Incidence of plasmablastic lymphoma in HIV positive and negative patients at a tertiary hospital in South Africa (2005-2017)

A mini-thesis submitted in partial fulfillment of the requirements for the degree of MSc (Dent) in Oral Medicine.

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III. KEYWORDS

Plasmablastic lymphoma

HIV

Tygerberg Hospital

IV. Abstract

Aim: The aim of the study was to investigate and describe the incidence of Plasmablastic Lymphoma (PBL) diagnosed at the Divisions of Anatomical Pathology and Haematopathology at Tygerberg Hospital from 2005 to 2017, and to ascertain a possible correlation with HIV infection, by identifying the number of HIV positive and negative patients diagnosed with Plasmablastic Lymphoma.

Method: This was a retrospective study using the case records of all newly diagnosed PBL patients from 2005 to 2017.

Results: Fifty-seven cases of PBL were diagnosed from 2005-2017. The overall result shows an increasing incidence of PBL in the intended period with the maximum incidence occurring in 2017. Most of the cases, 40.4%, were diagnosed in the age range 40-49-years. Forty-five patients were HIV-positive (78.9%) with (P value 0.011) and the majority of the patients were males (66.7%).

Conclusion: The study showed that there is an increasing incidence of PBL in the Tygerberg catchment area which is significantly associated with HIV positive patients.

V. DECLARATION

I, the undersigned, Hassan Elamin, hereby declare that the work contained in this dissertation titled; “Incidence of plasmablastic lymphoma in HIV positive and negative patients at a tertiary hospital in South Africa (2002-2017)” is my original work and has not been previously in its entirety or in any part submitted at any university for any degree or examination.

Hassan Elamin

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VII. DEDICATION

This thesis is dedicated to my Allah, my strength, my refuge and mine. Thank you, Lord, for your sincerity always.

To my wife and son; ***Amna*** *and* ***Yousif***, thank you so much for your love, support and understanding.

To my parents; **Elzain** and **Huda**, your immeasurable moral support through this journey are greatly appreciated.

Thank you.

VIII. LIST OF ABBREVIATIONS

NHL: Non-Hodgkin Lymphoma

HL: Hodgkin Lymphoma

PBL: Plasmablastic Lymphoma

HAART: Highly Active Antiretroviral Therapy

DLBCL: Diffuse large B-cell lymphoma

PCNSL: Primary Central Nervous System Lymphoma

HHV8: Herpesvirus-8

EBV: Epstein–Barr virus

BL: Burkitt Lymphoma

HIV: Human Immunodeficiency virus

AIDS: Acquired Immune Deficiency Syndrome

CHAPTER 1: Introduction

Lymphoma is a malignant tumor of the immune system. It is the second most common neoplasm found in the head and neck region in the wake of squamous cell carcinoma (Harnsberger *et al.,* 1987). The incidence of non-Hodgkin lymphoma is increasing in many regions and in the last 20 years the variation between different countries incidences increased up to 35 % (Walter *et al.,* 2015).

Lymphomas are generally classified into non-Hodgkin lymphoma(NHL) and Hodgkin lymphoma(HL), of which NHL comprises 90% of cases and 10% is HL (Walter *et al.,* 2015).

Worldwide, NHL is considered the tenth most commonly diagnosed malignancy and constitutes the seventh most diagnosed in the developed world (Ekström-Smedby 2006). In Sweden (2003), malignant lymphomas (NHL and HL) were the eighth most commonly diagnosed new cases of cancer among males and the tenth most common in females (Näsman *et al.,* 2009). In the USA however, NHL has risen to the fifth most common diagnosed malignancy (Näsman *et al.,* 2009).

In developing countries, the most common subtypes of NHL are diffuse large B-cell lymphoma (30%) and follicular lymphoma (20%) (Ekström-Smedby 2006). All other NHL subtypes have a frequency less than 10% (Jaffe 2001). The incidence in Brazil, India, Japan, Singapore, and Western Europe has also increased (Devesa and Fears 1992). A South African study reported an incidence rate of hematologic malignancies to be between 20–50% with NHL being the most common hematologic malignancy (Müller *el al.,*2005).

Studies have shown an increase in head and neck lymphomas over the years with the advent of HIV/AIDS (Brower 2011; Chetty *et al.*, 2012). NHL is known to affect 3–5% of individuals with HIV (Dolcetti *et al*., 2016); Vasudevan *et al*., 2016). The risk for developing NHL and HL is 60–200 times greater in HIV patients when compared to the 8–10-fold risk increase in the healthy population (Basavaraj *et al*., 2012); Gloghini *et al*., 2013). Oral NHL has been documented to have a more common incidence in patients with AIDS (Basavaraj *et al*., 2012) and although the incidence of Hodgkin lymphoma is increased in HIV, it is not seen as an AIDs-defining malignancy and not classified as an HIV related lymphoma (Chetty *et al*., 2012; Grewal 2015).

The head and neck is the second most frequent site for extranodal lymphomas after the gastrointestinal tract (Bussu *et al.,* 2013; Walter *et al*., 2015), with most of these cases occurring in the Waldeyer's ring (Regezi *et al*., 2008). With the pandemic of acquired immune deficiency syndrome (AIDS) particularly in developing countries, lymphomas have been shown to be responsible for 2% of oral neoplasms (Alli and Meer 2017).

1.1 Non-Hodgkin lymphoma in relation to HIV infection

HIV infection results in impaired cellular immunity, and therefore predisposes persons to develop neoplasms (Levine, 1994). As the lifespan of HIV-infected patients has increased, malignancies have become a known cause of morbidity and mortality in this population (Bräu *et al* 2007). Before the advent of highly active antiretroviral therapy (HAART), malignancies accounted for approximately 10 percent of HIV-related deaths. Since the routine implementation of HAART therapy, a cancer diagnosis is made in over 40 percent

of HIV-infected patients during the course of the HIV infection, and over 28 percent of HIV-related deaths are attributable to malignancy (Burgi *et al.,* 2005).

There are three AIDS-defining malignancies: Kaposi's sarcoma, non-Hodgkin lymphoma (NHL) of high-grade pathologic type and of B cell or unknown immunologic phenotype, and invasive cervical carcinoma (Shiels *et al.,* 2011).

Systemic NHL accounts for the great majority of AIDS-related lymphomas, while primary CNS lymphoma accounts for about 15 percent, and primary effusion lymphoma for less than 1 percent (Mantina *et al.,* 2010). Systemic NHL can be further be divided into common subtypes described in the World Health Organization (WHO) classification system. The most common systemic NHL subtypes seen in HIV-positive persons are: Diffuse large B cell lymphoma (DLBCL, approximately 75 percent); Burkitt lymphoma (approximately 25 percent); Plasmablastic lymphoma (less than 5 percent); T cell lymphoma (1 to 3 percent); and Indolent B cell lymphoma (less than 10 percent) (Guech-Ongey *et al.,* 2010).

The WHO 2008 classification of lymphoid neoplasms focused more on the pathological diagnostic approach in the classification however due to the recent molecular advances the 2016 WHO has incorporated the new genetic findings in the classification of lymphoid neoplasms. In the past, some studies have separated histologic subtypes into three general categories (highly aggressive, aggressive, and indolent) according to the usual clinical behavior of each of the lymphoid neoplasms (Levine *et al.,* 2002): Approximately 70 to 90 percent of AIDS-related lymphomas are highly aggressive and are almost exclusively the

immunoblastic variant of DLBCL and Burkitt lymphoma. Compared with the general population, the relative risk for highly aggressive lymphomas is increased more than 400-fold overall, and 650-fold and 260-fold for DLBCL and Burkitt lymphoma, respectively among patients with HIV. The aggressive lymphomas, predominately other variants of DLBCL, comprise about 20 percent of AIDS-related lymphomas. Compared with the general population, the relative risk is increased more than 110-fold for aggressive lymphomas (Dal Maso and Franceschi 2003). T cell lymphomas are uncommon in HIV disease. However, linkage of AIDS and Cancer registry data indicates an approximately 15-fold increase in these lymphomas in the HIV-positive population compared with the general population. They represented 2.6 percent of all HIV-associated NHL diagnosed at a large urban medical center between 1982 and 2001 (Arzoo et al., 2004). Multiple pathologic subtypes were seen.

While many NHL subtypes are seen in the general population,primary effusion lymphoma and plasmablastic lymphoma occurs predominantly in immunocompromised patients, particularly those infected with HIV. Plasmablastic lymphoma is estimated to be responsible for about 2.6 percent of HIV-related lymphomas (Carbone 2002).

Primary effusion lymphoma is one of the least common of the AIDS-related lymphomas, accounting for less than 5 percent of cases. Among patients with HIV, the incidence of primary central nervous system lymphoma (PCNSL) is 2 to 6 percent, but has been as high as 10 percent in an autopsy series in the pre-HAART era (MacMahon *et al.*, 1991).

In African countries, the WHO/IARC report showed that there is a higher incidence of

NHL and HL in Africa than Europe and North America (Globocan, 2012). According to (Oluwasola *et al.,* 2011), NHL is quite rare in most African countries; however, there is a higher incidence in North and sub-Saharan Africa due to the high number of BL cases in children in the tropical regions of Africa and the prevalence of HIV in sub-Saharan Africa (Oluwasola *et al.,* 2011).

Accurate histopathology diagnosis is critical for patient care and just as important for cancer registration and epidemiologic studies. In Africa, less than 50% of cancers are diagnosed using histopathology methods.

Plasmablastic lymphoma (3.6%) is only described in the studies utilizing the (2008) WHO classification. Less aggressive lymphomas like Follicular, Mantle Cell, MALT and Marginal zone lymphoma are much less frequently diagnosed in Africa. The rate of CLL/SLL is similar in all regions.

Abayomi *et al.,* (2011) and Wigge *et al.,* (2011) in South Africa reported an increase in the rates of DLBCL, Plasmablastic and Burkitt lymphoma with the increased incidence of HIV in South Africa. Alli (2016) found that over a 20year period from 1993-(2012), Plasmablastic lymphoma (159 cases) was the most common histologic subtype followed by diffuse large B-cell lymphoma (155 cases).

1.1.1 Risk factors

The risk of developing NHL in the setting of HIV increases directly with the level of immune system dysfunction. There are several multifactorial factors that increase the

incidence of AIDS-related malignancies. Furthermore, the different strains of HIV infection in Africa specifically have been attributed to the increased development of AIDS -related lymphomas in Africa (Pantanowitz *et al*. 2015). In addition, other viruses such as Epstein-Barr virus (EBV) co-infectionas well as HHV-8 are also involved in the pathogenesis of the subtypes of NHL (Armenian *et al.* 1996).

1.1.2 Effect of HAART

Although variable according to histologic subtype, the overall incidence of NHL was shown initially to decline with the widespread use of highly active antiretroviral therapy (HAART). However, the incidence of NHL in HIV seropositive patients remains above that of the non-HIV-infected population (Killebrew and Shiramizu 2004). Furthermore, while the incidence of AIDS-defining cancers decreased in the HAART era, the incidence of certain types of non-AIDS defining cancers, such as anal, lung, liver, and prostate cancers, as well as Hodgkin lymphoma, has increased, most likely reflecting prolonged survival of HIV-infected individuals in the HAART era (Petoumenos *et al.,* 2013).

Although a low viral load may be at least partially responsible, the most likely effect of HAART is the low proportion of patients with low CD4 levels, the group most likely to develop a high-grade NHL. Burkitts lymphoma, which can occur in those with relatively high CD4 counts, are being encountered with increasing frequency. The presenting clinical features of AIDS-related lymphomas are the same in the pre- and post-HAART eras.

1.1.3 B cell abnormalities

The hallmark of HIV infection is progressive loss of CD4 lymphocytes, but B cell dysfunction is also present as evidenced by abnormally low levels of antibodies to specific pathogens and a poor immune response to vaccines. Paradoxically, total serum levels of immunoglobulins are elevated, reflecting nonspecific polyclonal B cell activation (Moir and Fauci, 2009).

1.1.4 Genetic factors

HIV-infected patients who have the CCR5-32 deletion tend to have a more favorable prognosis with respect to the HIV infection; these patients also are less likely, by a factor of threefold, to develop an AIDS-related lymphoma. This protection, however, does not seem to apply to other AIDS-related neoplasms. It has been speculated that the reduced activity of CCR5 in those patients with the 32 base pair deletion results in a decrease in the mitogenic response to RANTES and, therefore, a lower risk of malignant transformation (Dean *et al*, 1999).

1.1.5 Family history

In the HIV-seronegative population, there is an elevated risk of lymphoproliferative disorders in those with a family history of such, particularly in a first-degree relative. This risk is presumed to apply to the HIV-positive population as well, although not yet demonstrated with clinical data (Wang *et al*., 2007).

1.1.6 HIV infection

It was previously thought that HIV does not infect the neoplastic cells of AIDS-related

lymphomas. (De Falco *et al*., 2003), however more recent studies show the direct involvement of HIV in the pathogenesis of lymphomas. Additionally, the Tat protein of HIV may be taken up by B lymphocytes, leading to deregulation of the oncosuppressor protein products of the pRb2/p130 gene. The Tat protein may also be active in the pathogenesis of tumors in the HIV-infected population by augmenting the angiogenic activities of bFGF and VEGF.

There have been new insights into the biology and management of both clonal proliferations with limited malignant potential, as well as the aggressive lymphoid neoplasms where more targeted and effective therapies are being investigated.

CHAPTER 2: Literature Review: PBL

2.1 Introduction

Plasmablastic lymphoma (PBL) is a rare subtype of non-Hodgkin lymphoma (NHL) (Delecluse, *et al.,* 1997). It has unique pathological and clinical features, such as the absence of CD20 expression, Epstein–Barr virus (EBV) positivity, characteristic oropharyngeal lesions, an aggressive clinical course, and a close association with human immunodeficiency virus (HIV) infection. The incidence of PBL associated with HIV has been estimated at approximately 2% of all lymphomas associated with HIV (Carbone and Gloghini, 2008). The estimated incidence of PBL is approximately 5% of all HIV-positive NHL cases (Gong *et al*., 2013) PBL cases in HIV-negative may arise from previously existing lymphoproliferative or autoimmune disorders (Castillo *et al*., 2015). This lymphoma is strongly associated with human immunodeficiency virus (HIV) infection with cases of co-infection together with human herpesvirus 8 (HHV8) and EBV reported (Lee *et al*., 2006). PBL has also been reported in older patients with associated immunosuppression due to their age and in patients who receive immunosuppressive therapy; however, cases of PBL have been reported in normal immunocompetent patients as well (Delecluse *et al.*, 1997).

As one of the acquired immunodeficiency syndrome (AIDS)- associated NHL, PBL case series have been reported since the 1990s. The aggressive nature of this malignancy, such as aggressive invasion into extranodal sites, rapid disease progression, and frequent relapse after remission suggests an extremely poor prognosis (Castillo *et al*., 2008; Castillo *et al*.,

2010; Castillo *et al*., 2012; Sarode *et al.,* 2010). The development of combination antiretroviral therapy (cART) has decreased the incidence and improved the prognosis of AIDS-related NHL, including PBL in western countries (Shiels *et al.,* 2011; Robbins *et al*., 2014). The incidence of AIDS- related NHL and the epidemiology of HIV infection and are slightly different in Japan from those in western countries. The number of HIV-1-infected individuals and patients with AIDS and multiple opportunistic diseases has been increasing continuously. It is disproportionately conspicuous from that in other industrialized countries. AIDS associated NHL is reported as one of the most difficult, life-threatening disorders in Japan (Nagai *et al.,* 2008).

Plasmablastic lymphoma (PBL), an aggressive subtype of NHL, is frequently seen in the oral cavity of patients with HIV. Since then, It has also been reported in other sites, which include the soft tissue omentum, lung, gastrointestinal tract, testes, nasal and paranasal regions, bones, bone marrow, skin, lymph nodes, and CNS (Chetty *et al.,* 2003; Schichman *et al.,* 2004). The frequency of oral involvement is higher in HIV positive (58%) than in HIV-negative patients (16%) (Castillo *et al.,* 2010). The peak of incidence for the oral and extraoral types occurs at 41 years (range 7–86 years) and 46 years (range 11–86 years), respectively, and both are more common in males (Raviele *et al.,* 2009).

2.2 Definition of PBL according to the WHO

Plasmablastic lymphoma (PBL) is a rare lymphoma often connected with immunosuppression [HIV] and frequently develops occurs in the oral cavity. It is also reported in patients who receiving immunosuppressive therapy; however, despite its

predisposition for the immunocompromised patients, PBL has also been diagnosed in patients with a competent immune system (Steven *et al*., 2018).

2.3 Epidemiology

PBL is primarily a disease of adults and affects men more than females. For the oral type, the M/F ratio is 5.7: 1 and 4: 1 for the extraoral type (Raviele, *et al*., 2009). There is a male preponderance among PBL patients, particularly the HIV-positive cases, with a mean age at presentation of 39 years in HIV-positive patients and 58 years in HIV-negative patients (Castillo *et al.*, 2008). PBL is very rare in children, with only five case reports in the literature (Castillo and Reagan. 2011).

The oral cavity is most frequently involved in the setting of HIV infection. Other extranodal sites can also be affected with a predilection for mucosal tissues. Additionally, it has been reported in HIV-negative persons, particularly those who have immunosuppression. In the last decade, several case reports and series have been published, accounting for 590 cases (Castillo *et al.,* 2015). PBL involving extraoral sites have been reported in several immunocompetent individuals (Morscio, *et al*., 2014).

PBL is rare and is said to account for approximately 2.6% of AIDS- associated lymphomas (ARLs) (Carbone and Gloghini 2008). The noticeable increase in published series and case reports could be a indication of an increased level of awareness of PBL among pathologists and clinicians (Bibas and Castillo, 2014). The actual incidence of PBL not associated with HIV infection has not yet been established. A review of 228 patients with PBL, 71 (31%) were HIV-negative and 157 patients (69%) were HIV-positive (Castillo et al., 2010).

Among the HIV-negative patients, 33% of the patients had some form of immunosuppression, often associated with solid organ transplantation or steroid therapy (Raviele, *et al*., 2009). The remainder of the HIV-negative patients were apparently immunocompetent. In a case series from Korea, no patients showed evidence of immunosuppression (Kim *et al*., 2009).

It is uncertain if there is an ethnic or racial predominance in PBL patients; cases have been reported in different populations from different continents (Castillo and Reagan 2011).

2.4 Pathogenesis

The pathogenesis of PBL is not well understood and is most likely concluded by the complexity of the biological pathways between HIV- associated immunodeficiency, co-infecting oncogenic viruses, molecular events, and chronic immune activation (Bibas and Castillo, 2014). It is suggested that ARLs may develop along four pathogenic pathways which involve EBV and HHV8 infection, p53, c-MYC, and BCL-6 gene irregularities (Carbone 2003). The contribution of HIV to PBL pathogenesis might develop through four predpminant mechanisms, namely, the degree and duration of immunosuppression or immunodeficiency, chronic B-cell proliferation and/or exhaustion due to chronic antigenic stimulation, loss of immune control of oncogenic herpes virus such as EBV, and a partial immune reconstruction or features unrelated to immune dysfunction (Montes-Moreno, et al 2010). Like to other ARLs, for example Burkitt lymphoma (BL) and immunoblastic and primary effusion lymphoma (PEL), PBL is strongly associated with Epstein-Barr virus (EBV) infection which is related to the prevention of B-cell apoptosis by many mechanisms

linked to EBV antigens (Castillo *et al*., 2015; Morscio, *et al* 2014).

EBV infection has been confirmed by the expression of EBV encoded RNA (EBER) (Castillo *et al.,* 2010). The association between PBL and HHV8 at this time is unclear. It has been suggested that Kaposi sarcoma-associated HHV8 plays a significant role in the pathogenesis of PBL and some studies have reported on the expression of HHV8-associated proteins in PBL (Cioc *et al.,* 2004; Verma *et al*., 2005); and a few other studies have not supported such an association (Teruya-Feldstein *et al.,* 2004; Brown *et al*., 2000). Furthermore, it is uncertain if these HHV8-associated PBL cases initiated from multicentric Castleman disease, placing them, ideally, in a different category (Isaacson *et al.*, 2008). On the basis of molecular, immunohistochemical and genetic studies, PBL most likely develops from terminally differentiated, post-germinal center active B-cells which are in transition from immunoblasts to plasma cells (Castillo *et al*., 2015).

During this process, chromosomal abnormalities most likely occur which are associated with the development of malignancy. Valera, et al (2010) have reported repetitive rearrangements involving MYC and the immunoglobulin gene; MYC gene rearrangements which involve the light chain genes and non-immunoglobulin genes have also been reported (Castillo *et al*., 2015). Nevertheless, it is not adequate to cause lymphoma, since decreased levels of the (8; 14)(q24; q32) have been identified in healthy persons by using extremely sensitive polymerase chain reaction (Janz *et al*., 2003). P16 gene hypermethylation has been reported (Arbiser *et al*., 2006), and in three separate reports, MYC upregulation by translocation between the MYC gene and immunoglobulin heavy

chain gene (MYC/IgH) was reported (Hassan *et al*., 2007). MYC translocations cells may allow PBL to escape from apoptosis. Along with the cell cycle defect caused by MYC translocations, the weakness of DNA in response to DNA, through the loss of p53,24 may also play a crucial role in causing the transformation of plasmablastic of low-grade lymphoproliferative B- cell disorders (Pasqualucci *et al*, 2014).

2.5 Histologic Findings

Often the histopathological features are equivocal, thus obtaining the correct diagnosis may be challenging. To obtain the correct diagnosis, evaluation of a tissue biopsy is necessary. The gold standard is an excisional biopsy, however, in a difficult to access site, a core needle biopsy and fine needle aspiration (FNA) may be completed in conjunction with suitable ancillary techniques for the differential diagnosis and diagnosis. PBL was first described as a specific clinicopathologic entity by Delecluse et al 1997 as an aggressive B-cell lymphoma which occurred in the oral cavity in the context of HIV infection and characterized histologically by sheets of plasmablasts with a sprinkling of plasma cells. In the years which followed, a spectrum of plasmacellular differentiation was introduced and currently is a common feature of PBLs that present outside the oral cavity (Hansra *et al.*, 2010).

The minimum histo-morphological criteria required to diagnose PBLs are a proliferation of monomorphic plasmablasts, which have centrally or eccentrically placed nuclei with a high nuclear-cytoplasmic ratio, a high mitotic index, moderate amount of eosinophilic cytoplasm, and the absence of neoplastic plasma cells in the background (Kane *et al*., 2009

Bibas and Castillo, 2014).

PBLs are characterized by a proliferation of large atypical cells with plasmablastic, immunoblastic, or plasmacytic morphological features. Eccentric nuclei with vesicular chromatin and a prominent central nucleolus or peripheral nucleoli. Mitotic figures and apoptotic bodies and tingible-body macrophages can be detected which result in a 'starry-sky' appearance. Often areas of necrosis can be seen together with smaller neoplastic cells with obvious plasmacytic differentiation (Delecluse *et al*., 1997; Stein *et al.,* 2008).

But, it must be noted that these histo-morphologic characteristics may also be seen in other neoplasms, namely, BL, PEL, plasmablastic PCM, DLBCL with plasmacytoid differentiation, and anaplastic lymphoma kinase- (ALK-) positive DLBCL which complicate the diagnostic process (Bogu sz *et al*., 2009).

2.6 Diagnosis

The histopathological and clinical features are usually unclear, thus rendering the correct diagnosis difficult. An integration of clinical, phenotypic, morphological, and molecular features is necessary. PBLs could become even more of a diagnostic enigma if the lesion is extraoral and presents in an immunocompetent patient. The differential diagnosis includes BL with plasmacytoid differentiation, immunoblastic DLBCL and other lymphoid neoplasms with plasmacytic features such as ALK-positive DLBCL, PEL both classic (body cavitybased) and solid (extracavitary) variants, and plasmablastic plasmacytoma/myeloma (Elyamany *et al.,* 2015). BL and Immunoblastic DLBCL may be omitted based on immunohistochemical stains and the characteristic immunophenotypic

pattern of PBL with CD20 negativity in combination with positive markers, CD138, of postgerminal center B-cells and plasma cells (Delecluse et al., 1997; Chetty et al., 2003). LCA and CD20 immunoreactivity is regularly depicted with BL and DLBCL and largely absent, but may be present in a small proportion of malignant cells in PBL. PBL is differentiated from ALK-positive DLBCL by the absence of ALK protein, and lack of HHV8 co-infection. This aids the dictinction between PBL and PEL. The distinction between plasmablastic PCM and PBL often depends on the clinical correlation (Chang et al., 2009). The detection of para-proteinemia in the blood and/or the excess of light chains, Bence Jones proteins in urine, hypercalcemia or anemia and lytic bone lesions supports the diagnosis of PCM over PBL. To distinguish PBL from plasmacytoma, the identification of a MYC gene rearrangement can be helpful as the MYC rearrangement in PBLs is rare.

The diagnosis of PBL can also be complicated by its morphologic similarity to myeloid malignancies particularly extramedullary myeloid tumors which can be omitted by the application of immunohistochemical studies of myeloid markers. Although there is a wide spectrum of differential diagnoses, the key differential diagnosis regarded is extramedullary plasmablastic myeloma. Although challenging, it is critical and clinically important to distinguish between these two neoplasms since treatment protocols differ drastically (Chang et al., 2009).

2.7 Broad therapy approach

Standard therapy has not yet been founded and PBLs remain a therapeutic challenge. Therapy generally involves chemotherapy with or without hematopoietic stem cell

transplantation and radiation (Saraceni *et al*., 2013). Various chemotherapy regimens including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), R-CHOP, and cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) are also possible options (Castillo *et al*., 2010 a; NCCN Practice Guidelines in Oncology 2010).

Individuals with a diagnosis of PBL whom do not receive chemotherapy ultimately die and have a median survival of 3 months (Castillo *et al*., 2010). The MYC gene translocation in some patients with PBL validates a more exhaustive assessment of more rigorous regimens. Due to the lack of CD20 expression, the use of the antiCD20 monoclonal antibody rituximab is of ambiguous value and is unlikely to be of value; however, it could be considered if fractional expression of CD20 is detected within these malignant cells (Bibas and Castillo, 2014). Although CHOP is frequently given as therapy for PBL (Castillo et al 2008, Casrillo *et al*., 2015), standard CHOP seems an inadequate treatment (National Comprehensive Cancer Network guidelines in Oncology 2014). Strengthening of initiation of chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT), which is thought to be a notable choice in HIV-negative patients with chemo-sensitive malignant disease, has also been shown to be possible in HIV positive patients (Dunleavy and Wilson, 2012; Al-Malki *et al.*, 2014). In the HIV positive group of patients, the addition of highly active antiretroviral therapy (HAART) also improved prognosis.

In a study of 70 patients with HIV-positive PBL who received chemotherapy, HAART was connected with a statistical inclination towards enhanced survival (Castillo et al., 2010).

Remarkably, HAART minus chemotherapy has been associated with spontaneous remission in some cases (Gilaberte *et al.,* 2005; Armstrong, *et al* 2007). The NCCN guidelines recommend against CHOP in favor of regimens such as infusion EPOCH, hyper CVAD, or CODOX-M/IVAC because of unsatisfactory therapeutic response and survival rates, (NCCN Practice Guidelines in Oncology 2010). However, Castillo and colleagues appraised therapy outcomes in patients receiving CHOP, CHOP-like, and other more intensive regimens and reported no statistical difference in the overall survival between the less and more intensive therapy regimens and only 25% of the patients reported in the scientific and medical literature were treated with more intensive regimens than CHOP (Castillo et al 2010a).

CHAPTER 3: Materials and Methods

3.1 Aim and objectives

3.1.1 Aim of study

To compare the incidence rate of Plasmablastic Lymphoma among positive and negative HIV patients, from 2005-2017, at Tygerberg Hospital**.**

3.1.2 Objectives

- To identify the number of HIV positive and negative patients diagnosed with Plasmablastic Lymphoma from 2005 to 2017.
- To classify the patients according to their age, gender

3.2 Study Design

This is retrospective cross sectional analytic record based study of a group of patients diagnosed with Plasmablastic Lymphoma.

3.3 Study setting

Divisions of Anatomical Pathology and Haematopathology, Tygerberg Hospital, Cape Town, South Africa. National Health Laboratory Services.

Tygerberg Lymphoma Study Group

3.4 Inclusion criteria

- Plasmablastic lymphomas diagnosed by morphological assessment, immunohistochemistry, flow cytometry and molecular technique.

3.5 Exclusion criteria

- Grey-zone' lymphomas and precursor lymphoid neoplasms were also excluded.

3.6 Methodology

A retrospective study of PBL cases diagnosed in the Division of Anatomical Pathology and Division of Haematopathology, Department of Pathology, National Health Laboratory Service, TAH. TAH is a 1380-bed tertiary referral academic hospital affiliated to Stellenbosch University and services approximately half of the total population of the Western Cape Province (total population of approximately 6.3 million people (Statistics South Africa 2016)). Cases were collected from 1 January 2005 to 31 December 2017; accessed from the ongoing Tygerberg Lymphoma Study Group database (HREC No: N07/03/068) established in 2007 in the Division of Haematopathology with the aim of documenting all lymphoma cases presenting at TAH (Abayomi, Somers et al. 2011). Patient data for this database was extracted from the DISA laboratory information system (DisaLab Version 04.16.04.373).

All relevant data was tabulated in three separate categories namely age, gender, and HIV-status. (appendex1)

3.7 Ethical consideration

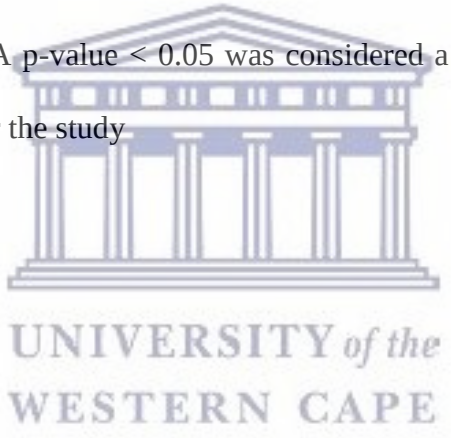
Cases that were collected form part of the ongoing Tygerberg Lymphoma Study Group database (HREC No: N07/03/068) established in 2007 in the Division of Haematopathology with the aim of documenting all lymphoma cases presenting at TAH

(Abayomi, Somers et al. 2011)

Approval of this specific study was obtained from the Biomedical Research Ethics Committee of the University of the Western Cape (ethical approval no: BM 18/3/9).

3.8 Data collection and statistical analysis

Type of lymphoma, biographical data, and relation to HIV was collected and recorded on a data collection sheet using MS Excel. Descriptive results were tabulated using frequencies, means and standard deviations. Statistical analysis was performed by means of comparisons and association analyses among data to evaluate if there are any statistically relevant associations or differences. A p-value < 0.05 was considered a significant difference. The Statistician was consulted for the study.



CHAPTER 4: Results

The results of this study are presented as tables and graphs. The demographic data of the 57 patients diagnosed with PBL during 2005 to 2017 are tabulated in Table 4-1 and the HIV status recorded according to the year Chi squire value = 60.7; P value = 0.011 < 0.05 significant (CI 95%). Of the 45 HIV positive cases the maximum number (6 cases) were reported in the years (2005), (2012), (2016) and 2017 and the minimum number (1 case) in the years (2009) and (2010). In the year (2008) no positive cases were reported (Table 4-5)

The majority of patients were in the age range of between 40-49 years in 23(40.4%) and the less common age group was less than 20 years at only 1(1.8%) patients (aged 12 years); summarized (Table 4-2). HIV status findings according to age group Chi squire value = 15.5; P value = 0.085 > 0.05 not significant (CI 95%).The maximum number of HIV positive cases, 16 cases, was reported among the patients in the age group 40-49 years and minimum number, 4 cases, was in the age group above 60 years. Patients that were less than 20 years of age were all HIV negative (Table 4-6).

The gender of patients with PBL were 38 males (66.7%) and 19 females (33.3%). Male to female ratio was 2:1 (Figure 3-2). HIV diagnosis findings according to gender Chi squire value = 1.15; P value = 0.207 > 0.05 not significant (CI 95%). Positive HIV diagnosis results reported in 29 males versus 16 cases of females; negative cases in males were 8 and in females were 2 cases (Table 4-7).

Table 4-1: Distribution of the cases according to year of diagnosis

Year of diagnosis	N	%
(2005)	7	12.3
(2006)	5	8.8
(2007)	4	7.0
(2008)	1	1.8
(2009)	1	1.8
(2010)	4	7.0
(2011)	5	8.8
(2012)	6	10.5
(2013)	3	5.3
(2014)	4	7.0
(2015)	3	5.3
(2016)	6	10.5
(2017)	8	14.0
Total	**57**	**100.0**

The Percentage of patients diagnosed with PBL ranged from 8(14%) in the year 2017 to 1 (1.8%) in the years 2008 and 2009.

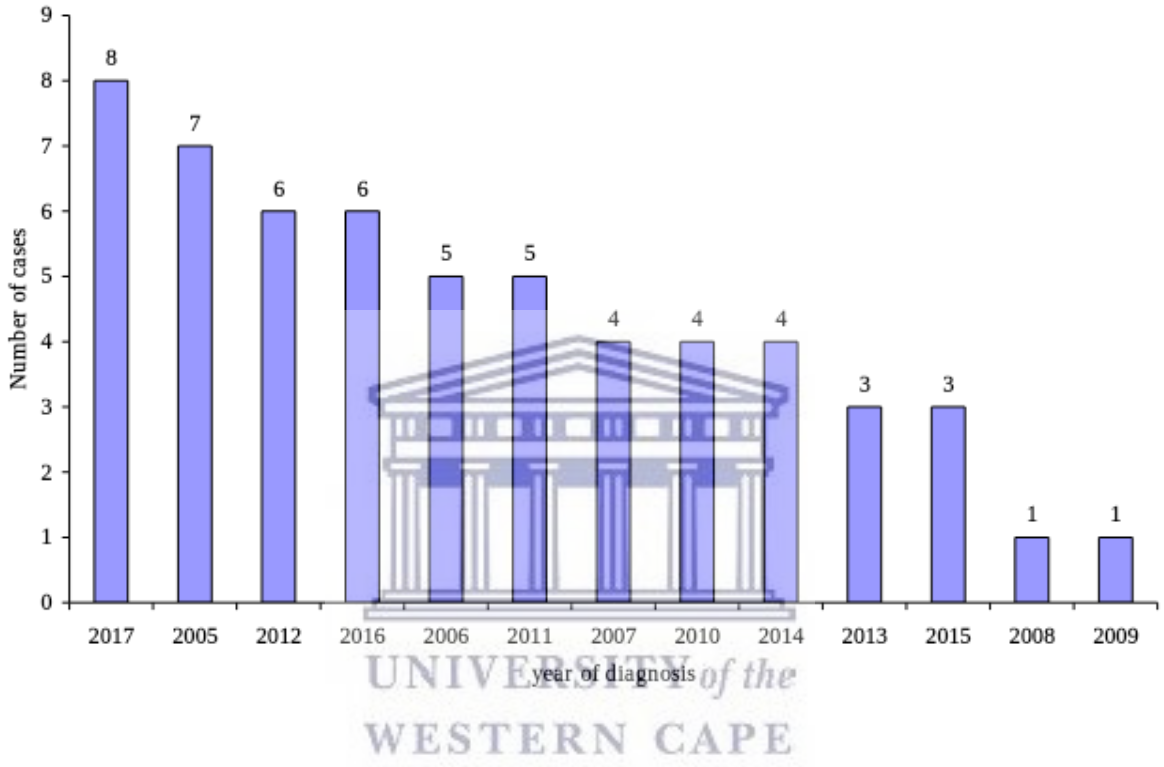


Figure 4-1: Distribution of the patients according to their year of diagnosis

Table 4-2 Distribution of patients according to age groups

Age group	N	%
< 20 years	1	1.8
20-29 years	7	12.3
30-39 years	14	24.6
40-49 years	23	40.4
50-60 years	7	12.3
> 60 years	5	8.8
Total	**57**	**100.0**

The commonest age group at diagnosis of PBL was the age group 40-49 years in 23(40.4%) of the patients and the less common was the age group less than 20 years which was only 1(1.8%) patients (aged 12 years).

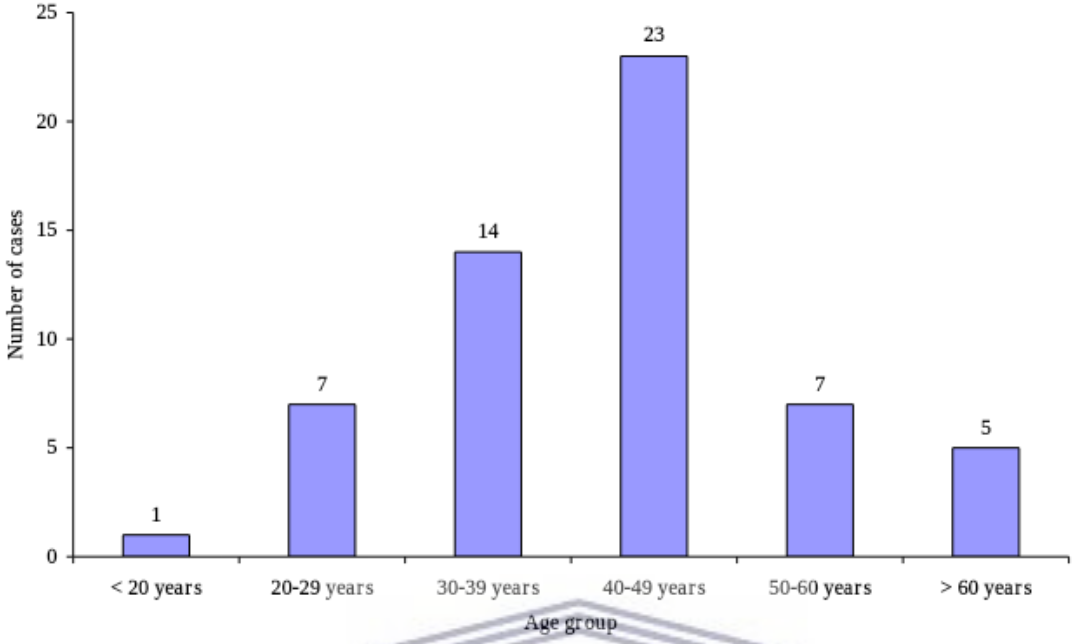


Figure 4-2: Distribution of the patients according to their age groups**.**

Table 4-3: Distribution of the cases according to gender

Gender	**N**	**%**
Male	38	66.7
Female	19	33.3
Total	**57**	**100.0**

Figure 4-3: 38 Patients were male (66.7%)19 were female were (33.3%). Male to female ratio was 2:1.

Table 4-4: Distribution of the cases according to HIV status

HIV diagnosis results	N	%
Positive	45	78.9
Negative	10	17.5
Unknown	2	3.5
Total	**57**	**100.0**

Patients with a positive HIV status cases were 45 (78.9%) and negative status were 10 (17.5%). Note that 2 (3.5%) patients had an unknown HIV status.

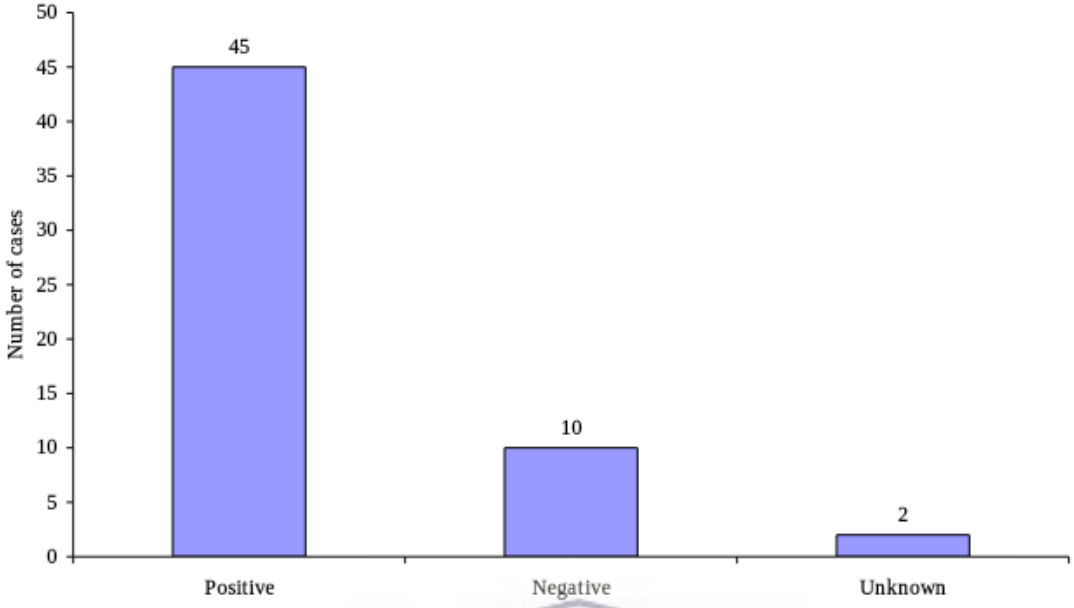


Table 4-5: Number of patients diagnosed as HIV positive and negative from 2005-2017

Year of diagnosis	HIV diagnosis results		
	Positive	**Negative**	**Unknown**
(2005)	6	1	0
(2006)	1	4	0
(2007)	4	0	0
(2008)	0	0	1
(2009)	1	0	0
(2010)	1	3	0
(2011)	5	0	0
(2012)	6	0	0
(2013)	2	1	0
(2014)	4	0	0
(2015)	3	0	0
(2016)	6	0	0
(2017)	6	1	1
Total	**45**	**10**	**2**

Chi squire value = 60.7; P value = 0.011 < 0.05 significant (CI 95%).

Out of the 45 HIV positive cases the maximum number (6 cases) were reported in the years (2005), (2012), (2016) and 2017 and the minimum number (1 case) in the years (2009) and

(2010). It should be noted that in the year (2008) no positive cases were reported.

Table 4-6: Patient HIV status in various age groups

Year of diagnosis	HIV diagnosis results		
	Positive	**Negative**	**Unknown**
< 20 years	0	1	0
20-29 years	5	2	0
30-39 years	14	0	0
40-49 years	16	6	1
50-60 years	6	1	0
> 60 years	4	0	1
Total	**45**	**10**	**2**

Chi squire value = 15.5; P value = 0.085 > 0.05 not significant (CI 95%).

The maximum number of HIV positive cases was (16 cases) reported among the patients in the age group 40-49 years and minimum number was (4 cases) in the age group above 60 years. The patient aged less than 20 years reported negative HIV result.

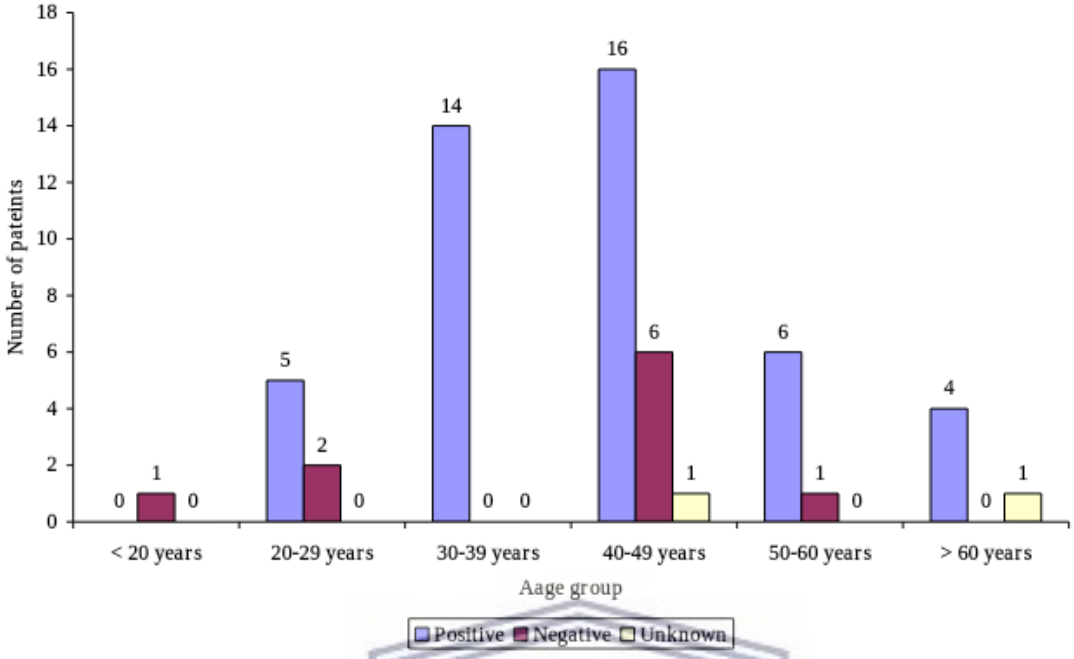


Figure 4-4: Patient HIV status in various age groups

Table 4-7: Patient HIV status according to gender.

HIV diagnosis results	Gender	
	Male	Female
Positive	29	16
Negative	8	2
Unknown	1	1
Total	38	19

Chi squire value = 1.15; P value = 0.207 > 0.05 not significant (CI 95%).

Positive HIV diagnosis results reported in 29 males versus 16 cases of females; negative cases in males were 8 and in females were 2 cases.

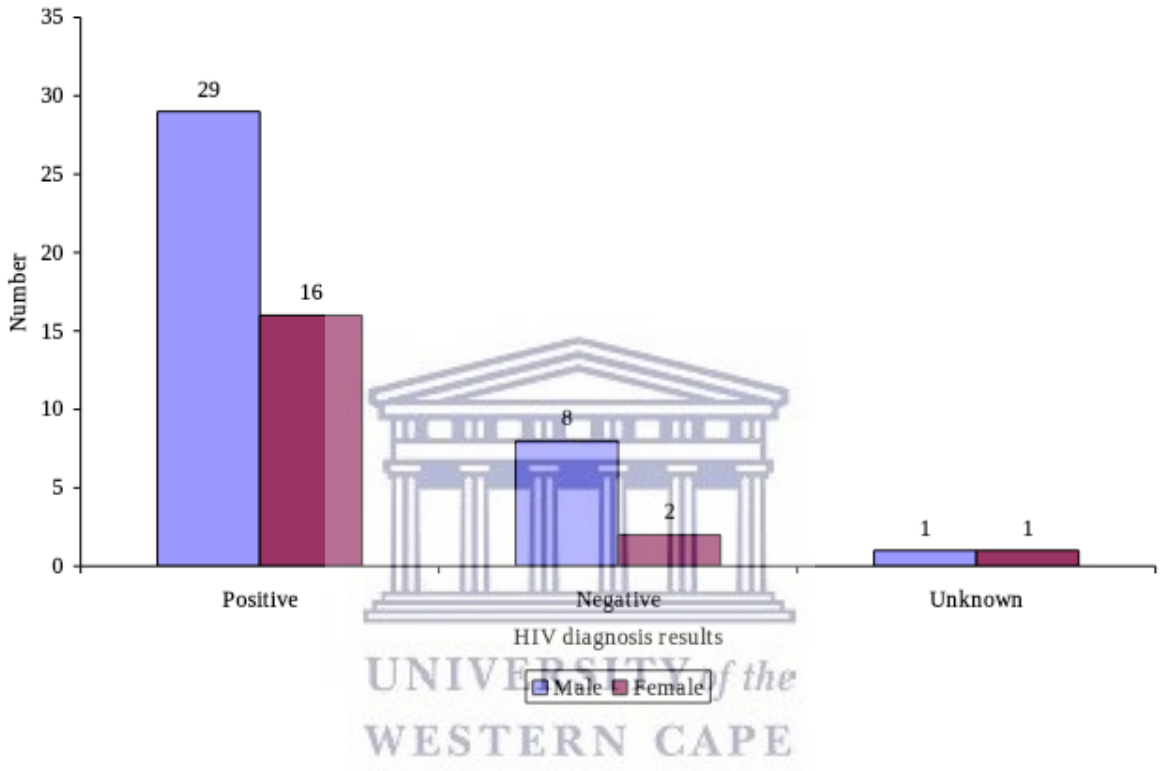


Figure 4-5: Patient HIV status according to gender.

CHAPTER 5: Discussion

PBL is a high-grade B-cell aggressive NHL cell initially diagnosed within the oral cavity of individuals with immunodeficiency, and it is estimated that the incidence of PBL accounts for approximately 5% of all HIV-positive patients with NHL (Choi et al., 2013). It is speculated that the HIV-negative PBL cases might derive from previous lymphoproliferative or autoimmune disorders and the incidence of HIV-negative PBL is still unclear. (Castillo et al., 2015).

In this study, 57 new cases of PBL at Tygerberg Hospital were diagnosed between 2005 and 2017. The peak incidence was in 2017, and the lowest was in 2008 and 2009, i.e. 8 patients (14%) and 1 patient (1.8%) respectively.

In terms of the incidence, 78.9% of the patients were HIV positive, correlating to published literature in developed and developing countries (Lee *et al*., 2006). Although NHL is considered rare in most African countries; there is a higher incidence in North and sub-Saharan Africa due to the high number of BL cases in children in the tropical regions of Africa and the prevalence of HIV in sub-Saharan Africa (Oluwasola *et al.,* 2011, Globocan, 2012). In 1976, Ibadan (Nigeria) reported one of the highest incidences of lymphoma cases globally, to the International Agency for Research on Cancer (Oluwasola *et al.,* 2011). Uganda also has a high incidence of reported number of cases HIV associated NHL (Tumwine et al, 2010), Onwubuya et al., 2015).

Several South African studies which have investigated PBLs, have shown 87% of PBLs occurring in HIV positive patients (Pather et al. 2013, Pather et al. 2015, Chetty et al. 2003).

A similar study at the same institution between 2002 and 2009 showed an increase in the incidence of all lymphomas. This included the rarer types such as PBLs and Burkitt lymphoma, in both HIV-negative and HIV-positive patients (Abayomi et al. 2011). This increased incidence is most likely the result of the roll-out of ART for HIV-positive patients in the public health sector in SA which only commenced in 2004. Another contributing factor might be urbanization due to migration of individuals from other parts of SA and from other African countries, to the Western Cape.

In the public sector, the initiation of ART in South Africa was implemented in patients with a CD4+ count of <200 cells/μL in 2004. This changed to <350 cells/μL in 2013 and then to <500 cells/μL in 2015 (Naidoo et al. 2018).

Commencement of ARTs did not have an impact on lymphoma frequency in the Western Cape (Chetty et al. 2012) which could be attributed to delay in beginning ART therapy, inadequate coverage, high viral loads, late presentation of the disease, socioeconomic factors such as lack of education and poverty, inaccessibility to health care facilities and the dependence of females on their partners.

In SA, by the end of 2015, ART coverage was 25% as opposed to the global trend of 46%. The remaining 75% of HIV positive individuals were at a higher risk of developing HIV associated lymphomas.

Infrastructure and compliance programs still need to be explored further, to ensure adherence to ART. There were new guidelines and policies of ART treatment launched by

the Western Cape government on 31 March 2017 (The Western Cape Government, 2016), where it is forecasted that the incidence of HIV will decrease by 60% in five years with a consequent decrease in HIV associated lymphomas such as PBL. The 2017 Adult Antiretroviral Therapy Guideline recommendation is to treat HIV-positive patients' independent of the baseline CD4+ count (Naidoo et al. 2018).

In a 20-year review in South Africa, Alli and Meer (2017) also showed that Plasmablastic lymphoma was the most common histologic subtype, seen more frequently as a result of its strong association with HIV/AIDS. The seeming increase in published series and case reports in the medical literature could be a reflection of an amplified awareness of PBL among clinicians and pathologists (Bibas and Castillo, 2014).

However, not all cases were linked to HIV and in this study, 17.5% of patients were HIV-negative. There are reports of a correlation between PBL and some forms of immunocompetent, i.e. organ transplant or patient on steroid therapy (Choi et al., 2014).

The definite incidence of PBL not associated with HIV remains undetermined (Castillo et al. 2011).

In this study, 38 (66.7%) were male patients and 19 (33.3%) were female. The male to female ratio was 2:1 which is analogous to published data comparable to many of previous studies from Tanzania (Mwakigonja *et al.*, 2010) and Nigeria (Onwubuya *et al*., 2015). This finding of a male predominance is paradoxical since between 2008 and 2012, a greater proportion of HIV positive females (34.7%) were receiving ART compared to males (25.7%) receiving treatment (Shisana et al 2012).

Sixteen patients were in the age range 40 – 49 years and 4 were above 60 years and all of these patients were HIV positive. The one patient that was less than 20 years was HIV negative. Of the 83 patients that were HIV positive in the Nigerian study (Onwubuya *et al*., 2015), the overall mean age of these patients was 41.7 years.

Study strengths and limitations

A strength of this study was the comprehensive laboratory information management systems at Tygerberg academic Hospital and the data collected over the period. This is a retrospective study design and the incomplete data on the HIV status of all the patients, proved a limitation. In addition, adequate data on the use of ART, was lacking. Data on patients that were diagnosed at other centers and subsequently referred to Tygerberg academic Hospital, were limited. The site of the primary tumor was not recorded.

Conclusion

The number of PBLs have increased over the years, is predominantly a malignant disease of adults, and affecting women less often than men. It is piquantly concomitant with HIV infection and, in this setting, the oral cavity is the most frequent site of involvement, but, other extranodal sites can also be affected in particular mucosal tissues. There is strong evidence that HIV plays a pivotal role in the pathogenesis of PBL however, the role of ART in lymphoma incidence in SA, is still unclear. The change in recent policy of ART availability to all HIV-positive patients' independent of CD4+ count suggests that patients will survive longer and are therefore at increased risk of developing PBL.

In SA, research is necessary in order to elucidate the oncogenic pathways involved in PBL. Further research is also necessary to profile the tumor at a genomic level in order to potentially improve the management and the prognosis of the patient.

This study also highlights the value of a regional as well as a national cancer registry which should ideally be linked to an HIV test result database for the monitoring of HIV-related malignancies such as PBL.

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4 Appendix 1

GROUP	AGE
A	0-9
B	10-19
C	20-29
D	30-39
E	40-49
F	50-59
J	60-69
H	70-79
I	80-89

Gender
Male
Female

HIV status
Positive
Negative
Unknown

5 Appendix 2

TYGERBERG LYMPHOMA STUDY GROUP (TLSG)
DIVISION OF HEAMATOLOGY
DEPARTMENT OF PATHOLOGY
MUTUAL DISCLOSURE AGREEMENT

Effective Date: 18 09 2017

In order to protect certain confidential information, TLSG, and the "Participant" (identified below) agree that:

1. **Disclosing Party:** The party disclosing confidential information ("Discloser") is both parties.
2. **Primary Representative:** Visiting party's representative for coordinating disclosure or receipt of confidential information is:
   Participant Name: HASSAN ELAMIN
   Company: UWC Dentistry
3. **Description of Confidential Information:** The confidential information disclosed under this Agreement is described as:
   TLSG and Division of Haematology, and their affiliate's and subsidiary's information including but not limited to data and details relating to TLSG database.
   Participant Confidential Information:
4. **Use of Confidential Information:** Confidential information shall not be disclosed to any third party and any party receiving confidential information ("Recipient") shall only make use of the confidential information.
5. **Confidentiality Period:** This Agreement and Recipient's duty to protect confidential information from disclosure will be for a period of three (3) years from the effective date of this agreement.
6. **Standard of Care:** Recipient shall protect the disclosed confidential information by using the same degree of care, but no less than a reasonable degree of care, to prevent the unauthorized use, dissemination, or publication of the confidential information as Recipient uses to protect its own confidential information of a like nature.
7. **Identification:** Recipient's obligations shall only extend to confidential information that is described in paragraph 3 and that is marked as confidential at the time of disclosure; or, is unmarked (e.g. orally or visually disclosed), but treated as confidential at the time of disclosure, and is designated as confidential in a written memorandum sent to Recipient's primary representative within thirty days of disclosure summarizing the confidential information disclosed.
8. **Exclusions:** This Agreement imposes no obligation upon Recipient with respect to information that: (a) was in Recipient's possession before receipt from Discloser; (b) is or becomes a matter of public knowledge through no fault of Recipient; (c) is rightfully received by Recipient from a third party without a duty of confidentiality; (d) is disclosed by Discloser to a third party without duty of confidentiality on the third party; (e) is independently developed by Recipient; or (f) is necessary to be disclosed in judicial or administrative process.
9. **Warranty:** Discloser warrants that it has the right to make the disclosures under this Agreement. NO OTHER WARRANTIES ARE MADE BY EITHER PARTY UNDER THIS AGREEMENT. ANY INFORMATION EXCHANGED UNDER THIS AGREEMENT IS PROVIDED "AS IS".
10. **Restrictions:** Regarding materials constituting confidential information, Recipient shall not analyze or permit a third party to analyze any such materials except as agreed to in writing signed by the provider of such materials. Recipient further agrees to abide by any restrictions or conditions respecting the export or

Page 1

reexport of technical information disclosed hereunder or the direct product thereof now or hereafter imposed by applicable governments.

11. **Rights:** Neither party acquires any intellectual property rights under this Agreement.

12. **Return of Confidential Information:** Recipient agrees to return all confidential information at Discloser's request, except that Recipient may retain, for its records, one confidential copy of such information for purposes of evidencing compliance with this Agreement.

13. **Miscellaneous:** (a) This Agreement imposes no obligation on either party to purchase, sell, license, transfer or otherwise dispose of any technology, services or products; (b) This Agreement does not create any agency or partnership relationship; (c) All additions or modifications to this Agreement must be made in writing and must be signed by both parties; (d) This Agreement is made under, and shall be construed according to, the laws of South Africa e) If the Participant signing this Agreement is representing a company, he or she represents and warrants that he or she has the authority to execute this Agreement on behalf of the company and that the Participant and all of its officers, directors, agents, and employees (and those persons holding similar positions with the company) will be bound by this Agreement.

PARTICIPANT

(Authorized Signature)

HASSAN ELAMIN

(Printed Name)

OF

(Title)

TLSG
DIVISION OF HAEMATOLOGY
DEPARTMENT OF PATHOLOGY
FACULTY OF MEDICINE AND HEALTH SCIENCES
STELLENBOSCH UNIVERSITY
TYGERBERG
7505

(Authorized Signature)

Prof Emmanuel Akinola Abeyomi on behalf of TLSG
(Printed Name & Title)

6 Appendix 3

DR GREWAL

MEMORANDUM OF UNDERSTANDING (MOU)

Between

Prof. Akin Abayomi
Head of Division
Division of Haematology Pathology
Stellenbosch University Faculty of Medicine and Health Sciences (SU FMHS)

and

Name and Title DR. HASSAN ELAMIN
Rank/Position DR
Division ORAL MEDICINE
Institution UWC - DENTISTRY

I. PURPOSE & SCOPE

1. The purpose of this MOU is to promote the development and maintenance of a sound and productive relationship between the two parties [insert Name and Title DR. HASSAN ELAMIN and the Principal Investigator of the Tygerberg Lymphoma Study Group (TLSG), Professor Akin Abayomi] by:

   - Providing a clear outline of the expectations of each party;
   - Clarifying from the outset the agreed roles and responsibilities of each party within the proposed collaboration between;
   - Ensuring a mutually productive collaboration

Title of project: INCIDENCE OF PLASMABLASTIC LYMPHOMA

Main Supervisor and division: PROF A. GREWAL TYGERBERG (NHLS)

Co-supervisors and division: DR. R. GREWAL

Ethics approval status: 2002 2016

Hospital approval status:

II. BACKGROUND

Prof Akin Abayomi in 2006 started a study group, which consisted of several divisions and departments, as he was interestrd in studying the impact of HIV on lymphomas. At the time, the group consisted of Prof Wright, HOD of Anatomical Pathology, Prof Jacobs, Head of Clinical Haematology, Dr Ravnit Grewal (registrar haematology) and Avril Sommers (medical

1

technologist]. The idea was to first construct a database where all lymphomas are documented retrospectively from 2002 and then once that was performed to the satisfaction of the team, prospective data would be collected for the purposes of studying lymphomas at our institution. This group over the years applied and received several grants including NIH, MRC and CANSA for this study. Since 2006 the database is continuously being refined and updated due to non-standardization in documentation of the different laboratory information systems used. In that regard there are several MMED studies within the division of Haematology pathology studying the various lymphomas. The staff members have also changed significantly over time.

Although there have been many divisions involved, the application for funding and responsibility for the administration and direction of this group has been done mainly by the staff hired and funded from grant funding within the division of Haematopathology.

The retrospective overall large study has the following ethics number:... N07/03/068 .... The prospective study has the following ethics no... N12/11/077.....

DR. HASSAN ELAMIN Incidence of Plasmablastic Lymphoma at Tygerberg 2002 - 2016

[Insert Title and Name] would like to study [title of project] at Tygerberg Hospital using the data that has been collected by the TLSG

III. RESPONSIBILTIES OF PROF. ABAYOMI *ET AL.* UNDER THIS MOU

Prof. Abayomi and/or his representatives shall undertake to:

- Provide access to TLSG database on
- Consult with the registrar to monitor the project

DR. HASSAN ELAMIN

IV. RESPONSIBILITIES OF [Insert Title and Name]. *ET AL.* UNDER THIS MOU

DR. HASSAN ELAMIN

[Insert Title and Name] and/or his representatives shall undertake to:

- Ensure to refine the current TLSG data base on **[insert lymphoma investigated]** PLASMABLASTIC LYMPHOMA
- Share the refined data on **[insert lymphoma investigated]** with the TLSG. PLASMABLASTIC LYMPHOMA
- Not to share the data with any other parties outside of the TLSG (excluding publication of the data by either conference presentation or scientific article)

2

V. IT IS MUTUALLY UNDERSTOOD AND AGREED BY BETWEEN THE PARTIES THAT:

a. There shall be no cost incurred for either party under the terms of this agreement

b. Any academic output shall be credited to all divisions that are part of the TLSG

c. Lymphoma diagnosis involves a long enquiry and is in fact considered intellectual property of the pathologists and therefore for any publication, the anatomical pathologist and a haematopathologist whose research interest area is lymphoma must form part of the publication. This concept is agreed upon by all Heads of the various disciplines in Pathology and has been discussed at a minuted meeting of the Pathology Research Committee where each representative of the various pathologies meets with the Dean of Research and the HOD of Ethics

d. Prof Abayomi, PI of the larger study or his delegated co-PI forms part of the publication with his interaction and acceptance.

e. Both parties agree that all data generated during study belongs to TLSG. Copies of all data (raw and analyzed) must be submitted to the TLSG on completion of the study

f. There are no additional studies to be conducted using this data.

g. The parties will be entitled to share in any financial benefits which may accrue to the TLSG as a result of this project

h. Should any patents emanate from this particular study, the TLSG and [Insert Title and Name] will register it DR. HASSAN ELAIMAN

VI.

EFFECTIVE DATE AND SIGNATURE

This MOU shall be in effect from (DD/MM/YYYY) 18.09.17to 18/09/18

Prof. Akin Abayomi

22/09/2017

Date

Dr. Hassan Elamin

[Insert Title and Name]

22/09/2017

Date

7 Appendix 4

TYGERBERG HOSPITAL
REFERENCE: Research Projects
ENQUIRIES: Dr GG Marinus
TELEPHONE NO.: 021 938 4762

Ethics Reference: 2016/08/098

TITLE: Impact of HIV on the incidence and pattern of lymphoma cases in the TAH, A 5year retrospective study to date.

Dear Prof A Abayomi

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 46/2002, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

4. Researchers in assessing Provincial Health Facilities, are expressing support to provide the National Health Research Department with an electronic copy of the final findings within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (HealthResearch@westerncape.gov.za)

DR GG MARINUS
MANAGER: MEDICAL SERVICES [RESEARCH CO-ORDINATOR]

DR D ERASMUS
CHIEF EXECUTIVE OFFICER

Date: 30/12/2016

TYGERBERG HOSPITAL

Ethics Reference: N07/05/068

TITLE: **Impact of HIV on the incidence and pattern of lymphoma cases in the TAH, A 5year retrospective study to date.**

BY _____
An authorized representative of Tygerberg Hospital

NAME _____
Dr P E Clapparelli
(021) 938 5883
Director

TITLE _____

DATE 30/11/2016