non-Hodgkin's lymphomas***

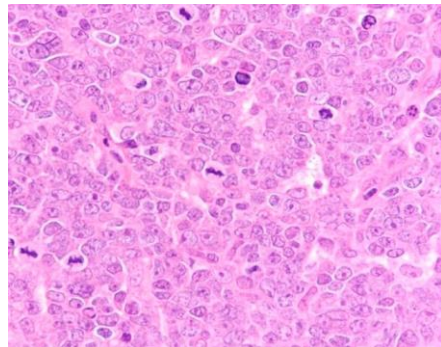
NHL can be classified as the aggressive and non-aggressive (indolent) subtypes and are of B (85—90%) and T lymphocytes or Natural Killer (10—15%) cell origin<sup>5, 6, 35</sup>. The WHO (2016) classification of NHL are based on mature B cell neoplasms which includes diffuse large B cell, follicular, mantle cell, Burkitt's lymphomas which are considered highly aggressive. The mature T & Natural Killer neoplasms are systemic lymphomas such as T cell lymphoma of childhood, extranodal NK/T cell lymphomas (nasal type), adult cell and peripheral T cell lymphomas<sup>28</sup>. The most common aggressive subtypes are DLBCL, BL, NK/T and peripheral T cell lymphomas<sup>17, 35</sup>. Indolent forms include marginal zone, follicular, low grade B cell, lymphocytic lymphoma and MALT B cell lymphomas. The immunohistochemical markers for NHL are CD3, CD5, CD10, CD20, CD23, CD30, CD38, CD79a, CD138, Bcl-2, Bcl-6, IRTA-1, MUM1/IRF4, Bcl-1/cyclin D1, TdT, ALKc and Ki-67/Mib1<sup>32</sup>.

**1.2.5.2.1 The DLBCL** are heterogeneous group of lymphoid malignancies and the most common NHL. They highly aggressive type of NHL linked to EBV, HIV infection and autoimmune conditions such as Rheumatoid arthritis and systemic lupus erythematosus<sup>29</sup>.

They occur at all ages with a mean of 60 years and a male predominance<sup>17</sup>. They are the 4<sup>th</sup> most common paediatric malignancy<sup>29</sup>. DLBCL account for about 20-30% of NHL in Western countries and have three variants, namely the germinal centre B (GCB), activated B cell like (ABC), and primary mediastinal large B-cell lymphoma arising from thymus<sup>35, 36, 37</sup>. The GCB subtype arises from the centroblasts in the germinal centre whilst the ABC one arises from the plasmablasts in post germinal centre. Both subtypes are associated with BCL2 translocation, t (14:18) juxtaposing the BCL2 gene and immunoglobulin H locus thereby causing dysregulation of the anti-apoptotic BCL2 protein. They are positive for CD10, CD20, CD30, CD79a, CD138 and MUM1/IRF4<sup>11, 22, 29, 38</sup>.

DLBCL are predominantly composed of three morphological variants, namely centroblastic, immunoblastic and anaplastic. They present as a diffuse proliferation of large B cell lymphoid cells with large oval, irregular or lobulated nuclei. Prominent nucleoli and abundant clear cytoplasm are also seen. They may also show diffuse proliferation of sheets of intermediate to large sized B lymphocytes, high mitotic figures and abundant apoptotic debris without a conspicuous starry-sky pattern (Fig. 4)<sup>39, 40</sup>. The plasmacytoid differentiated cells

are seen in some cases. The centroblastic variant shows vesicular chromatin and membrane bound nucleoli, with multi-lobulated centroblasts. The immunoblastic variant shows round prominent central nucleoli <sup>17,40</sup>.



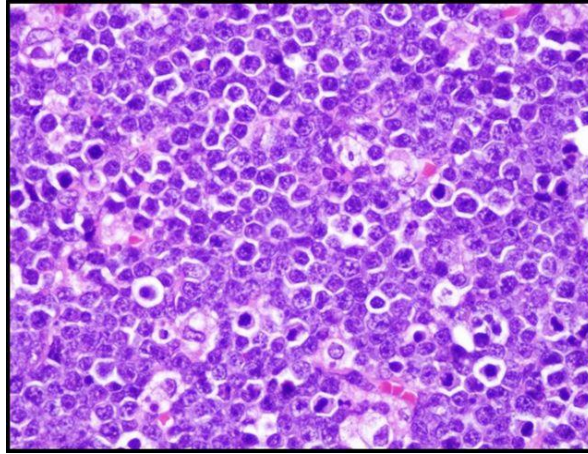
**Figure 4 Diffuse large B cell lymphoma: immunoblastic variant. The cells are round with prominent central nucleoli (www.webpathology.com, 2017)**

**1.2.5.2.2 Burkitt's lymphomas** are highly aggressive and account for 50% of NHL and are considered to be more common paediatrics than adults. They have peak age between 4 and 7 years with a male to female ratio of 2:1 <sup>41,42,44</sup>. BL are highly associated with EBV and HIV infection in their lymphomagenesis <sup>11, 43</sup>. They arise within the germinal centre or post germinal centre B cells, mainly from centroblasts. These are mature B cell lymphomas that exhibit extremely high proliferation characteristics and are mainly the extranodal forms. Lymphomagenesis involves t (8; 14) (q24; q32) translocation with subsequent c-myc rearrangement and overexpression. *MYC*-*IGH* translocation is the most frequent aberration involving the *MYC* gene. Other translocations involving *BCL2* and *BCL6* have been implicated in the etiology of BL. This dysregulation results in increased genomic instability with a subsequent increase in DNA replication, uncontrolled cell proliferation, escapes from immune surveillance and down-regulation of apoptosis <sup>4,45</sup>. Three clinical variants have been observed namely endemic which are common in the African children and in malaria endemic zones, the sporadic (worldwide distribution) and immunodeficiency associated types. EBV infection tends to play a vital role in their lymphomagenesis by inhibiting apoptosis, thus contributing to the development and maintenance of these lymphomas. Immunohistochemistry shows positivity for CD20, CD10 and CD 79a <sup>44</sup>.

Histologically, BL are characterized by monotonously uniform or slightly pleomorphic medium sized neoplastic cells with round nuclei and multiple basophilic paracentric nucleoli. The cytoplasm is moderately abundant and highly basophilic with multiple vacuoles seen in



Giemsa or Haematoxylin and Eosin (H and E) stains. They have a high mitotic index. The small non-cleaved cells intermixed with many tangible bodies of macrophages and apoptotic debris seen as the “starry sky” pattern. The lymphoma cells are blastoid with many cytoplasmic vacuoles <sup>46</sup>.



**Figure 5: BL: "starry sky" pattern (www.webpathology.com, 2017)**

**1.2.4.2.3 Mantle cell lymphomas (MCL)** are mature B cell neoplasms which exhibit an aggressive behaviour and account for 4 to 10% of all lymphomas <sup>47</sup>. They are more prevalent in males than in females with an average age of 60 years. They arise from naïve, pre-germinal centre B cells and are characterized by t (11; 14) (q13; q32) translocation where cyclin D1 is juxtaposed to IGH resulting in dysregulation and overexpression of cyclin D1. Cyclin D1 drives lymphoma cells through G1/S phase of cell cycle control, disrupts DNA response pathways and active cell survival mechanisms <sup>11, 13, 36</sup>. The MCL has two variants namely; the classic and blastoid. The blastoid variant is more common in middle aged and older people. They may be presented as medium to large sized lymphoblastic-like or pleomorphic cells with scant cytoplasm. They have slightly irregular dark nuclei which are seen under a light microscope and are associated with a high mitotic index. They are positive for CD5, CD20, CD19 and CD43 <sup>44, 47, 49</sup>.

**1.2.5.2.4 Extranodal Marginal zone B cell lymphoma** arise from mature B cells in lymphoid tissues and are related to mucosa associated lymphoid tissues (MALT) exhibiting a slow growing indolent pattern. They are more frequently found in the seventh decade, with an average age of 60 years but less frequent in the middle aged and rarely in children. They exhibit t (11; 18) translocation <sup>13, 50</sup>. The chronic antigenic stimulation such as chronic

inflammation (*H. pylori*) or autoimmune disorders, usually initiates and promotes progression to genetic instability leading to chromosomal abnormalities resulting in lymphomas. The ocular adnexia type is associated with *Chlamydia psittaci*<sup>13, 15, 33</sup>. The marginal zone B cell shows multiple growth patterns under low power, namely the diffuse inter-follicular and nodular patterns of infiltration patterns. The diffuse patterns of lymphoid epithelial cells are predominantly small to medium sized cell types on H and E staining under light microscope. The small cells (lymphocytic or centrocytic) appear as diffuse or vaguely nodular infiltrates with round to indented nuclei with a fine chromatin structure and scant distinct rims of clear cytoplasm<sup>13, 50, 51</sup>. Under high power, the marginal zone B cell lymphoma may present with a heterogeneous morphology varying from centrocyte, monocytoid, plasmacytoid and plasma cells with varying numbers of interspersed centroblasts and immunoblasts. The centrocyte-like cells has a slightly irregular nuclear membrane and coarse chromatin structure. The monocytoid cells have a central nucleus with condensed chromatin and an indistinct nucleoli surrounded by an abundant cytoplasm. The extra-nodal marginal B cell lymphoma shows a markedly increased monocytoid cells<sup>50</sup>.

**1.2.5.2.5 Follicular lymphomas (FL)** are derived from the germinal centre of the B cell lineage, mainly from centrocytes and are seen in the older population with an average of 60 years. They are basically indolent malignancies. They are characterized by chromosomal translocations that dysregulate the expression of BCL2. The t (14; 18) (q32; q21) translocation juxtaposes the BCL2 gene and the IgH locus. Increase in BCL2 expression results in resistance to apoptosis and in addition they also express MYC translocation<sup>11, 36, 33, 52, 53</sup>. Histologically, they appear as monomorphous small cells (centrocytes) of crowded follicles in the indolent types. The aggressive types shows an increased proportion of large cells (centroblasts) which diffusely infiltrate lymph nodes and lead to the effacement of the follicular architecture. Malignant follicles show a diffuse architecture of variable number of centrocytes and centroblasts which exhibit a starry-sky pattern. They may also show immature chromatin and frequently increased mitotic activities. Immunohistochemistry shows positivity for CD19, CD20 and CD79a<sup>49, 53</sup>.

**1.2.5.2.6 Extranodal NK/T cell lymphomas (polymorphic reticulosis or lethal midline granuloma)** are aggressive malignancies of the NK and cytotoxic T lymphocyte cell lineages. These are destructive neoplasms which affect midline structures such as the nose with a



median age of 50 years. They are common in Asians (52%) and Latin Americans (3%), and uncommon in Western countries including North America and Europe (0.3%). They are considered to be locally invasive malignancies that affect adults and rarely children, with a male predilection<sup>3,45</sup>. Their lymphomagenesis is due to deletion of chromosome 6q21 and is highly associated with EBV infection<sup>45, 54, 55</sup>. Histologically, they present as a mixture of normal appearing small lymphocytes and a variable number of small and large atypical lymphoid, plasma cells, eosinophils and histiocytes. Neoplastic cells have distinct rims of clear cytoplasm and exhibit angio-centricity and angio-destruction leading to zonal destruction<sup>54</sup>.

### ***1.2.6 Clinical staging of lymphomas***

Staging of lymphomas is based on the Ann Arbor classification namely (Appendix 3). Stage I and II are indolent, stages III and IV are aggressive<sup>2, 6, 33, 49, 56</sup>. Stage I and II have better prognosis and treatment outcome compared to stage III and IV

### ***1.2.7 Sites of lymphoma and clinical presentation in the head and neck***

The most common sites of lymphomas manifesting in the head and neck are the oropharynx (Waldeyer's ring: 40—70%), nose and paranasal sinuses, oral cavity, salivary glands, orbit, deep facial spaces and skin<sup>2, 6</sup>. Lymphomas of head and neck manifest most frequently as painless multiple cervical lymphadenopathies located in the cervical region and may also involve other areas such the axial and inguinal lymph nodes<sup>5</sup>. This diagnostic feature helps to differentiate them from other conditions such as squamous cell carcinoma, epidermoid and other metastatic nodules. The clinical presentation is similar to that of metastatic squamous cell carcinoma except that it does not adhere to the skin and deep plane of the neck, less bulky, fleshy and usually do not ulcerate<sup>5, 19</sup>. The most common clinical signs and symptoms are painful swelling, ulceration, paraesthesia, dysphagia and dysphonia<sup>2, 5, 6, 32</sup>. Furthermore, the patient may present with generalized/ constitutional B symptoms inclusive of fever ( $> 38^{\circ}\text{C}$ ), weight loss greater than 10% in 6 months, drenching night sweats, pruritus and fatigue<sup>32</sup>.

#### **1.2.7.1 Waldeyer's ring**

Waldeyer's ring is the most common site of involvement among NHLs presenting in the head and neck and account for 10-15% of extranodal lymphomas. It is made up of lymphoid tissues consisting of palatine, lingual, pharyngeal and tubal tonsils<sup>3, 4, 5</sup>. The palatine tonsils

are mostly involved and present as painless unilateral swelling which may cause dysphagia and dyspnoea. The most common types of lymphomas manifesting in this site include DLBC, follicular, BL and mantle cell types<sup>5, 6, 32</sup>.

#### **1.2.7.2. Nasal cavity and paranasal sinuses**

The nasal cavity and paranasal sinuses are the second most common sites affected by lymphomas in the head and neck. These lesions may manifest as nasal masses, epistaxis, rhinorrhoea, pain and/ or nasal obstruction. Paranasal symptoms may present as facial swelling or paralysis. The late signs may be non-healing ulceration, locally aggressive septal and bone destruction extending to the orbit, nasopharynx, palate, brain and cheek<sup>3, 5, 7, 57, 58</sup>.

Extranodal NK/T cell lymphoma of the nasal type and DLBCL are the commonest histological types of NHL manifesting in the nose and paranasal sinuses. They may be associated with HIV and EBV infections<sup>32</sup>. Imaging of the nasal cavity and paranasal sinuses is mainly by Computed Tomography (CT scan) and Magnetic Resonance Imaging (MRI) which show diffuse tumour infiltration along the walls of the nasal cavity and erosion. The lesion appears iso-dense to muscle on CT scan. On MRI, the lesion appears iso- intense on T1W1 and iso- intense or hyper -intense on T2W<sup>57, 58</sup>.

#### **1.2.7.3 Salivary glands**

Salivary gland lymphomas are very rare neoplasms and represent 2—5 % of all salivary gland neoplasms and affect mainly the parotid gland. Clinical features include swelling of the gland, paresis, paraesthesia and dry mouth<sup>6, 5, 59</sup>. It may be associated with Sjogren's syndrome<sup>5</sup>. Common histological types are extranodal marginal zone B cell of MALT type, follicular B cell and DLBCL<sup>6</sup>. Salivary gland imaging is mainly by ultrasound (US), CT scan and MRI. On ultrasound, the NHL may manifest as small multiple nodular lesions with hyper-vascularization. CT scanning can either be non-enhanced or enhanced. On the enhanced CT the lesion shows variable enhancement ranging from solid, solid cystic, diffusely mixed solid masses or multiple solid nodules especially in extra nodal marginal zone B cell of MALT type<sup>59</sup>.

MRI may show areas of hypo-intense/ iso-intense on T1W and focal nodular hyper intense areas within the gland on T2W<sup>57, 59</sup>.

#### **1.2.7.4 Thyroid gland**

Thyroid lymphomas are rare neoplasms which account for 5% of all thyroid tumours and are associated with Hashimoto's thyroiditis in 80% of cases. They have a female predilection with median age of 60 years<sup>3, 6</sup>. They manifest as rapidly enlarging anterior neck masses which may be unilateral or bilateral, rubbery hard and do not adhere to tissue planes. They may have compressive symptoms such as hoarseness of the voice, dyspnoea and dysphagia. The thyroid tumour mass is usually hard on palpation. Cervical lymphadenopathy is common in these neoplasms. B systemic symptoms may manifest in the course of the lymphoma. They occur mainly in seventh decade with a female predilection and female to male ratio of 3:1<sup>2, 6, 15, 60, 61</sup>. The most common histological forms are DLBCL, extranodal marginal zone, follicular, MALT lymphoma of thyroid gland and rarely classic HL and T cell lymphomas. Imaging modalities for the thyroid gland are US, CT scan and MRI. Ultrasound shows single, multiple masses or diffuse infiltration with extra-nodal extension. A solitary mass appears homogenous with no calcifications, necrosis or cystic degeneration within the nodule. The diffuse lymphoma may appear as a heterogeneous hypo-echoic parenchyma with structures resembling septae. The CT scanning can be with or without contrast. The lesion will appear hypo-dense and are poorly enhancing. On MRI the lymphoma will be hypo-intense to muscle on both T1W1 and T2W<sup>5, 37, 57, 60</sup>.

#### **1.2.7.5 Oral cavity**

Oral cavity lymphomas are rare and account for about 2—3% of all neoplasms presenting in the head and neck; and are mainly NHL type<sup>6</sup>. NHL present in the oral cavity as painful swellings, which may be ulcerated and are frequently located in the lingual tonsils, palate, gingiva and retro-molar trigone<sup>2, 8, 61</sup>. Rapidly growing lesions may affect the underlying bone such as palate, maxilla and mandible resulting in loosening of the involved teeth and precipitating facial asymmetry<sup>2, 5</sup>. They may mimic oral infection such as periodontitis, osteomyelitis or other malignancies<sup>44</sup>. The commonest forms of NHL in the oral cavity are DLBCL and BL<sup>32</sup>.

#### **1.2.7.6 The orbit**

Ocular lymphomas are mainly NHL that may affect one or both eyes and are very rare neoplasms. They occur in the 5<sup>th</sup> – 7<sup>th</sup> decades with a mean age of 65 years and show a female predominance<sup>43</sup>. Primary ocular lymphoma is the second most common eye cancer in adults

<sup>39, 57, 62</sup>. The lesions can be intraocular or adnexia involving the conjunctiva and lacrimal glands. The clinical features may include proptosis; diplopia, blurred or decreased vision, conjunctival masses, photosensitivity and redness of eye. The most common histological forms are follicular, extra nodal marginal zone, DLBCL and Mantle cell lymphomas <sup>39, 57, 62, 63</sup>.

#### **1.2.7.7 Other craniofacial sites**

Lymphomas found in the ear are rare <sup>64, 65</sup>. They may be located in the external auditory canal, middle and inner ear presenting as a mass causing ear blockage, hearing loss defect and facial nerve paralysis. In their case study, Bruschini et al reported that primary NHL arising from the external auditory meatus are DLBCL, follicular and T cell lymphomas. These lesions can affect one or both ears <sup>34</sup>. Classic Nodular sclerosis type of HL was reported by Maithrea and others (2016) where the presenting symptom was facial nerve palsy <sup>64</sup>.

#### **1.2.8 TREATMENT OF LYMPHOMAS**

Treatment of lymphomas is based on the type of lymphoma, stage, and bulkiness, presence of symptoms (B symptoms), erythrocyte sedimentation rate (ESR), age and general health of patient. The current treatment modalities are chemotherapy, radiation therapy, immunotherapy and radio-immunotherapy. Stem cell transplantation and surgical interventions may be a viable option in persistent or large lesions <sup>66</sup>. Surgical intervention may be utilized for debridement of necrotic lesions debulking of large lesions and reconstruction. Complications associated with treatment of lymphomas include second cancers and other lesions such as infections due to the weakened immune system, infertility and alopecia<sup>67, 68</sup>.

## **1.3 PROBLEM STATEMENT AND JUSTIFICATION**

### **1.3.1 PROBLEM STATEMENT:**

Studies on the pattern of lymphomas in the head and neck have been mainly retrospective and have shown wide geographic and clinical variations. These studies have been predominantly done in developed countries. Sub-Saharan Africa studies show that the head and neck lymphomas are mainly associated with HIV and EBV infections as exemplified in the studies done by Mwamba et al. in the Nigeria, Opie in South Africa and Sasco and others <sup>11, 42, 43, 69, 70</sup>.

Studies done in Sub-Saharan Africa were mainly on the head and neck malignancies without stating the clinical pattern of lymphomas <sup>12, 14, 25</sup>. Histopathology audit studies on head and neck malignancies done in Kenya by Dimba et al reported that the prevalence of lymphomas was at 6.05% for both HL and NHL which is in agreement with other parts of the world <sup>14</sup>. Therefore, these studies done in the Sub-Saharan Africa have shown that there is still insufficient data regarding the clinical profile of lymphomas especially in the Kenyan population, thus the need to for this study.

**1.3.2 JUSTIFICATION:** There has been hardly any study done on the clinical and histological characteristics of lymphomas in Kenya. Therefore, this study should provide more information on the pattern of lymphomas thereby providing insights into their biologic behaviour, and also allow for comparison with what is observed elsewhere. Studies done by Mwanda et al. were only on BL whereas this study was on the different types of lymphomas of the head and neck at KNH and UNDH <sup>71</sup>. The study was to find the current clinical profile and histological characteristics of head and neck lymphomas at the two centres in Nairobi. The outcomes of the study may inform policy makers on current disease burden and may serve as guide in protocol formulation for definitive and supportive care for those affected.

## **1.4 RESEARCH QUESTION**

**RESEARCH QUESTION:** What are the clinical characteristics and histological types of head and neck lymphomas presenting at the KNH and UNDH?

## **1.5 STUDY OBJECTIVES**

### **1.5.1 Broad objective**

To describe the clinical and histological characteristics of head and neck lymphomas in patients seen at KHN and UNDH.

### **1.5.2 Specific objectives:**

1. To determine the socio-demographic pattern of patients presenting with lymphomas manifesting in the head and neck.
2. To determine the clinical characteristics of lymphomas of the head and neck by site, size and nodal/extra nodal involvement.
3. To describe the histological pattern of lymphomas manifesting in the head and neck.

## 1.6: VARIABLES

The following tables shows independent and dependent variables

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### Independent variables

1. Demographics	Age, Gender, Nationality and Residence
2. Site of lesion	Waldeyer's ring, Nasal and Paranasal sinuses Oral cavity Orbit Ear canal Neck
3. HIV status	Positive, Negative, Unknown

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### Dependant variables

1. Clinical signs & symptoms	Painless swelling Dysphagia Dysphonia Mucosal ulceration Teeth mobility Obstruction Discharge Visual problems, Proptosis, Epiphora Ear: Hearing loss, Facial nerve palsy B symptoms: Night sweats, weight loss, fever
2. Size of lesion (cm)	
3. Radiological features	CT scan: MRI
4. Histological characteristics	Routine morphological histology Immunohistology Both morphology and immunohistology

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## CHAPTER 2: MATERIAL AND METHODS

**2.1 Study design:** This was descriptive cross sectional retrospective hospital based study of patients diagnosed with head and neck lymphomas. The study duration was from January 2010 to May 2019; eight years and five months.

**2.2 Study area:** The study was be conducted in KNH and UNDH. KNH is the tertiary and largest national referral hospital in Kenya located in Nairobi County. It has an encatchment area mainly from central part of the country and referrals from the different parts of the country. The core business of the hospital is to provide specialized health care services, facilitate training and research in collaboration with the University of Nairobi. The hospital operates an emergency/ casualty department on a 24 hour basis, day clinics and in- patients with a capacity of 2000 beds.

UNDH is a tertiary learning institution which offers dental treatment ranging from basic to specialized ones. It also receives referral patients from other dental centres from within and outside Nairobi.

**2.3 Study population:** The study population included files for the in-patients and out-patients with head and neck lymphomas. The study included patients of all age groups and gender who present at the two centres.

### 2.4 Sampling procedure

2.4.1 Sampling method: The convenience sampling method was used to obtain data for this study in which all patients with head and neck lymphomas were recruited.

2.4.2 Sample size: The sample size of patients with head and neck was calculated using Cochran's formula <sup>72</sup>.

$$n_0 = \frac{z^2pq}{e^2}$$

Where:  $n_0$  = required sample size

$z$  = value at 1.96 which corresponds to 95% confidence level

$p$  = proportion in target population with particular characteristics

$q$  = (1-p)

$e$  = degree of desired of desired accuracy, expressed as a proportion of 0.05, margin of error



$$n_0 = \frac{(1.96)^2 \times 0.05 \times (1.0 - 0.5)}{(0.05)^2} = 73$$

The prevalence of head and neck lymphomas is about 5% as reported in literature <sup>2</sup>. The paediatrics population are patients below the age of 18 years.

## **2.5 Inclusion and Exclusion criteria**

### ***2.5.1 Inclusion criteria***

Patients files with a diagnosis of lymphomas manifesting in the head and neck, availability of histology, immunohistochemistry or both

### ***2.5.2 Exclusion criteria***

Patients files without histopathological and/or immunohistochemistry diagnosis of head and neck lymphoma

## **2.6 Data collection**

Patient files were retrieved from KNH and UNDH registry using ICD 10 codes (Appendix 4). Data was obtained from the patient files that met the inclusion criteria, files were reviewed for presence of head and neck lymphoma diagnosis (Histology, Immunohistochemistry or both), history of presenting complaint, duration of presenting complaint and available imaging modalities. Clinical presentation of lymphomas and staging were recorded.

The HIV status of individual patients were reported as positive, negative or not available. The type of treatment offered to the patient was also recorded. The data was recorded in a predesigned data collection form (Appendix 1). Confidentiality was maintained by the researcher as the data was coded to remove identifiers. The data was then recorded on windows spread sheet with a password.

## **2.7 Data Analysis and Presentation**

The data was coded, entered on the computer and analysed using SPSS version 25. The data was analysed and presented as means and frequencies. The study population was described using age and sex which will be analysed and presented as means and percentages. The student t-test and Chi-square tests were used for data analysis. Both 95 % confidence intervals (95 % CI) and P-value <0.05 were used to test the statistical significance of results. Analysis was done by the assistance of qualified statistician. The results were then presented

as tables, pie-charts, graphs and description of clinical and histological characteristics of lymphomas.

## **2.8 Ethical considerations**

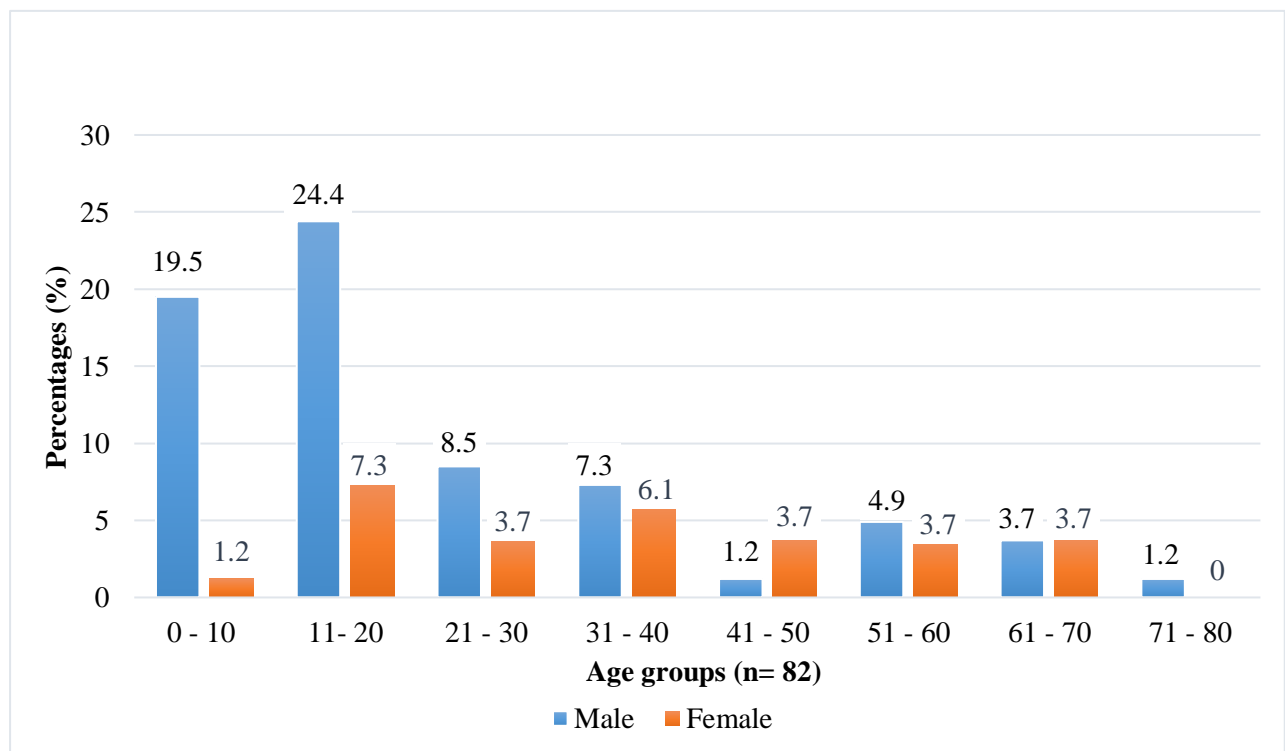
The study was approved by KNH-UoN Ethics Research Committee on 02<sup>nd</sup> October 2018 (P432/06/2018), (Appendix 5). Furthermore, authority was sought and granted by KNH and UNDH to access patient files. The patient's information were coded and names were not used to maintain confidentiality. The findings of this study will be published in a scientific journal or presented in scientific meetings.

## CHAPTER 3: RESULTS

The main aim of the study was to describe the clinical and histological characteristics of head and neck lymphomas in patients seen at KHN and UNDH.

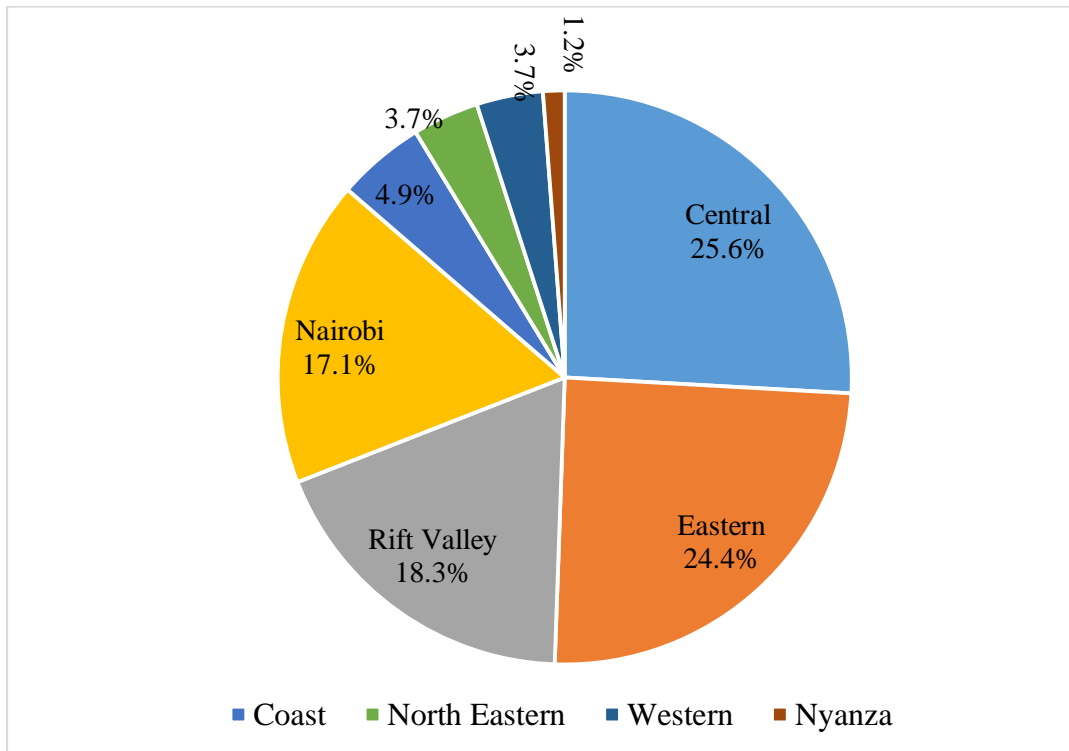
### 3.1 Patient socio- demographics

The study duration was 8 years 5 months, from January 2010 to May 2019 and a total of 82 patients with head and neck lymphomas were seen at KNH and UNDH. The age of the patients ranged between 3 and 77 years with a mean age of 26.5 (SD=19) years while the median was 18.5 (IQR=28) years. There were 57 (69.5%) males and 25 (30.5%) females translating to a male to female ratio of 2.3: 1. A non-parametric binomial test (Pearson Chi squared,  $\chi^2$  at 95%) showed a statistically significance difference of  $\chi^2= 12.488$ ,  $df= 1$ ,  $p = 0.01$  in gender distribution between males and females ( $p < 0.05$ ). There were 37(45.1%) children and 45 (54.9%) adults with head and neck lymphomas. Most lymphomas were reported in the second, followed by the first, then third decades and the least in the eight decade.



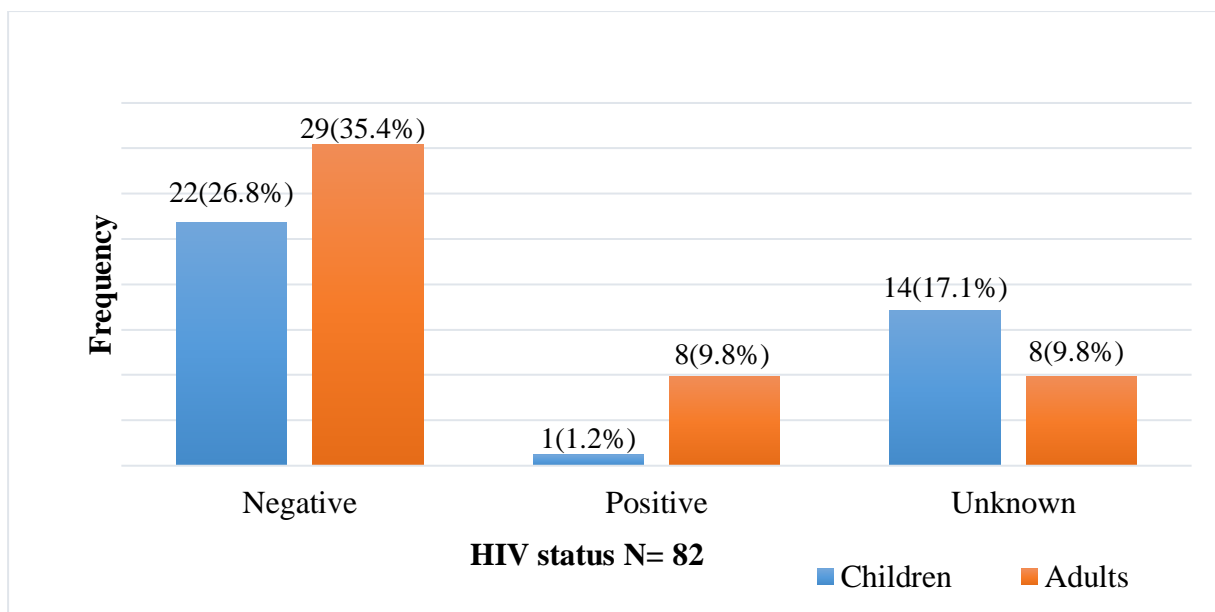
**Figure 6: Distribution of head and neck lymphomas by age groups and gender.**

The patients who presented with head and neck lymphomas showed distribution from different parts of the country with more patients from Central province n= 21 (25.6%), Eastern province n=20 (24.4%), Rift valley province n= 15 (18.3%) and Nairobi n=14 (17.1%). These provinces are in relatively in close proximity to KHN and UNDH. There were few patients from the Coast n=4 (4.9%), North Eastern n= 3 (3.7%), Western n=3 (3.7%) and Nyanza n=1 (1.2%). These provinces are far from KNH and UNDH.



**Figure 7: Provincial residence of patients with head and neck lymphomas**

Most patients were inpatients 77 (93.9%), while the outpatients were 5 (6.1%). Out of the 82 patients with head and neck lymphomas, there were 60 patients with known HIV status; negative n= 51 (62.2%), positive n= 9 (11.0%) and those with unknown status n= 22 (26.8%). For children, 23 of 37 (65.7%) with known HIV status whilst for adults 37 of 45 (82.2%) with known HIV status.



**Figure 8: HIV status in patients with head and neck lymphomas**

**Table 1: Distribution of HIV status with gender and age groups in patients with head and neck lymphomas**

Variable	HIV N= 82			P Value
	Positive Available n= 9	Negative n= 51	Not n= 22	
<b>Gender</b>				
M	5	36	16	0.618
F	4	15	6	
<b>Age groups (years)</b>				
<18	1	22	14	0.530
≥18	8	29	8	

There were more males who were HIV negative compared to females in both children and adults. However, there was no statistical significance difference for gender and HIV infection,  $\chi^2= 0.962$ ,  $df = 2$ ,  $p= 0.618$ . The children and adults and HIV infection showed no statistical significant difference as  $\chi^2= 7.690$ ,  $df= 2$  and  $p= 0.530$ . There were more children  $n = 14$  (63.6%) with unknown HIV status compared to adults.

### 3.2 Clinical characteristics of head and neck lymphomas

#### 3.2.1 Site and of head and neck lymphomas

Most head and neck lymphomas were located in the neck n= 47 (57.3%), then maxilla and mandible n= 26 (31.7%). Fewer lymphomas were located in the Waldeyer's ring n= 4 (4.9%), nose and orbit accounted for n= 3 (3.7%) and n=2 (2.4%) respectively. Non parametric test (Pearson Chi squared,  $\chi^2$  at 95%) showed no statistical significant difference for left and right side of neck ( $\chi^2= 1.043$ , df= 1, p= 0.307), maxilla ( $\chi^2= 0.09$ , df= 1, p= 0.763) and mandible ( $\chi^2= 0.67$ , df= 1, p= 0.796). The male n= 57 (69.5%) to female n= 25 (30.5%) ratio of 2.3:1 for lymphomas in different sites in the neck. The correlation between lymphomas and site showed no statistical significant difference ( $\chi^2= 6.846$ , df= 8, p= 0.533).

**Table 2: Site of head and neck lymphomas**

Site	Frequency (%)	Total Frequency (%) n=82
Neck: Left	27 (32.9)	47 (57.3)
Right	20 (24.4)	
Maxilla: Left	5 (6.1)	11 (13.4)
Right	6 (7.3)	
Mandible: Left	8 (9.8)	15 (18.3)
Right	7 (8.5)	
Waldeyer's ring	4 (4.9)	4 (4.9)
Nose and Paranasal sinuses	3 (3.7)	3 (3.7)
Orbit	2 (2.4)	2 (2.4)

#### 3.2.2 Head and neck lymphomas duration at time of diagnosis

The duration of lymphomas at the time of diagnosis ranged from 1 to 48 months, with the mean of 12.5 (SD=12.6) months and the median was 6 months. There were 55 patients with head and neck lymphomas who presented at 12 months and below at diagnosis. Those who presented more than 12 months had relapsed on treatment n =12, treated for tuberculosis n =3, rhabdomyosarcoma n = 2 and others with unknown reasons for delayed treatment. There was no statistical significant difference for males and female at diagnosis ( $\chi^2= 5.002$ . df= 13, p= 0.975). The correlation of HL and NHL at the time of diagnosis showed no statistical significant difference ( $\chi^2= 15.188$ , df= 12, p= 0.231).

There was no statistical significant difference shown between children and adults for duration of lymphomas at diagnosis ( $\chi^2= 10.277$ ,  $df= 12$ ,  $p= 0.592$ ).

**Table 3: Duration of head and neck lymphoma at time of diagnosis**

Duration (Months)	Frequency n=82 (Percentage, %)		
	Male	Female	Total
1	3	1	4 (4.9)
2	5	3	8 (9.8)
3	4	4	8 (9.8)
4	3	1	4 (4.9)
5	3	1	4 (4.9)
6	10	3	13 (15.9)
7	3	2	5 (6.1)
9	1	0	1 (1.2)
12	8	3	11 (13.4)
18	5	3	8 (9.8)
24	5	2	7 (8.5)
30	1	0	1 (1.2)
36	3	0	3 (3.7)
48	3	2	5 (6.1)

### ***3.2.3 Clinical signs and symptoms***

The most prevalent clinical signs and symptoms of head and neck lymphomas were painless swelling, facial asymmetry, teeth mobility, dysphagia, dysphonia, blindness, proptosis, epiphora, nasal obstruction and discharge, and the B symptoms. B symptoms were drenching night sweats, fever and weight loss. Painless swelling n= 45 (54.9%) was the most common symptom and facial asymmetry n= 80 (97.6%) being most common clinical signs. Most patients presented with bilateral cervical lymphadenopathy n= 71 (86.6%) while eleven (13.4%) with unilateral lymphadenopathy. There were no mucosal or skin laceration associated with lymphomas.

**Table 4: Clinical signs and symptoms of head and neck lymphomas**

Clinical signs and symptoms	Frequency n= 82	Percentage (%)
Painless swelling	45	54.9
Teeth mobility	10	12.2
Dysphagia	23	28.0
Dysphonia	12	14.6
Blindness	2	2.4
Proptosis	2	2.4
Epiphora	5	6.4
Obstruction	4	4.9
Discharge	4	4.9
<b>B symptoms</b>		
Anorexia	74	90.2
Weight loss	74	90.2
Fever	71	86.6
Night sweats	59	72.0

### 3.2.4 Clinical staging of head and neck lymphomas at presentation

Ann Arbor classification of lymphomas at the time of diagnosis were stage I and II n= 21 (25.5%) stage III and IV n= 32 (39%) and those not staged accounted for n= 29 (35.4%). Those who were clinically staged, n= 53 (59.2%) presented with B symptoms and 4 (4.9%) without symptoms. Clinical staging of head and neck lymphomas showed statistically significant difference in HL and NHL ( $\chi^2= 51.878$ ,  $df= 7$ ,  $p< 0.001$ ). There were more HL, n= 45 (54.9%), which were clinically staged in this study compared to NHL n= 8 (9.7%).

**Table 5: Clinical Staging of head and neck lymphomas**

Stage	Type Frequency n= 82 (%)		
	HL n= 47	NHL n= 35	Total n= 82
IA	1 (1.2)	0	1 (1.2)
IB	1 (1.2)	0	1 (1.2)
IIA	2 (2.4)	0	2 (2.4)
IIB	15 (18.3)	2 (2.4)	17 (20.7)
IIIA	1 (1.2)	0	1 (1.2)
IIIB	13 (15.9)	6 (7.3)	19 (23.2)
IVB	12 (14.6)	0	12 (14.6)
Not staged	2 (2.4)	27 (33.0)	29 (35.4)



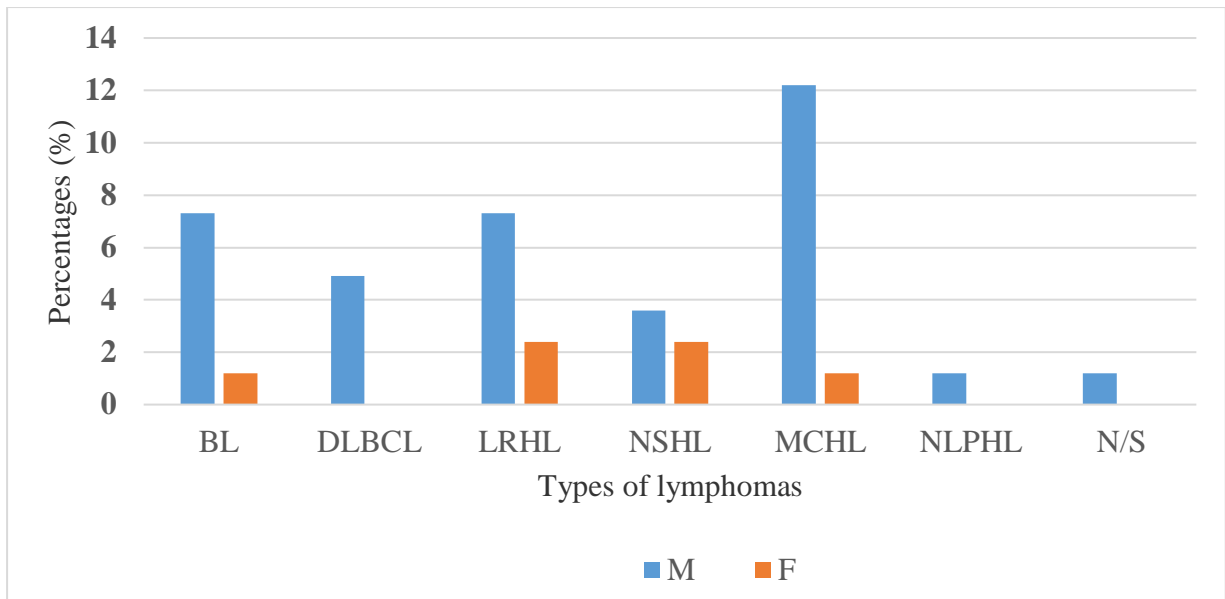
### 3.3 Histological characteristics of head and neck lymphomas

The diagnosis of head and neck lymphomas was based on histology and immunohistochemistry n=33 (40.2%). Tissue biopsy accounted for n= 65 (79.3%) and fine needle aspirate n=17 (20.7%) patients. HL were n= 47 (57.3%) and NHL n= 35 (42.6%), a ratio of 1.4: 1. There was no statistically significant difference in occurrence of HL and NHL (p = 0.15). Classical HL n=46 were significantly more than Nodular lymphocyte predominant HL. Mixed cellularity HL more common in adults compared to children, with frequencies n=17 (20.7%) and n=11 (13.4%) respectively. There was no statistical significance difference between children and adults for head and neck lymphomas ( $\chi^2=1.756$ , df= 1, p= 0.185). Most of the aggressive type of NHL were clinically diagnosed at 12 months and below, n= 8 out of 12 in BL and n= 13 of 16 in DLBCL.

For children, the age ranged from 3 years and 18 years with n= 37, 31 males and 6 females. There were 45 adult patients; 26 males and 19 females, with an age range from 18 and 77 years.

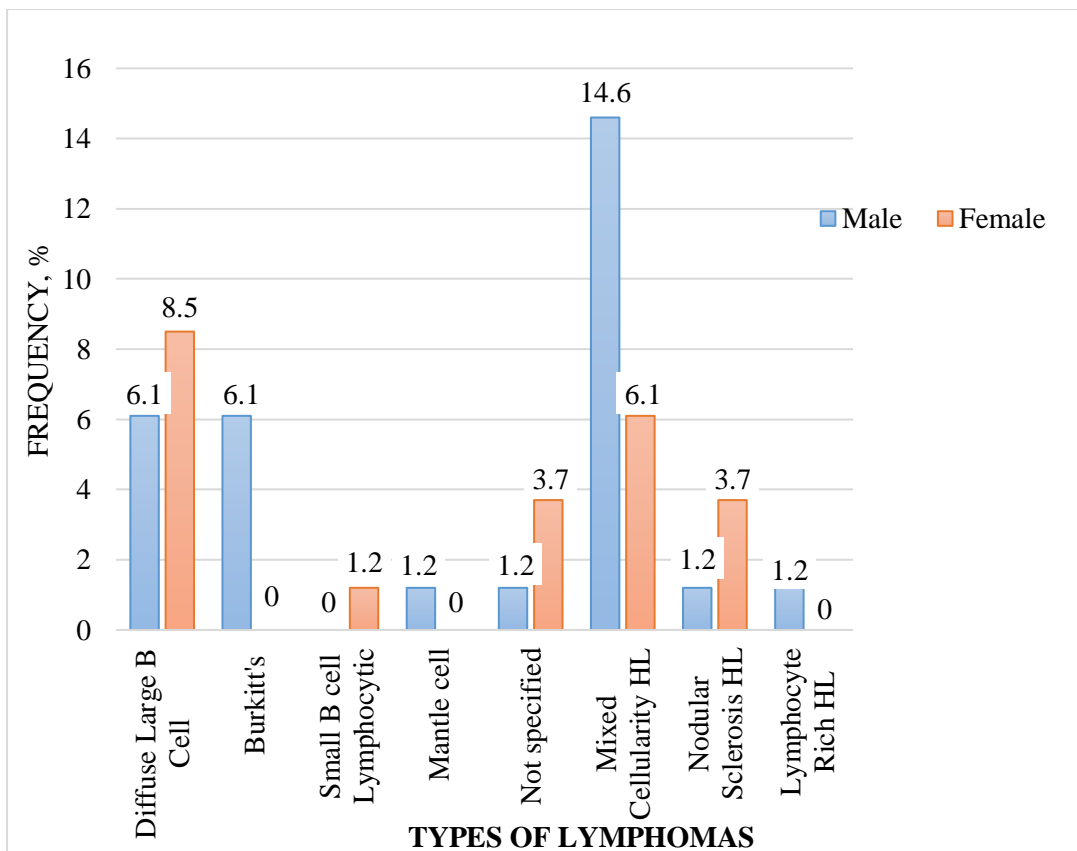
**Table 6: Histological types of head and neck lymphomas**

Type of lymphoma	Frequency (%) n= 82	Children (%) n= 37	Adults (%) n= 45
<b>Hodgkin lymphoma</b>	<b>47 (57.3)</b>		
Classic HL			
Mixed cellularity	28 (34.1)	11 (13.4)	17 (20.7)
Nodular sclerosing	9 (11.0)	5 (6.1)	4 (4.9)
Lymphocyte rich	9 (11.0)	8 (9.8)	1 (1.2)
Nodular lymphocyte predominant	1 (1.2)	1 (1.2)	0
<b>Non Hodgkin lymphoma</b>	<b>35 (42.6)</b>		
DLBCL	16 (19.5)	4 (4.9)	12 (14.6)
BL	12 (14.6)	7 (8.5)	5 (6.1)
ML	1 (1.2)	0	1 (1.2)
Small lymphocytes	1 (1.2)	0	1 (1.2)
Non specified	5 (6.1)	1 (1.2)	4 (4.9)

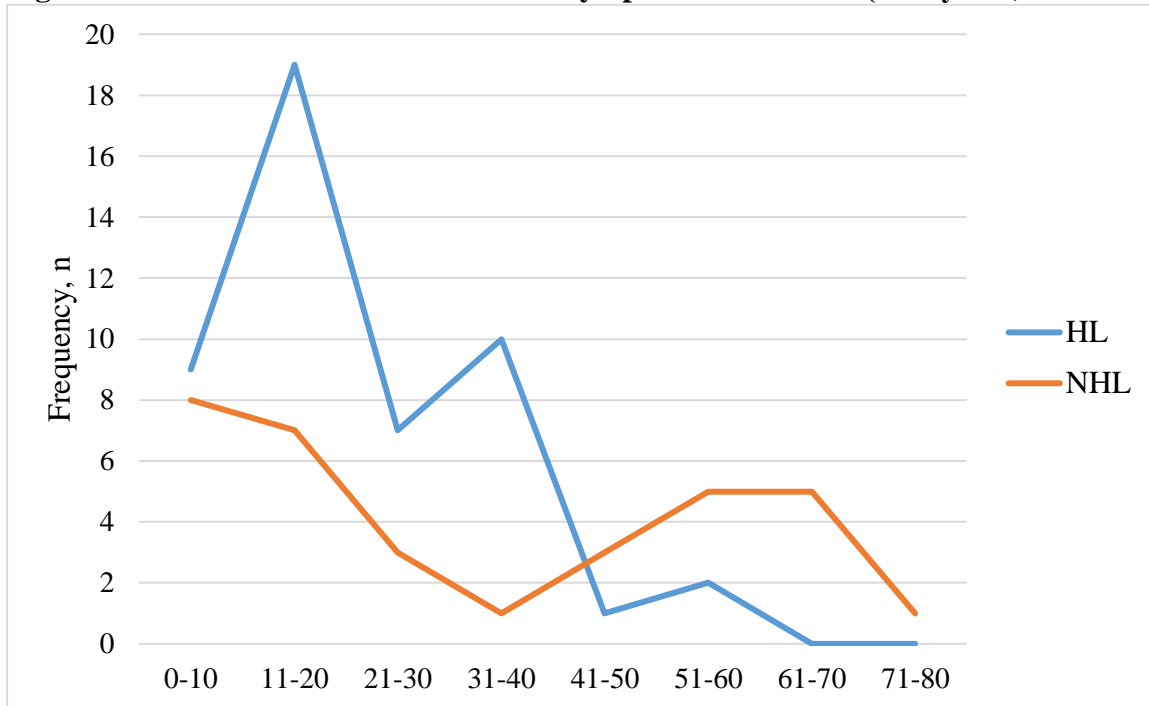


**Figure 9: Distribution of head and neck lymphomas in children (< 18 years)**

**Key:** BL Burkitt's lymphoma, DLBCL Diffuse large B cell, NSHL Nodular sclerosis HL, LRHL Lymphocyte rich HL, MCHL Mixed cellularity HL, NLPHL Nodular lymphocyte predominant HL and N/S non- specified.



**Figure 10: Distribution of head and neck lymphomas in adults (≥ 18 years)**



**Figure 11: Pattern of occurrence of head and neck lymphomas (n= 82)**

HL shows bimodal peaks in the second and fourth decades. The patients who presented with NHL had the highest peak in the first decade then decreased gradually, then showed an upward trend after the fourth decade with plateau in sixth and seventh decades.

**Table 7: Distribution of the types of head and neck lymphomas in age groups and gender**

	Lymphomas (n= 82)		P Value
	HL (n=47)	NHL (n=35)	
<b>Age groups (years)</b>			
<18	25	12	<b>0.103</b>
≥18	23	22	
<b>Gender</b>			
Male	34	23	<b>0.648</b>
Female	14	11	

There were more HL n= 25 (30.5%) than NHL n= 12 (14.6%) in children. In adults, HL n= 23 (28%) slightly more than NHL n= 22 (26.8%). NHL showed an increase with age. The distribution of lymphomas between age groups (children and adults) showed statistically no significance difference ( $\chi^2=2.266$ ,  $df=1$ ,  $p= 0.103$ ). There were more males compared to

females in both HL and NHL. Gender and occurrence of lymphomas showed no statistical significant difference ( $\chi^2= 0.095$ ,  $df= 1$ ,  $p= 0.648$ ).

**Table 8 Distribution of HIV infection in the histological types of head and neck lymphomas**

Variable	HIV (n= 82)			P Value
	Positive n= 9	Negative n= 51	Not Available n= 22	
Type				
HL	2	35	11	0.033
NHL	7	16	11	

HIV positive patients n= 7 (8.5%) with NHL, six adults and one child. NHL were the aggressive types, namely; DLBCL n= 4 (4.9%) and BL n= 2 (2.4%). There were two adult patients with classic HL. The types of head and neck lymphomas and HIV status showed statistical significant difference ( $\chi^2= 7.331$ ,  $df= 2$ ,  $p= 0.033$ ).

**Table 9: Treatment modalities of head and neck lymphomas**

TREATMENT MODALITY	FREQUENCY n= 82 (%)
HL (n= 47)	ABVD 23 (28.0)
	ABVD + ICE 1 (1.2)
	CHOPP 14 (17.1)
	CHOPP + DXT 3 (3.7)
	CHOPP + ABVD 2 (2.4)
	CHOPP + 6 MP 1 (1.2)
	NONE 2 (2.4)
NHL (n= 35)	CHOP 7 (8.5)
	CHOP + Surgery 1 (1.2)
	CHOP +MTX 10 (12.2)
	R-CHOP 5 (6.1)
	CHOP + ICE/ DHAP/ESHAP/CVP 3 (3.7)
	VAC 1 (1.2)
	VAC + MTX 2 (2.4)
	NONE 6 (7.3)

**Key**

ABVD: Adriamycin, Bleomycin, Vincristine, Decarbazine

ICE: Ifosfamide, Carboplatin, Etoposide

CHOP: Cyclophosphamide, Doxoubicin, Vincristine, Prednisolone

R- CHOP: Rituximub, Cyclophosphamide, Doxoubicin, Vincristine, Prednisolone

CHOPP: Cyclophosphamide, Doxoubicin, Vincristine, Procarbazine, Prednisolone

VAC: Vincristine, Adriamycin, Cyclophosphamide

IT-Met: Intra- thecal Methotrexate

6- MP: 6- Mercaptopurine

CVP: Cyclophosphamide, Vincristine, Prednisolone

ESHAP: Etoposide, Methyl-prednisolone (Solumedrol), Cytarabine, Cisplatin

DHAP: Rituximub, Dexamethasone, Cytarabine, Cisplatin

DXT: Radiotherapy

NONE: No treatment administered

Chemotherapy for HL and NHL being ABVD and CHOP respectively. Other drug combinations were used as shown in table 8. Three patients were treated with radiotherapy as salvage therapy. Only one patient was offered surgical management of lymphoma in the maxilla.

## **CHAPTER 4: DISCUSSION**

### **4.1 Discussion**

This study was carried out to determine the clinical profile and histological characteristics of head and neck lymphomas in patients seen at KNH and UNDH. Lymphomas are the third most common head and neck neoplasms which present with serious morbidity and mortality. The morbidities includes functional and aesthetic deficiencies. Most studies on head and neck lymphomas were done in developed countries whilst those done in Sub- Saharan Africa are mainly related to HIV infection and are usually combined with other head and neck neoplasms or BL only <sup>4, 6, 17, 18,25, 66, 70,73, 75</sup>. Most of the patients were managed using chemotherapy alone or combined with radiotherapy and only one done debulking <sup>62,63,75</sup>.

#### **4.1.1 Socio-Demographic patterns of patients**

The present retrospective study yielded useful information regarding the profile of head and neck lymphomas such as most common types of lymphomas and low use of immunohistochemistry in diagnosis. Head and neck lymphomas are considered to be rare conditions with wide range of age distribution. A total of 82 patients were included in this study with age range from 3 years to 77 years. The mean age of 26 years was lower than what was reported in literature which was on the sixth and seventh decades <sup>17, 20, 75</sup>. The gender distribution of head and neck lymphomas was higher in this study with ratio of M: F 2.1: 1 compared Picard et al which reported a ratio of 1.4: 1 <sup>17</sup>. Chi et al reported no gender difference in prevalence of head and neck lymphomas <sup>73</sup>. Naresh reported M: F ratio of 1.3: 1 which was also lower than this study<sup>78</sup>. There were more males than males compared to female in this study which is similar to those in literature <sup>73,74</sup>. There were more adults who were HIV positive compared to children and were associated with NHL.

#### **4.1. 2 Clinical characteristics of head and neck lymphomas**

The most common site for head and neck lymphomas was the neck, mainly the HL which was similar to that reported by Storck et al <sup>75</sup>. NHL were found to be more common in the jaws and this was differing from other studies where the common site was the Waldeyer's ring <sup>2, 6, 8, 17, 18</sup>. The most common site for NHL was the mandible which is different from that in literature <sup>74</sup>. Few patients presented with lymphomas in the nose and the orbit with and this

was agreement with literature <sup>63, 64</sup>. The ocular lymphomas were found on children which deferred from that in literature which was reported to occur in the 5<sup>th</sup> to 7<sup>th</sup> decades <sup>63</sup>.

The duration of head and neck lymphoma at clinical diagnosis ranged from 1 to 48 months and the mean age of 6 months was similar to what was reported in literature <sup>17, 74, 75</sup>. Most of the aggressive NHL were clinically diagnosed at 6 months or below and this was comparable to other studies <sup>17, 75</sup>.

The clinical presentation of head and neck lymphomas was frequently a rapidly expanding swelling either painful or painless accompanied with B symptoms. Some signs and symptoms were specific to site of lymphoma such as teeth mobility in the oral cavity, dysphagia and dysphonia in oro-pharyngeal and nasopharyngeal respectively. This was comparable to studies done in other parts of the world <sup>3, 5, 19</sup>. B symptoms were present in most patients, with the most common being weight loss followed by fever then drenching night sweats and this was higher than what was reported by Picard et al and Chi, et al <sup>17, 18</sup>. The staging of lymphomas was based on Ann Arbor classification which is based on lymph node involvement. Most of the lymphomas in the study were stage III and IVB. This was contrary to what was reported in literature where most patients presented at early stages <sup>17, 18</sup>.

#### **4.1.3 Histological characteristics of head and neck lymphomas**

Diagnosis of lymphomas was based on routine histopathology and immunohistochemistry or both reports from fine needle aspirate cytology (FNAC) or tissue biopsies. The low uptake of immunohistochemistry is a challenge in Sub-Saharan Africa as reported by Naresh, et al and has impact on treatment of lymphomas <sup>73</sup>. Head and neck lymphomas were of B cell lineage and there were no NK/T lymphomas. There were more HL compared to NHL which is higher than reported in other studies <sup>18, 73, 75</sup>. HL is considered to be a childhood disease which showed bimodal peaks in the second and fourth decades which was different from other studies which reported the second peak to be above 50 years <sup>20</sup>. Classic HL (cHL) were more prevalent compared to nodular lymphocyte predominant type; the mixed cellularity and nodular being the most common in both children and adults <sup>73</sup>. This observation is consistent with the study done by Huh in Korean population <sup>20</sup>. For HL, the mean age in children was 11.08 and median 12 years which is lower than what was reported in literature <sup>73</sup>. In the adult population, the mean age was 47.6 and the median 52 years which was similar to other studies <sup>2</sup>.

NHL showed increasing tendencies with age which is consistent with literature. They were more common in males than in females which is consistent with the study by Huh<sup>20</sup>. For children, the mean age was 8.7 and the median of 4.3 years whilst for adults the mean age was 31.5 and median 32 years. This was lower than what was reported in literature<sup>73, 76, 77</sup>. The aggressive NHL subtypes, BL and DLBCL were reported in this study to be lower than what was reported in literature where they reported the occurrence to 50% of all head and neck lymphomas<sup>25, 26, 73, 76, 77, 78</sup>. For BL in children, the mean age was 7.9 and median of 7.0 years which was higher than reported by Naresh et al<sup>73</sup>. There were fewer cases of BL in adults with mean of 30 and median of 26 years which was similar to that reported in literature<sup>73, 76, 79</sup>. BL were more common in males than females which is similar to studies done elsewhere<sup>73, 79</sup>. DLBCL was more common in adults compared to children with an increasing tendency with age and showed female predominance in adults which was consistent with other studies<sup>20, 49, 73</sup>. In children, the mean age was 9.3 and median 7.5 years which was similar to that reported in literature<sup>73</sup>. For the adults, the mean age was 51.6 and the median was 56 years which was lower than what was reported in literature<sup>73, 76, 79</sup>.

#### **4.2 Conclusion**

1. The head and neck lymphomas showed male predominance in both children and adults.
2. Head and neck lymphomas showed a wide range of clinical presentation which includes painless rapidly expanding swellings with no ulceration and B symptoms.
3. There were more HL compared to NHL in this study.
4. BL in children and DLBCL in adults were the commonest NHL.
5. There was low uptake of immunohistochemistry (IHC) for diagnosis of lymphomas which has negative impact on treatment and prognosis of disease.
6. The outcome of this study compares well with studies done elsewhere in the world

#### **Recommendations**

1. The use of immunohistochemistry as definite diagnosis lymphoma typing is imperative to improve treatment outcomes.
2. Larger sample size studies to interrogate HIV trends and types of lymphomas may be necessary.
3. Introduction of synoptic reporting for lymphomas to capture full biological details for cancer registries.



**Limitations:** The study was retrospective and information was source from patient records of which some vital information may have been missing, such as lymphomas size at presentation, HIV status, imaging reports to enhance lymphoma staging.

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## APPENDIX 1: DATA COLLECTION TOOL

### A. Demographic data

1. Hospital Number..... Study Number.....
2. Age (years): .....
3. Gender: M  F
4. Nationality .....
5. Residence .....
6. Presenting complaint.....  
.....  
.....  
.....
7. Category: Outpatient  Inpatient
8. HIV status: Positive  Negative  Not Available

### B. Clinical presentation

1. Site of lesion.....
2. Size of lesion.....
3. Duration.....
4. Lymphadenopathy: Yes  No
5. Pain:  No pain
6. Swelling/deformity/facial asymmetry: .....  
.....  
.....
7. Oropharynx: Dysphagia  No dysphagia   
Dysphonia  No dysphonia
8. Teeth involvement: Mobile  Non mobile
9. Eye symptoms: Blindness  No blindness   
Proptosis  No proptosis

- Epiphora  No epiphora
10. Nasal symptoms: Obstruction  No obstruction
- Discharge  No discharge
11. Ear symptoms: Hearing loss  No hearing loss
- Facial nerve palsy  No facial nerve palsy
12. Constitutional symptoms: Anorexia  Weight loss  Fever

**C. Histological lymphoma types:** Routine morphology

Immunohistochemistry/Ancillary

## APPENDIX 2: WHO CLASSIFICATION

**Table: 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms**

<b>Mature B-cell neoplasms</b>	
Chronic lymphocytic leukemia/small lymphocytic lymphoma	
Monoclonal B-cell lymphocytosis*	
B-cell prolymphocytic leukemia	
Splenic marginal zone lymphoma	
Hairy cell leukemia	
Splenic B-cell lymphoma/leukemia, unclassifiable	
Splenic diffuse red pulp small B-cell lymphoma	
Hairy cell leukemia-variant	
Lymphoplasmacytic lymphoma	
Waldenström macroglobulinemia	
Monoclonal gammopathy of undetermined significance (MGUS), IgM*	
μ heavy-chain disease	
γ heavy-chain disease	
α heavy-chain disease	
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*	
Plasma cell myeloma	
Solitary plasmacytoma of bone	
Extrasosseous plasmacytoma	
Monoclonal immunoglobulin deposition diseases*	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	
Nodal marginal zone lymphoma	
Pediatric nodal marginal zone lymphoma	
Follicular lymphoma	
In situ follicular neoplasia*	
Duodenal-type follicular lymphoma*	
Pediatric-type follicular lymphoma*	
Large B-cell lymphoma with IRF4 rearrangement*	
Primary cutaneous follicle center lymphoma	
Mantle cell lymphoma	
In situ mantle cell neoplasia*	

Diffuse large B-cell lymphoma (DLBCL), NOS  
 Germinal center B-cell type\*  
 Activated B-cell type\*  
 T-cell/histiocyte-rich large B-cell lymphoma  
 Primary DLBCL of the central nervous system (CNS)  
 Primary cutaneous DLBCL, leg type  
 EBV1 DLBCL, NOS\*  
 EBV1 mucocutaneous ulcer\*  
 DLBCL associated with chronic inflammation  
 Lymphomatoid granulomatosis  
 Primary mediastinal (thymic) large B-cell lymphoma  
 Intravascular large B-cell lymphoma  
 ALK1 large B-cell lymphoma  
 Plasmablastic lymphoma  
 Primary effusion lymphoma  
 HHV81 DLBCL, NOS\*  
 Burkitt lymphoma  
 Burkitt-like lymphoma with 11q aberration\*  
 High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements\*  
 High-grade B-cell lymphoma, NOS\*  
 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

### **Mature T and NK neoplasms**

T-cell prolymphocytic leukemia  
 T-cell large granular lymphocytic leukemia  
 Chronic lymphoproliferative disorder of NK cells  
 Aggressive NK-cell leukemia  
 Systemic EBV1 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  
 Sézary syndrome  
 Primary cutaneous CD301 T-cell lymphoproliferative disorders

Lymphomatoid papulosis  
 Primary cutaneous anaplastic large cell lymphoma  
 Primary cutaneous gd T-cell lymphoma  
 Primary cutaneous CD81 aggressive epidermotropic cytotoxic T-cell lymphoma  
 Primary cutaneous acral CD81 T-cell lymphoma\*  
 Primary cutaneous CD41 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, ALK1  
 Anaplastic large-cell lymphoma, ALK2\*  
 Breast implant–associated anaplastic large-cell lymphoma\*

### **Hodgkin lymphoma**

Nodular lymphocyte predominant Hodgkin lymphoma  
 Classical Hodgkin lymphoma  
 Nodular sclerosis classical Hodgkin lymphoma  
 Lymphocyte-rich classical Hodgkin lymphoma  
 Mixed cellularity classical Hodgkin lymphoma  
 Lymphocyte-depleted classical Hodgkin lymphoma  
  
 Posttransplant lymphoproliferative disorders (PTLD)  
 Plasmacytic hyperplasia PTLN  
 Infectious mononucleosis PTLN

Florid follicular hyperplasia PTLN\*  
 Polymorphic PTLN  
 Monomorphic PTLN (B- and T-/NK-cell types)

Classical Hodgkin lymphoma PTLN  
 Histiocytic and dendritic cell neoplasms  
 Histiocytic sarcoma  
 Langerhans cell histiocytosis  
 Langerhans cell sarcoma  
 Indeterminate dendritic cell tumor  
 Interdigitating dendritic cell sarcoma  
 Follicular dendritic cell sarcoma  
 Fibroblastic reticular cell tumor  
 Disseminated juvenile xanthogranuloma  
 Erdheim-Chester disease\*

Provisional entities are listed in italics.  
 \*Changes from the 2008 classification.

### **APPENDIX 3: ANN ARBOR CLASSIFICATION AND THE COTSWOLD MODIFICATIONS**

<b>Stage</b>	<b>Features</b>
I	Involvement of a single lymph node region or lymphoid structure (e.g. spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
For all stages	
A	No symptoms
B	systemic symptoms: Fever (38 <sup>0</sup> C), drenching sweats, weight loss (10% body weight over 6 months); usually occurs in stage III and IV in 20 to 30% of patients.

For Stages I to III:

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

#### Cotswold modifications

Massive mediastinal disease has been defined by the Cotswold meeting as a thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography.

The number of anatomic regions involved should be indicated by a subscript (e.g., II<sub>3</sub>)  
Stage III may be subdivided into: III<sub>1</sub>, with or without splenic, hilar, celiac, or portal nodes; III<sub>2</sub>, with para-aortic, iliac, mesenteric nodes

Staging should be identified as clinical stage (CS) or pathologic stage (PS)

A new category of response to therapy, unconfirmed/uncertain complete remission (CR) can be introduced because of the persistent radiologic abnormalities of uncertain significance.

## **APPENDIX 4: ICD 10 CODES**

Malignant neoplasms of lymphoid, hematopoietic and related tissues

### **C81 Hodgkin Lymphoma**

C81.0 Nodular lymphocyte predominant HL

C81.1 Nodular sclerosis HL

C81.2 Mixed cellularity HL

C81.3 Lymphocyte depleted HL

C81.4 Lymphocyte rich HL

C81.7 Other HL

C81.9 HL, unspecified

### **C82 Follicular lymphomas**

### **C83 Non follicular Lymphomas**

C83.1 Mantle cell lymphoma

C83.3 Diffuse Large B cell Lymphoma

C83.7 Burkitt's lymphoma

### **C84.5 Mature NK/T cell Lymphoma**

## Appendix 5: KNH –UON ERC Approval



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Ref: KNH-ERC/A/350

2<sup>nd</sup> October 2018

Vusumuzi Ndumiso Tsabedze  
Reg. No. V60/74760/2014  
Dept. of Oral and Maxillofacial Surgery  
School of Dental Surgery  
College of Health Sciences  
University of Nairobi

Dear Vusumuzi

**RESEARCH PROPOSAL – CLINICAL PROFILE AND HISTOLOGICAL CHARACTERISTICS OF HEAD AND NECK LYMPHOMAS IN PATIENTS AT KENYATTA NATIONAL TEACHING AND REFERRAL HOSPITAL AND UNIVERSITY OF NAIROBI DENTAL HOSPITAL (P432/06/2018)**

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 2<sup>nd</sup> October 2018 – 1<sup>st</sup> October 2019.

This approval is subject to compliance with the following requirements:

- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
- c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
- e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
- f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
- g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

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For more details consult the KNH- UoN ERC website <http://www.erc.uonbi.ac.ke>

Yours sincerely,



**PROF. M. L. CHINDIA**  
**SECRETARY, KNH-UoN ERC**

- c.c. The Principal, College of Health Sciences, UoN  
The Director, CS, KNH  
The Chairperson, KNH-UON ERC  
The Assistant Director, Health Information, KNH  
The Dean, School of Dental Science, UoN  
The Chair, Dept. of Oral and Maxillofacial Surgery, UoN  
Supervisors: Dr. Elizabeth A.O.Dimba, Dr.Tom Mulama Osundwa, Dr.Kavin Wakoli, Dr. Jamilla A. Rajab

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## Appendix 6: Approval of Addendum



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8<sup>th</sup> April, 2019

Dr. Vusumuzi Tsabedze  
Reg. No.V60/74760/2014  
Dept. of Oral and Maxillofacial Surgery  
School of Dental Sciences  
College of Health Sciences  
University of Nairobi

Dear Dr. Vusumuzi

**Re: Approval of Addendum – Clinical profile and Histological characteristics of Head and Neck Lymphomas in patients at Kenyatta National Teaching and Referral Hospital and University of Nairobi Dental Hospital (P432/06/2018)**

---

Your communication of 28<sup>th</sup> March 2019 refers.

Upon review of your request, the KNH-UoN ERC has granted you permission to incorporate a retrospective arm into your research. Authority has also been granted to access files for patients with head and neck lymphomas from 2007 to 2017 at Kenyatta National Hospital and University of Nairobi Dental Hospital.

These changes are incorporated in the revised proposal and are acceptable.

Yours sincerely,

A handwritten signature in blue ink, appearing to be "M.L. Chindia", written over a circular stamp.

**PROF. M.L. CHINDIA**  
**SECRETARY, KNH- UoN ERC**

cc. The Principal, College of Health Sciences, UoN  
The Director, Clinical Services, KNH  
The Chairperson, KNH-UoN ERC  
The Dean, School of Dental Sciences, UoN  
Supervisors: Dr. Elizabeth A.O. Dimba, Dr. Tom Mulama Osundwa

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## Appendix 7 Originality report

Turnitin Originality Report

CLINICAL PROFILE AND HISTOLOGICAL CHARACTERISTICS OF HEAD AND NECK  
LYMPHOMAS IN PATIENTS SEEN AT TWO REFERRAL CENTRES IN NAIROBI,  
KENYA by Vusumuzi Ndumiso Tsabedze



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