OROFACIAL MANIFESTATIONS OF BURKITT'S LYMPHOMA IN MALAWI

by

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ABSTRACT

Burkitt's lymphoma (BL) accounts for 40-50% of all childhood malignancies in Malawi. It is a highly aggressive, fast growing, mature B-cell non-Hodgkin's Lymphoma (NHL). It has one of the highest proliferation rates of any human tumour, with a doubling time of 24-48 hours making it the fastest growing human tumour. There are three forms of BL: endemic or the African form (eBL), sporadic or non-endemic form (sBL) and the immunodeficiency-associated form in HIV-AIDS. The African form most often involves the maxilla or mandible. The survival rate of a child with BL is dependent upon rapid diagnosis and treatment.

The purpose of this study was to determine the orofacial manifestations in children with BL in Malawi. It was anticipated that the findings may assist in the education of oral and other health care workers in the early recognition of BL for prompt referral. Oral health workers are a critical component of the referral chain since these lesions can be life threatening.

The present study was done in two parts: the first was a retrospective record-based study from 2005 to 2007 consisting of a sample of 661 cases suspected of BL and the second, a prospective study from June 2008 to October 2009 documenting 19 cases of suspected and confirmed cases of BL. A structured data capture sheet was used for data collection and a data capture sheet together with a short questionnaire collected information for the prospective study.

In the retrospective study, two thirds presented with BL at various sites of which the abdomen was the most common site. The 5 to 9 year age group predominated with an average peak incidence of 7 years and accounting for 60.0% of all the cases. The maxilla was the most common site for orofacial BL accounting for 13.7% followed by the mandible (7.2%), cheeks (5.7%), maxilla and mandible (4.5%) and cervical lymph nodes (4.1%). Of the 397 with BL, 41.4% were tested for HIV and 37.97% were HIV-negative while 5% were HIV-positive. There was a male preponderance with a ratio of male to female of 1.6 to1.

In the prospective study, females predominated with a male to female ratio of 1 to1.1 and the mandible was the most common site accounting for 19.04%. The age group 5-9 years predominated with 68.4% relative frequency. In both studies, Lilongwe predominated with orofacial BL cases. Initial findings at presentation were intraosseous mass, mobile or loose teeth, displaced teeth, cervical and/or submandibular lymphadenopathy, intraoral swelling, trismus, jaw deviation, Bell's palsy, salivation, gingival enlargement, bleeding tumour, ulceration, bony or soft tissue deformity, infected tumour causing halitosis and gingival growths. Difficulties with breathing, speech and eating was largely due to bilateral swelling of both the maxilla and mandible and in other cases unilateral swelling involving both maxilla and mandible.

Generally, the trend of BL had decreased from 2005 to 2007 possibly due to better access to health services, increased use of bed-treated mosquito nets for malaria prevention and knowledgeable healthcare workers. This study therefore re-iterates the need for all oral healthcare workers and other healthcare workers to be educated on the orofacial manifestations of BL for prompt referral, management. This would result in a better prognosis since BL is curable as it responds favourably to chemotherapy. The community also needs to be educated on the early signs and symptoms of BL and the importance of visiting a hospital as soon as possible.

DECLARATION

I, Jessie Mlotha, the undersigned, hereby declare that the thesis entitled "*Orofacial Manifestation of Burkitt's Lymphoma in Malawi*" is my original work and that it has not been previously in its entirety or in part submitted for any degree or examination at any other university, and that all the sources used or quoted have been indicated and acknowledged by complete references.

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Jessie Mlotha Date

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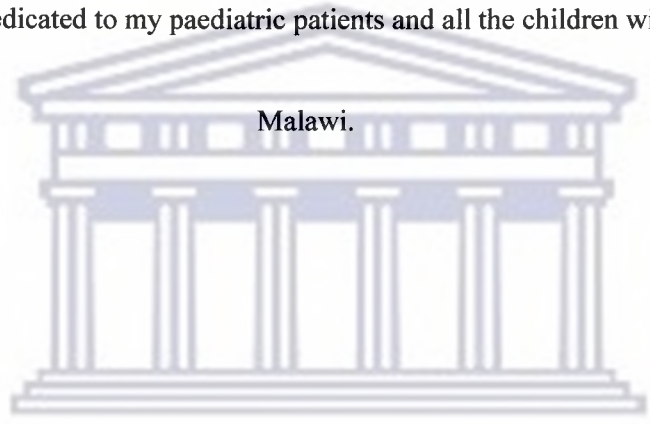
AIDS	Acquired immunodeficiency syndrome
ALL	Acute lymphoblastic leukaemia
Ara C	Cytarabine
BL	Burkitt's lymphoma
BMA	Bone marrow aspirate
CBC	Complete blood count
CHOP	Cyclophosphamide, Doxorubicin, Oncovin, Prednisone
CNS	Central nervous system
CODOX	Cyclophosphamide, Oncovin, Doxorubicin
COM	Cyclophosphamide, Oncovin, Methotrexate
CPM	Cyclophosphamide
CR	Cure rate
CT	Computed tomography
CTX	Cyclophosphamide
CXR	Chest x-ray
DOX	Doxorubicin
eBL	*endemic* Burkitt's lymphoma
EBV	Epstein-Barr virus
EFS	Event free survival
FBC	Full blood count
FNA	Fine needle aspirate
FNB	Fine needle biopsy
GC	Geminal centre
HAART	Highly active antiviral therapy
HC	Hydrocortisone
HIV	Human Immunodeficiency Virus
HL	Hodgkin's lymphoma
IL	Interleukin
IVAC	Ifosfamide, Vincristine, Ara C, Cyclophosphamide
KCH	Kamuzu Central Hospital
KS	Kaposi's sarcoma
LDH	Lactate dehydrogenase
LFT	liver function test
LMB	Leucovorin, Methotrexate, Bleomycin
LP	Lumbar puncture
MRI	Magnetic resonance imaging
MTX	Methotrexate
NCI	National Council Institute
NHL	Non-Hodgkin's lymphoma
O	Oncovin
OR	Odds ratio
P falciparum	Plasmodium falciparum
p	Probability
QECH	Queen Elizabeth Central Hospital
sBL	*sporadic* Burkitt's lymphoma
TB	Tuberculosis
US	United States
UWC	University of the Western Cape
VCR	Vincristine

DEDICATION

This work is dedicated to my paediatric patients and all the children with cancer in Malawi.



CHAPTER ONE

Introduction

Cancer is one of the major threats to public health in the developed and increasingly in the developing world. It is the second most common cause of death in the world (Peterson, 2005). Global epidemiology has shown that head and neck cancers constitute 5% and 50% of all cancers respectively and the orofacial region is a common site (Ajayi et al. 2007a). Oral cancer is a growing public health problem and is common in several regions of the world. Oral malignant neoplasms are the sixth common malignancy in the world, and when malignancy of the pharynx is included they are the third most common malignancy in the developing world (Ajayi et al. 2007a; Parkin et al. 1993).

Non-Hodgkin's lymphoma (NHL) refers to a group of malignant neoplasms that arise from cellular elements of lymphoid or extranodal tissues. Extranodal lymphomas are seen almost exclusively as NHL and account for 10% to 20% of all cases of NHL. They constitute about 35% of all intermediate- and high-grade NHL and 10% of low-grade NHL respectively (Ugboko et al. 2004). One of the commonest malignancies of the orofacial region is Burkitt's lymphoma (Kalyanyama et al. 2002) classified under non-Hodgkin's lymphoma.

Burkitt's lymphoma (BL) is a highly aggressive, fast growing, mature B-cell non-Hodgkin's lymphoma that is rare outside of Africa (Feinberg, 2007). In 1958, Denis Parsons Burkitt first described it as "rapidly growing jaw and abdominal lymphoid tumours in East African children" (Burkitt, 1958). According to Burkitt, it has a strict geographic distribution and occurs in zones where malaria is endemic (Greenberg, 2003). As with other tumours, the exact cause and mechanisms of BL are not known but there is evidence linking it to holoendemic malaria, the Epstein-Barr virus (EBV) and immuno-suppression in AIDS (Rainey et al. 2007; Huang et al. 2005).

BL accounts for 50% of all childhood malignancies in Malawi (Banda, 1995) and it is a major public health problem. The aggressiveness and doubling in size of a tumour within a short duration (24-48 hours) (Brady et al. 2007) can have life threatening consequences in the orofacial region. BL is also known to infiltrate dental tissues (Tsui et al. 2000). The survival of a child with BL depends on rapid diagnosis and treatment.

Diagnosis is primarily made on clinical diagnosis and confirmed by histological studies and immunophenotyping with flow cytometry. Knowledge of the presenting signs and symptoms is key to the diagnosis of BL.

It is anticipated that documentation of the orofacial manifestation of BL and knowledge of BL will assist the dental staff and other health care workers involved in the chain of referral to rapidly diagnose and make a prompt referral for treatment and better prognosis. Also the dental staff and other health workers will urge the patients and guardians to use bed-treated mosquito nets to prevent malaria and its transmission since malaria plays a role in the aetiology of BL.

CHAPTER TWO

Literature Review

2.1 Introduction

Lymphomas are malignant lesions that can arise from any type of lymphoid tissue but mostly from B-cells. They frequently involve the cervical lymph nodes but are rare in the mouth (Ajayi et al. 2007b). According to Hoffbrand et al. (2001), lymphomas are a heterogenous group of diseases caused by malignant lymphocytes which usually accumulate in lymph nodes and cause the characteristic clinical feature of lymphadenopathy. Occasionally, they may 'spill over' into blood ('leukaemic phase') or infiltrate organs outside the lymphoid tissue (Hoffbrand et al. 2001). They comprise Hodgkin's lymphoma (HL) and the more common non-Hodgkin's lymphoma (NHL). HLs arise from the lymphoid tissues whereas NHLs arise from cellular elements and extranodal sites. In the head and neck area, they involve the Waldeyer's ring while in the abdomen they involve the Peyer's patches (Greenberg et al. 2003). There are predisposing factors to NHLs which include gluten-induced enteropathy, AIDS, EBV, malaria, helicobacter infection and hepatitis-C infection (Hoffbrand et al. 2001). NHLs vary from highly proliferative and rapidly fatal diseases, to some of the most indolent and well-tolerated malignancies found in humans. These lymphomas are subdivided into low-grade and high-grade and with some falling into intermediate grade. Low-grade disorders are relatively indolent, respond well to chemotherapy and are very difficult to cure whereas high-grade lymphomas are aggressive and need urgent treatment but are often curable. Burkitt's lymphoma (BL) is an NHL of high-grade mature B cell lymphoma that doubles its size within 24-48 hours calling for rapid diagnosis, urgent referral and prompt treatment (Brady et al. 2007; Huang et al. 2005).

2.2 Historical Background

Burkitts lymphoma was first described in 1887 by Sir Albert Cook, a British missionary doctor working in Mengo, Uganda, in East Africa at the turn of the century, who noticed a common malignancy among young African children that predominantly affected the jaws and sometimes various abdominal organs (Orem et al. 2007; Burkitt, 1983; Adatia, 1966).

Half a century later, Denis Burkitt, a surgeon, working in Kampala, Central Africa noticed similar lesions and abdominal masses in children. Some presented with grossly distorted faces, with lesions involving one or both sides of the face and upper and lower jaws, sometimes accompanied by proptosis. He noticed that some children had huge abdominal masses, accompanied occasionally by disease in the facial bones, although there was usually no lymph node involvement. He published his findings in 1958, calling the lesion a 'sarcoma of the jaws' (Burkitt, 1958). With remarkable energy, undivided attention, limited resources and more than a sense of curiosity, he began to dwell on the

geographic distribution of the disease by embarking on a 10 000-mile safari (Burkitt, Nelson and Williams, 1963). He found that the incidence of the condition was directly related to the altitude of the location. With more information gathered from other parts of Africa, Haddow recognized that the disease is common in areas with a mean temperature over 60° F and rainfall over 20 inches/ year (Haddow, 1963). This lymphoma was found to occur throughout tropical Africa except at high altitudes or in areas where the climate was relatively cool. Occurrence was greater in areas with greater rainfall. These geographic and climatic associations suggested an association with falciparum malaria. The first hypothesis to explain the geographical distribution of the tumour was that it reflected the distribution of some vectored virus (Burkitt, 1968; Burkitt, 1963).

In 1961, Burkitt made the acquaintance of Epstein, an experimental pathologist, and shared samples of the lymphoma with him. Within these lymphomas, Epstein and colleagues isolated the virus from the Burkitts lesion known as Epstein-Barr virus (EBV); a pleiotropc virus, and was the first description of a virus involved in the pathogenesis of a tumor in humans (Epstein, Achong and Barr, 1964). The fact that between 80-90% of African cases of Burkitt's lymphoma contain multiple copies of EBV DNA genome (Olweny et al. 1977; Lindhal et al. 1974) and that most affected children had raised titres of EBV added credibility to the hypothesis. Furthermore, in the setting of the florid reactive lymphoid hyperplasia that occurs in response to malaria, it was proposed that EBV could be oncogenic. Although only limited chemotherapeutic agents were available at that time and in that place, an excellent response could be obtained, eventually attaining up to 80% long-term survival. In present-day Africa, BL continues to account for most childhood malignancies. A second form of BL is now found in Africa: HIV-associated Burkitt's lymphoma, occurring mainly in adults (Ferry, 2006).

2.3 Epidemiology

With time, it was recognized that BL could occur outside the African continent, but the prevalence was much lower than in Africa. These sporadic cases of BL are of identical histopathological appearance but differ in number of other aspects. In the *United States* (US), BL is a very rare form of cancer with about 100 new cases occurring each year. These sporadic BLs account for 1-2% of all adult lymphomas in the US and Western Europe (Feinberg et al. 2007). In *India,* a total of 1600 cases of childhood malignancies were seen in the year 2003 to 2006 with an average of 400 per year. 12.4 % of these were lymphomas both Hodgkin's and NHLs. BL comprised 9.1% of all lymphomas giving a total of 19 patients (Bosco et al. 2007). According to Patil et al. (2007), BL accounts for 0.76% of all solid malignant tumours among children in India (Patil et al. 2007).

BL is endemic in certain regions of equatorial Africa and other tropical locations between latitudes 10° south and 10° north. Incidence in these areas of endemic disease is 100 per million children (Huang et al. 2005). The endemic EBV-associated BL has an incidence of 5-10 per 100 000 children and accounts for 74% of childhood malignancies in African equatorial belt. It is most common in children

and in Africa, the mean age is 7 years and outside Africa it is 11 years. In *Tanzania*, a study showed that BL accounted for 88.2% of all malignancies in children (Kalyanyama, 2002), in *Nigeria* BL accounted for 53% of the malignant tumours in children and adolescent and affected more males than females at a ratio of 3:1 (Ajayi et al. 2007b).

Zimbabwe, although a country outside the BL belt, reported an age standardized incidence of 2.3 per million from 1990-94 as compared to *Malawi* with 27.6 per million from 1991-98, Uganda 36.1 per million from 1992-95, Nigeria 18.0 per million from 1985-92, 2.5 per million blacks US and 0.6 per million whites US from 1983-92 (Tables 1-3) (Banda et al. 2001).

In *Cameroon,* 27% of all malignant tumours in children were BL during the 3 year period from 1988 to 1992. Of the 39 children with BL, 15 were females and 24 were males, 18 tested EBV+, 25 had malnutrition. In 29 (74%) children, the Burkitt lesion was in the maxilla, 7 (18%) in the abdomen and 3 (8%) in other sites (Doumbe et al. 1997). In *Kenya*, BL accounted for 33.5% of all paediatric tumours while in some parts of Uganda, BL accounted for 50% of all paediatric tumours (Kalyanyama et al. 2002; Makata et al. 1996).

Malawi, like other African countries in the central and eastern region, has a high prevalence of childhood malignancies of which BL constitutes 40-50% (Banda et al. 2001; Banda, 1995). Concomitant with malignancies other features of BL include low birth weight, high infant and under-five mortality rates due to malaria, severe anaemia, malnutrition, neonatal sepsis, HIV/AIDS, meningitis and pneumonia (WHO, 2006). The large majority of children with BL come from rural areas where there are no facilities for its management. BL has one of the highest cell proliferation rates of any human tumour, doubling time of tumour is 24-48 hours making it the fastest growing human tumour (Brady et al. 2007). In this regard, it is imperative considering the aggressive nature of the tumour, that all health care workers are familiar with the orofacial manifestations of BL to expedite early detection and prompt referral to central hospitals (tertiary level care) for management.

Table 1: Standardised incidence rates for NHL (Malawi, other African countries and USA)

			East Africa			West Africa		USA
			Malawi	Zimbabwe	Uganda	Mali	Guinea	SEER
			1994-98	1993-95	1995-97	1988-92	1992-95	88-92
	Site	Gender	Blantyre	Harare	Kampala	Bamako	Conackry	Black
	Oesophagus	M	15.4	19.6	13	1.7	0.6	13.8
	Oesophagus	F	9.3	9.5	14.2	0.8	0.8	3.9
NHL		M	4.3	4.5	7.4	2.6	2.3	12.3
NHL		F	3.3	3.8	5.7	0.4	1.3	7

Source: Banda et al. 2001

Table 2: Childhood cancer (age standardised incidence per million) in Blantyre and in other registries in Africa and the USA

Region	East Africa			West Africa		USA	
Country	Malawi	Zimbabwe	Uganda	Nigeria	Mali	SEER	SEER
City	Blantyre	Harare	Kampala	Ibadan	Bamako	White	Black
Cancer type	1991-1998	1990-1994	1992-1995	1985-1992	1987-1995	1983-1992	1983-1992
Leukaemia	0.7	23.1	10.6	8.3	3.1	46.9	29.4
Lymphoma	37.7	12.5	52.9	27.1	17.2	15.1	10.6
Burkitt's lymphoma	27.6	2.4	36.1	18.0	1.7	2.5	0.6
Brain	0.4	12.0	2.3	11.1	1.4	31.8	27.4
Neuroblastoma	0.0	4.0	1.0	0.2	0.0	12.8	9.6
Retinoblastoma	6.2	10.5	11.1	7.4	24.5	4.9	5.3
Wilms' tumour	5.2	16.5	8.0	4.9	12.2	10.1	8.8
Kaposi's sarcoma	7.6	10.6	67.5	0.0	0.0	0.0	0.0

Source: Banda et al. 2001

Table 3: Cancers in children aged 0-14, Blantyre, Malawi, 1991-1998

Cancer type	Number of cases				Relative frequency (%)		Rates (per million)		
	0-4 y	5-9 y	10-14 y	All	M	F	Crude	ASR	% M.V.
Leukaemia	0	2	0	2	1.0	1.2	0.8	0.7	50
Lymphomas	15	60	23	98	1.8	57.6	38.9	37.7	71.4
Burkitt's lymphoma	12	49	11	72	2.0	42.4	28.6	27.6	68.1
CNS	0	1	0	1		0.6	0.4	0.4	100
Neuroblastoma	0	0	0	0					
Retinoblastoma	13	2	0	15	0.7	8.8	6.0	6.2	100
Wilms' tumour	7	6	0	13	1.2	7.6	5.2	5.2	92.3
Bone tumours	0	0	3	3	2.0	1.8	1.2	1.2	33.3
Connective tissue	4	1	2	7	0.4	4.1	2.8	2.8	85.7
Kaposi's sarcoma	7	5	7	19	1.7	11.2	7.5	7.6	78.9
All	48	81	41	170	1.4	100	67.4	66.5	76.5

Source: Banda et al. 2001

It can be seen from Table 1 that NHLs have a male preponderance and this is also true for BL in most studies of childhood malignant cancers in Africa. Some studies even showed a male to female ratio of 8:1 in Ajayi et al. 2007a. On the contrary, in Table 3, the relative frequency of BL for males and females was 2.0% and 42.4% respectively. According to Ajayi et al. (2007a, b), BL occurred mostly in the first decade of life and maxilla was the most predominant site.

2.4 Pathological features

Burkitt's lymphoma (BL) is a highly aggressive, fast growing, mature B-cell non-Hodgkin's Lymphoma (NHL). There are three forms of BL: endemic or the African form (eBL), sporadic or non-endemic form (sBL) and immunodeficiency-associated form in HIV-AIDS. The African form most often involves the maxilla or mandible. The involvement of abdominal organs such as the kidneys, ovaries, or retroperitoneal structures, is slightly less common. In contrast, the sporadic form usually involves abdominal organs, with the most common involvement of the distal ileum, cecum, or mesentery and less common involvement of other abdominal organs, pelvic organs, and facial bones (Brady et al. 2007; Huang et al. 2005, Goldenberg, 2001).

Diagnosis of BL is mainly by clinical examination and partly by different investigations, but the type of test or investigation depends to a large extent on the time and cancer site or type. According to Souhami et al. (2003) diagnosis is made by removing an enlarged lymph node or part of it, and examining the cells under a microscope (biopsy). Biopsies may also be taken from other body tissues. Additional tests include blood tests, x-rays, scans, lumbar punctures and bone marrow samples which are used to give more information about the type of lymphoma and how far it has spread in the body. This information is also useful in deciding the appropriate treatment to apply (Souhami et al. 2003; Hancock et al. 2000).

"Bone marrow aspiration or biopsy is essential for every patient with BL because frequent presence of unexpected bone marrow involvement has important implications for treatment planning. Paracentesis or thoracentesis is needed for cytogenic studies if ascites or pleural effusion is present. Head or spinal CT scan or MRI is indicated if neurologic signs and symptoms are present. Abdominal CT scan or ultrasound scan is required to evaluate the extent of disease such as involvement of retroperitoneal and mesenteric lymph nodes, liver, kidneys, ovaries and other structures. Chest x-ray (CXR) is necessary to rule out lung metastases and mediastinum involvement. Chest CT may be performed if CXR is abnormal. General laboratory studies should include Full blood count and differential counts, electrolytes, uric acid and creatinine. Bone scan and plain bone radiographs are needed for patients with symptoms of bone involvement" (Huang et al. 2005).

2.5 Causes of Burkitt's Lymphoma

Burkitt lymphoma has been directly associated with Epstein-Barr virus (EBV) and indirectly with prevalence of malaria (Carpenter et al. 2008). Carpenter et al. (2008) in a case control study in Uganda found that cases were 5 times more likely than controls to have raised levels of both EBV and malaria antibodies (OR = 5.0; p = 0.003), suggesting that EBV and malaria may act synergistically in the pathogenesis of childhood Burkitt lymphoma.

2.5.1 Epstein-Barr Virus (EBV)

EBV is a human lymphotrophic herpes virus that was named after Tony Epstein and Yvone Barr in 1964. It is a member of the herpesviridae family. The EBV genome is a linear double-stranded DNA of 172 kbp and was the first herpes virus genome to be completely sequenced. It has a narrow tissue tropism limited to B cells and epithelial cells of primate origin. It can immortalize B cells both in vitro and in vivo (Brady et al. 2007). Although the causes of BL are not clearly known, there is ample evidence supporting the association of EBV with the African BL form, while the relationship is less clear in the sporadic form. However, EBV is associated with about 20% of sporadic cases.

The lymphocytes have receptors for EBV and are its specific target. In the African form, the hosts are believed to be unable to mount an appropriate immune response to primary EBV infection, possibly because of coexistent malaria or another infection that is immunosuppressive (Huang et al. 2005; Goldenberg, 2001). The host is unable to generate an adequate T-lymphocyte response (ie. EBV-specific cytotoxic T cells) against B cells that are heavily infected latently with EBV. This subsequently results in excessive B cell proliferation. It has been known for many years that the fundamental transforming event in BL is the translocation of the *c-myc* gene, and the events that bring about this translocation and those that allow cells to survive with the constitutive expression of *c-myc* gene have been the subject of intense investigation (Brady et al, 2007). Epstein-Barr virus (EBV) infection, malaria, immunodeficiency and spontaneous, somatic mutation can all contribute to the origin and maintenance of BL. Generally in all three variants, the *c-myc* oncogene is activated via a specific chromosomal translocation that results in disordered cell proliferation (Feinberg, 2007). In 90% of all cases of BL, the proto-oncogene *c-myc* is translocated from its normal position on chromosome 8 to a location close to the enhancers of the antibody heavy chain genes on chromosome 14. In all other cases, *c-myc* has been translocated close to the antibody light chain genes on chromosome 2 or 22. In every case, *c-myc* is in a region of vigorous gene transcription. Overproduction of the *c-myc* product may change lymphocytes into neoplastic cells (Huang et al. 2005).

2.5.2 Malaria

The role of malaria in the pathogenesis of BL was first suggested by Dalldorf (1967), who observed that intense and persistent malarial infection resulted in hyperplasia of the lymphoreticular system. He postulated that, under these circumstances, the EBV might be oncogenic (Tsui et al. 2000; Dalldorf, 1967). According to Brady et al. (2007), the role of malarial infection in the pathogenesis of eBL is clear for the geographical co-incidence of the two diseases. It is generally thought the association between malaria and BL varies from a combination of immunosuppression and B cell activation. For example, cytotoxic T-cell mediated control over the outgrowth EBV-infected B cells is impaired during acute malaria infection and it has been found that peripheral EBV loads may be five times higher during acute malaria compared to levels observed during convalescence or in healthy individuals. EBV loads are generally higher in areas of holoendemic malaria compared to areas where malaria is sporadic and shows increased persistence in children with a history of severe rather than mild malaria possibly owing it to higher viral activation. However, eBL also develops at a later age in individuals who have migrated from malaria-free high altitude areas to lower, malaria-endemic areas (Brady et al. 2007).

In keeping with the above findings, it has also been found that the malarial parasite Plasmodium falciparum can directly activate B cells via a cystein-rich interdomain region 1α (C1DR1 α) on the P falciparum erythrocyte membrane protein 1 (PfEMP1) which binds to surface Ig. The activation of B cells by C1DR1α and subsequent protection from apoptosis has been postulated to play a role in enhancing survival of Germinal Centres (GC) B cells bearing oncogenic mutations (Lyke et al. 2004). In addition, with the activation of B cells, it is possible that proliferation of B cells is enhanced by IL-10. Serum levels of this cytokine are raised in children suffering from acute P falciparum malaria compared to healthy controls (Brady et al. 2007; Lyke et al. 2004).

It is also important that nearly all the epidemiological characteristics of Burkitt's lymphoma (BL) can be explained on the basis of relationships of BL to the intensity of the host response to Plasmodium falciparum. The major epidemiological associations are: the high degree of geographic correlation between the incidence rate of BL and the intensity of P. falciparum transmission, both at a global level and within individual countries; the close correlation between the age incidence of BL and the age of acquiring maximum levels of antimalarial immunoglobulin; the relative protection from BL by residence in urban areas, where levels of malaria transmission are lower, compared with rural areas; the decline in BL incidence in areas where death rates due to malaria have declined and, within such areas, a differential decline in BL incidence in people making better use of health facilities; the older age of onset in patients who have migrated from low-intensity to high-intensity malaria areas as compared with patients born in the high-intensity areas - the higher absolute age-specific incidence rate in those above age ten in this immigrant group being consistent with the hypothesis that intense

malaria infection and consequent host defence response serve as the major triggering event in the pathogenesis of the lymphoma; the inverse geographic correlation between the average age of onset of BL and the intensity of falciparum malaria infection.

An inverse association of BL with sickle-cell trait (AS haemoglobin) would provide strong evidence for the role of intense falciparum malaria, but most studies to date have not achieved statistical significance. Time-space clustering and reports of seasonal variation in BL incidence would indicate that a precipitating factor operates over a relatively short time-span, at least in some areas. Combining the evidence concerning cytogenetics, Epstein-Barr virus (EBV) and falciparum malaria, the following three-phase model for the oncogenesis of BL could account for virtually all the currently known facts and be tested by further laboratory and field studies: Primary infection with EBV, perhaps early and intense, leads to the immortalization of large numbers of B lymphocytes. Severe falciparum malaria then leads to an intense host response with particular proliferation of the EBV-infected B lymphocytes. Finally, the great increase in the B lymphocytes provides a much higher statistical opportunity for the emergence of the cytogenetically abnormal BL cell (Morrow, 1985).

Rainey et al. (2007) did a study to determine if the strong relationship between BL and malarial transmission still stands. They found a positive trend between BL incidence rates and malaria transmission intensity, supporting an aetiological role of malaria in BL oncogenesis. However lack of tribal association in this study strengthens the role of environmental rather than genetic factors on BL incidence as reported in other studies (Rainey et al. 2007).

However, a recent study in Uganda has shown that BL is directly associated with EBV and indirectly with prevalence of malaria. The use of antibodies against malaria and EBV in this study, suggests that EBV and malaria may act synergistically in the pathogenesis of childhood BL. They further recommended malaria prevention measures as a way to prevent this childhood cancer (Carpenter et al. 2008).

2.5.3 HIV and AIDS

The incidence of lymphoma in patients with HIV infection greatly exceeds that of the general population. It may be the first indication of HIV infection (Mukerji and Hilfer, 1993). The increased risk for lymphoma appears to be related to multiple factors, including the transforming properties of the retrovirus itself, the immunosuppression and cytokine dysregulation that results from the disease, and most importantly, opportunistic infections with other lymphotrophic herpes viruses such as Epstein-Barr virus and human herpesvirus 8 (Blinder et al. 2008; Grogg et al. 2007)). Rare adult cases have been reported to occur and are often associated with immunodeficiency, particularly HIV-AIDS (Mwanda, 1999).

Immunodeficiency-associated BL occurs mainly in patients infected with HIV, but also occurs in allograft recipients and individuals with congenital immunodeficiency. In the early years of the AIDS epidemic, BL cases were described in homosexual men and were the first descriptions of NHL arising in association with HIV infection. More recent literature indicates that BL accounts for 30% to 40% of NHL in HIV sero-positive patients (Ferry, 2006). NHL was one of the first cancers identified as being AIDS-related (Beral et al. 1998) but African studies suggest that the risk associated with HIV is very much lower than in Europe and North America (Newton et al. 1995). However, the incidence of NHL is not high at least in comparison with the US, and a substantial proportion of NHL is BL, which is largely confined to childhood age group. Furthermore, a recent study in Uganda has reported that the risk of this cancer is not influenced by HIV infection (Parkin et al. 2000). In addition to this, Malawi has long been known to be an area of endemic BL since late 1960s (Banda et al. 2001; McGlashan, 1969).

Prior to the advent of highly active antiviral therapy (HAART), BL was estimated to be 1000 times more common in HIV sero-positive individuals than in the general population (Ferry, 2006). HIV-associated BL shares some pathogenic features with eBL. HIV infection in this case is analogous to malaria disease because it leads to polyclonal B cell activation, and permits poorly controlled proliferation of EBV^+ B cells. The genetic instability of the $EBV^{+/-}$ aberrantly regulate B cells and lead to a greater risk of c-myc rearrangement, and then to lymphoma (Ferry, 2006).

In a series of 399 patients with AIDS who presented with head and neck manifestations, 8% presented with BL as a rapidly enlarging neck mass. Unlike other HIV-associated lymphomas, however, BL tends to occur in patients whose CD4 counts exceed 200/ mm^3. These patients like those with sBL typically present with extranodal disease that most commonly involves the abdomen (Feinberg et al. 2007).

According to Brady et al. (2007) BL occurs in HIV carriers where tumours can develop prior to the severe immunosuppression coincident with the onset of AIDS. Approximately 30% of such AIDS-associated tumours are EBV^+ (Brady et al. 2007). Also, HIV has been shown to drive B-cell proliferation and protect B cells from apoptosis. Furthermore, it has been shown to induce the production of cytokines such as interleukin (IL)-6 and IL-10 that drives the proliferation of B cells (Brady et al. 2007).

In a separate study in Malawi, Sinfield et al. (2007) showed that the impact of HIV epidemic still remains uncertain on the risks of cancers other than Kaposi's sarcoma (KS) and non-Burkitt NHL. However, it showed that in cases of KS, NHL and BL, there appeared to be a significant difference in the presentation of HIV sero-positive and sero-negative children whereby a total of 351 BL cases were determined. Of these, 278 children were HIV sero-negative, 62 children's sero-status was not known

while 11 were HIV sero-positive. 3 of the HIV sero-positive children presented with the disease at unusual sites such as knee, brain and inguinal lymph nodes as compared with 14 (5%) of HIV sero-negative with the commonest sites in the face or cheek (150 cases), the abdomen (86 cases) and the orbit (24 cases) (Sinfield et al. 2007).

"Immunosuppression is probably part of the mechanism of HIV-associated BL, but this can develop prior to the severe loss of immunity characteristic of AIDS, suggesting that severe immunosuppression is not a prerequisite for BL development. Additionally, EBV-associated tumours in post-transplant patients, in whom immunosuppression is severe, tend to display III type EBV gene expression profile rather than the restricted pattern frequently seen in eBL" (Brady et al. 2007).

2.6 Differential Diagnosis

The differential diagnosis of BL is broad and the precise diagnosis based on histological, immunophenotype and genetic features remains the critical first step in planning appropriate therapy (Ferry, 2006). Table 4 shows the differential diagnoses of BL based on clinical features, morphology, usual immunophenotype and genotype.

Table 4: Differential Diagnoses of Burkitt's lymphoma

Type	Clinical Features	Morphology	Immunophenotype	Genotype
Burkitt's and Burkitt-like	Children > adults; male > female; extranodal > nodal, bulky, rapidly growing masses	Uniform/slightly pleomorphic medium-sized cells, starry-sky pattern	$CD20^+$, $CD10^+$, Bcl-6^+, Bcl-2^-, $CD5^-$, TdT^-, monotypic sIg^+, Ki67 ~ 100%	t(8;14), t(2;8) or t (8;22) (myc and IgH or IgL); no bcl-2 or bcl-6 translocation
Diffuse large B cell	Adults > children; nodal or extranodal; May be large mass lesions, often localized	Large, oval irregular or lobated nuclei, scant cytoplasm	$CD20^+$, $CD10^{-/+}$, Bcl-$2^{+/-}$, monotypic $sIg^{+/-}$	bcl-2 and bcl-6 abnormalities common, myc abnormal in a minority
Precursor B-lymphoblastic Lymphoma	Children > adults, leukaemia > lymphoma	Small- to medium-sized cells, variable size and shape	$CD3^{+/-}$, $CD7^+$, $CD4^+/8^+$, $CD1A^+$, TdT^+	Variable, often hyperdiploid, no myc rearrangement
Precursor T-lymphoblastic Lymphoma	Adolescents and young adults > children and older adults, male >female	Small- to medium-sized cells, variable in size and shape	$CD20^+$, $CD10^+$, Bcl-6^+, Bcl-2^-, Ki67~100 %, polytypic expression	Variable
Mantle cell Lymphoma Blastoid variant	Middle-aged and older adults, male > female; usually widespread disease in nodes and other sites	Medium- to large-sized lymphoblastic cells with scant cytoplasm	$CD20^+$, $CD5^+$, $CD10^-$, Bcl-6^-, Bcl-2^+, cyclin $D1^+$, monotypic sIg^+	t(11;14) (bcl-1 and IgH)
Florid follicular Hyperplasia	Children > adults, Early HIV infection; lymphadenopathy	Large irregular follicles, many blast cells and mitoses	$CD20^+$, $CD10^+$, Bcl-6^+, Bcl-2^-, Ki67~ 100 %,	Nodal abnormalities

Source: Ferry, 2006; p380

Other tumours to be considered and ruled out in the BL diagnosis are primary abdominal tumours in childhood including Wilms tumour, neuroblastoma and peripheral neuroectodermal tumour. In the bone marrow it must be differentiated from B and T precursor and myeloid leukemias. In peripheral B-cell lymphomas, the major differential diagnosis is with diffuse large B-cell lymphoma (Huang et al. 2005). When lymphoma is included in the differential diagnosis of an oral lesion, a biopsy specimen which has not been traumatized should be taken from the centre of the oral lesion and the pathologist must be informed of the possibility of the lymphoma as it is easily confused with other lesions as described above. Special staining with Giemsa and periodic acid-Schiff and typing with immunochemistry are useful in making the diagnosis (Greenberg et al. 2003). BL is characterized by the presence of a "starry sky" appearance (also observed in other highly proliferative lymphomas), imparted by scattered macrophages with phagocytes cell debris (Huang et al. 2005). According to Tsui et al. (2000), other differential diagnoses to be considered with presentation of a mass in the mandible are osteogenic sarcoma, osteomyelitis, Langerhan's disease, malignant lymphoma, giant cell tumour and histoplasmosis (Tsui et al. 2000).

2.7 Staging of BL

Staging of BL is important because it helps to determine the extent of the Burkitt lesion, mode of treatment e.g, monotherapy or multi-agent chemotherapy, treatment outcome and/ or prognosis. There may be more than four methods of staging lymphomas, but the most commonly used systems are the National Cancer Institute [NCI] (Table 5) (Huang et al. 2005) or otherwise called Ziegler Staging (Kazembe et al. 2003), Ann Arbor, St. Jude (Table 6) and Murphy's classification. The Ann Arbor staging was originally developed for Hodgkin's lymphoma (HL) and is commonly used in adults. Its usefulness is limited by the fact that HL and NHL have different patterns of spread. For this reason, the Murphy/St Jude modification of the Ann Arbor system (Table 7) is commonly used as depicted in Table 7, and it is used to stage NHLs in children and young people and sometimes adults. The system of staging describes how many groups of lymph nodes are affected, where they are in the body, and whether other organs such as abdomen, CNS or bone marrow are involved (Feinberg et al. 2007; Souhami et al. 2002; Hancock et al.2000).

Table 5: The NCI system (Huang et al. 2005)

Stage	Criteria for the extent of disease
A	Single solitary extra-abdominal site
AR	Intra-abdominal, more than 90% of tumour resected
B	Multiple extra-abdominal tumours
C	Intra-abdominal tumour
D	Intra-abdominal plus one or more extra-abdominal sites

Table 6: St. Jude's modification of the Ann Arbor Staging system

Stage 1	There is a single extranodal tumour or there is a nodal lymphoma in one area of the body (but not including the central lymph nodes within the chest – the mediastinum – or the abdomen)
Stage 2	Can be any of the following: • There is a single extranodal tumour and nearby lymph nodes are affected. • There are two single extranodal tumours on the same side of the diaphragm (with or without nearby lymph nodes being affected). • The lymphoma started in the stomach or intestines – nearby nodes may or may not be affected. • The lymphoma is in two or more areas of lymph nodes on the same side of the diaphragm.
Stage 2R	The lymphoma was in the abdominal area but has been completely removed by surgery
Stage 3	Can be any of the following: • There are two single extranodal tumours on opposite sides of the diaphragm. • The lymphoma started in the lungs, chest area or thymus gland. • The lymphoma is affecting the area within or around the spinal cord. • The lymphoma started in the abdomen and affects a large area. • Two or more nodal areas are affected on opposite sides of the diaphragm
Stage 3A	The lymphoma is in the abdominal area only and cannot be removed by surgery
Stage 3B	The lymphoma is affecting several organs within the abdomen
Stage 4	Any of the above, plus – at the time of diagnosis – the central nervous system (brain and spinal cord) and/or the bone marrow are also affected

Source: Souhami et al. 2002; Hancock et al. 2000

Table 7: Murphy/St Jude's staging system

Stage	Criteria for extent of disease
I	A single tumour Iextranodal) or single anatomic area (nodal) with the exclusion of the mediastinum and abdomen
II	A single tumour (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tumour, usually in the ileocal area, with or without involvement of associates mesenteric lymph nodes only, grossly completely resected
III	Two single tumours (extranodal) on opposites of the diaphragm Two or more nodal areas above or below the diaphragm All the primary intrathoracic tumours (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease, unresected All paraspinal or epidural tumours, regardless of other tumour site(s)
IV	Any of the above with initial CNS and/ or bone marrow involvement

Source: Feinberg et al. 2007

Approximately 30% of patients present with limited-stage disease (I or II), while 70% present with widespread disease (III or IV) (Ferry, 2006). Patients who often present with bulky disease are highly likely to have an elevated lactate dehydrogenase (LDH) level. If patients have any of the three clinical variations then they are at a high risk for spread to the central nervous system (CNS) and bone marrow (Ferry, 2006).

2.8 Clinical presentation

Signs and symptoms of BL depend on the form. In the Western world, where sBL is common, the most common symptom is an abdominal swelling that starts in the bowel. BL may also affect other organs such as the eye, the ovaries, kidneys and glandular tissue such as the breast, thyroid or tonsil. The classical African type of BL or eBL, usually affects the jawbone. Patients most often present with swelling of the affected jaw or other facial bones, loosening of teeth and swelling of the lymph nodes, which are non-tender and rapidly growing, in the neck or below the jaw line. Abdominal presentation is slightly less common. It can spread to the nervous system, damaging the nerves causing possible weakness or paralysis. It may also affect the lymph nodes or bone marrow.

Some patients may experience a loss of appetite and tiredness. Other symptoms known as B symptoms may be evident such as sweating at night, unexplained high temperatures and weight loss (Souhami et al. 2002; Hancock et al. 2000). In addition, the rapid growth of the BL tumour causes significant metabolic derangement and renal function impairment (Huang et al. 2005). Less common presentation of BL includes an epidural mass, skin nodules, CNS symptoms and bone marrow involvement. Rare cases can present as acute leukemia (L3-ALL), fever, anaemia, bleeding and adenopathy (Huang et al. 2005).

In endemic areas, involvement of the jaws is the presenting feature in 50-70% (Biggar, Nkrumah and Perkins, 1979; Burkitt and O'Connor, 1961) of cases while in non-endemic areas the figure is about 15% (Svoboda, Aaron and Albano, 1991). In endemic areas the incidence of jaw involvement is highest at the age of 3 years and drops steadily thereafter, and the maxilla is affected more often than the mandible in a ration of 2:1 (Adatia, 1968), while in sporadic areas the mandible is more commonly involved (Sariban, Donahue and Magrath, 1984).

The most common oral signs according to Tsui et al. (2000) include loosening of teeth, disturbance of eruption, swelling of the jaw, and anaesthesia or paraesthesia when the inferior dental nerve or maxillary nerve is involved. Pain is not a prominent feature. The overlying oral mucosa or skin is not usually affected. Rarely, the oral presentation may be periodontal, related to tooth extraction, or trauma, or it may be in the parapharyngeal space.

Radiologically, the earliest sign is a break in or loss of the lamina dura, followed by enlargement of the developing tooth crypts. Small foci of radiolucent areas then develop which fuse and enlarge to adjacent areas. BL is also unique in that it is the only malignancy that actually infiltrates the dental tissues including dental pulp, the developing follicle and the periodontal ligament. Kramer (1965) has speculated that the odontogenic epithelium, which exerts an inductive influence on the mesodermal tissues, may have a role in involving the jaws in BL. What is peculiar is that after successful chemotherapy, the previously infiltrated dental tissues are able to return to normal.

A Japanese case of BL was presented in which the intra-oral and panoramic images showed alveolar bone destruction with an infiltrative border, displacement of lower molars, root resorption, and loss of lamina dura and the follicular cortex of a developing tooth, similar to descriptions in previous reports. Computed tomography revealed that a primary lesion occupied the mandible and extended to the muscles of facial expression and to the sublingual and submandibular spaces. Another soft tissue mass was evident in the contralateral parapharyngeal space. Results of a survey of the Japanese literature are also presented; they indicate differences in the clinical features between Japanese cases and African and American cases of BL (Hanazawa et al. 1998).

There have also been other rare cases of BL that have been reported in the literature. Liu et al. (2000) reported an isolated case of a 14 year old boy in China that presented with mobile teeth in all four jaw quadrant with corresponding radiographic detection of alveolar bone crest destruction and periapical bone resorption in the absence of clinically detectable jaw tumour. Seventeen days later, radiographs showed clearly distinguishable signs of more extensive alveolar bone destruction compared with the initial radiographs (Liu et al. 2000). Tsui et al (2000) also reported on a 4 year old Chinese boy who presented with acute mandibular swelling without associated systemic disturbance. The swelling was of four days duration. Clinically, he had a slightly tender sessile firm non-fluctuant mass about 2 cm in diameter in the buccal sulcus opposite the lower first and second deciduous molars of the right mandible. The overlying mucosa looked normal with no ulceration or erythema. The right lower first and second molars were not carious but slightly mobile (Tsui et al, 2000).

Other cases included an 80 year old Palestinian living in California (US) presented with a rapidly expanding tongue base mass causing obstruction of the airways (Brady et al. 2007) and a 9 year old Indian girl with BL, she presented with a swelling in the left lower jaw fifteen days after extraction of a carious posterior tooth. The swelling was asymptomatic and had rapidly increased over a period of 15 days. She gave a history of difficulty in chewing and bleeding from the gums of lower left teeth on brushing. On examination, the child had bilateral enlarged submandibular lymph nodes that were palpable, and tender (Patil et al. 2007).

2.9 Treatment and treatment outcomes of BL

Chemotherapy is the best treatment option for this aggressive disease in all its stages because of its dramatic response to chemotherapy (Huang et al. 2005). But the cure rate depends to a large extent on the stage of the disease at initial diagnosis and immunosuppressive state in AIDS (Huang et al. 2005). The drugs that are used to treat BL are as follows: Cyclophosphamide (CPM), Methotrexate (MTX), Vincristine (VCR) also known as Oncovin (O), Doxorubicin (Dox), Cytarabine (Ara C), Ifosfamide (I), Steroid (Prednisone or Dexamethasone or Hydrocortisone), Rituximab, Bleomycin, Leucovorin, and Etoposide (Feinberg et al. 2007; Huang et al. 2005; Souhami et al. 2002). Table 8 depicts the different combination chemotherapy protocols.

Table 8: Chemotherapy combination protocols

Treatment Protocol	Drug Combination
COMP	CPM + VCR (O) + MTX + Prednisone
CHOP	CPM + VCR (O)+ DOX + Prednisone
CHOP/CODOX-M	CPM + VCR (O)+ DOX + MTX + Prednisone
NHL-BFM 90 OR CODOX-M/IVAC	Prednisone + Dexamethasone + VCR (O) + DOX + CPM + I + Etoposide + ara C + MTX
French LMB-89	High dose CPM + high dose MTX/ Leucovorin, + Ara C + VCR (O) + DOX + Prednisone
NCI-89-C-0041F	CPM + VCR (O) + DOX + MTX, alternating with Ara C, ETOPOSIDE and Ifosfamide
CCG-5961	Reduction in intensification of the French LMB-89 regimen
Rituximab	Monoclonoal antibody therapy that recognizes target and stick to specific proteins on the surface of cancer cells and can stimulate the body's immune system to destroy the cell. This treatment is usually given with chemotherapy (Hancock et al. 2000, Souhami et al. 2002; Ferry, 2006)

Sources: Feinberg et al. 2007 ; Ferry, 2006 ; Huang et al. 2005 ; Souhami et al. 2002

These drugs can be used alone or in combination. For example, CPM alone has been curative for 80% children from Africa with localized disease and/ or early stage disease (Huang et al. 2005). Kazembe et al. (2003) used CPM monotherapy and found a survival rate of 63.5% in the children with BL involving the head only and 33.3% with the primary disease involving the abdomen or other sites (Kazembe et al. 2003). In another study in Uganda, CPM or CHOP were used in 280 children with BL in all stages and survived free of disease beyond five years (Hesseling et al. 2003). However, a combination therapy has greatly improved treatment outcomes especially in patients with extensive disease. In a separate study in Malawi, Hesseling et al. (2003) carried out a BL trial in Malawi using French LMB-89 without DOX and a reduced dose of MTX, CPM, and Ara C. The projected event free survival (EFS) rate in 44 children stage I-III was 57%. The morbidity of treatment was unacceptably high when 10 deaths occurred due to bone marrow suppression, gastrointestinal toxicity and infections (Hesseling et al. 2003).

sBL and immunodeficiency-associated BL do not share eBL's exquisite sensitivity to chemotherapy, so that historically the prognosis had been poor, particularly among adults. Short-duration, high-intensity chemotherapy, sometimes combined with CNS prophylaxis, yields excellent survival in children: patients with localized disease have a >90% 5-year survival rate, and children with widespread disease (including leukemic presentation) may achieve a >90% complete response (CR) rate, with an event-free survival (EFS) rate at 4 years of 65% in patients with leukemic presentation, and 79% for those presenting with stage IV lymphoma reported in one series (Bowman et al. 1996). When similar aggressive chemotherapeutic regimens have been administered to adults, good outcomes have been achieved, with CR rates of 65%–100% and overall survival (OS) rates of 50%–70% (Ferry, 2006; Blum, 2004).

It must also be emphasized that patients presenting with disseminated disease respond less well to chemotherapy and tend to have a less favourable survival rate (Huang et al. 2005). Consequently in AIDS patients the disease is advanced at diagnosis and involves extranodal sites. So normally, these patients present with wide dissemination and bone marrow involvement. Due to underlying immunosuppression and leucopenia, most of them do not tolerate systemic chemotherapy well. As a result, death occurs shortly after diagnosis (Huang et al. 2005).

Patients with HIV may be treated with intensive therapy but requires close observation, with transfusion support and antibiotic therapy as needed. HAART may improve outcome, allowing patients a better chance of being able to tolerate full-dose chemotherapy. Patients developing Burkitt's lymphoma in a post-transplant setting may also be difficult to treat, but may show a good response to therapy that includes a combination of chemotherapy, decreased immunosuppression, and rituximab (Gong et al. 2003), although mortality appears to be high among the small numbers of cases reported with three of five patients in one series succumbing to complications of therapy (Ferry, 2006; Xicoy et al. 2003).

Patients with BL that is extensive have a high risk of tumour lysis syndrome even before chemotherapy is initiated due to rapid tumour cell turnover. In such cases, patients should receive allopurinol and aggressive hydration with alkalinisation starting as soon as BL is suspected. Other studies such as electrolytes (potassium, sodium, calcium, uric acid, phosphate and creatinine should be monitored closely and renal dialysis available when needed (Huang et al. 2005). Half of the patients relapse after chemotherapy but may respond to bone marrow transplantation (Greenberg et al. 2003). Other treatment modalities include surgical care, bone marrow transplant and supportive care. However, surgical care can be employed only in patients with small, completely resectable abdominal tumours or patients with obstruction who cannot begin chemotherapy immediately.

2.10 Prognosis of BL

Although the most important prognostic features have yet to be determined, some features of BL that have been associated with adverse outcome in adults and children include older age, advanced stage, poor performance status, bulky disease, high LDH, and CNS or marrow involvement. It should also be noted that patients with more extensive disease particularly CNS and bone marrow involvement have a worse prognosis, but long term survival rates as high as 80% can be achieved with more aggressive chemotherapy regimens. Among pediatric patients, a poorer prognosis is associated with age over 15 years. Adults with advanced stage BL do more poorly than children with the disease (Huang et al. 2005). A good prognosis is associated with resectable abdominal disease. Failure to achieve a CR is a very poor prognostic sign. A granulomatous response to the lymphoma has been associated with localized disease and a favorable outcome in cases of sBL (Ferry, 2006).

2.11 Oral and Dental Considerations

Malignant lesions of the orofacial region are not uncommon but they constitute the main life-threatening disease apart from maxillofacial trauma that may be encountered in dental practice (Ajayi et al. 2007a). BL is of interest to dental practitioners or oral surgeons for a number of reasons (i) they may be the first people to come across the lesion; (ii) in eBL, jaw involvement as a presenting feature is 50-70% while in sBL it is 15% (iii) BL is the only malignancy that actually infiltrates the dental tissues including the dental pulp, the developing tooth follicle and the periodontal ligament and (iv) BL may be the first indication of HIV infection (Tsui et al. 2000).

Asymptomatic enlargement of the cervical lymph node is a common early sign of lymphoma and dentists and other oral health workers should play a significant role in early detection by routine examination of the neck. Any suspicion of lymphoma should increase when lymphadenopathy appears without any signs of infection, more than one lymph node chain is involved, or a lymph node of 1 cm or greater in diameter persists for more than one month (Greenberg et al. 2003).

Patients with acute swelling in or around the jaws often present to dental or oral surgeons. In most cases, the cause is acute infection of odontogenic origin and appropriate treatment is given. In rare cases, the diagnosis is not obvious and the differential diagnosis of a malignancy may be missed if one does not suspect it and if there are no other clinical clues such as loss of weight or neurological deficits. This is particularly so in previously healthy young children (Tsui et al. 2000). The purpose of this study is to document the orofacial manifestations in children with BL. It is anticipated that the findings may assist in the education of oral and other health care workers in the early recognition of BL for prompt referral. Oral health workers are a critical component of the referral chain since these lesions can be life threatening.

2.12 Concluding remarks

Based on the literature review, BL continues to dominate childhood cancers in the equatorial region with an average peak incidence at 7 years. 40% of BL involves the orofacial region and the maxilla is the predominant site with male preponderance. Therefore BL should always be considered in children aged 0-15 years with unexplained swelling. The presentation will definitely depend on the site of the lesion while management depends on the extent of the disease (disease staging). That is, monotherapy with cyclophoshamide can be administered with a cure rate of at least 63.5% with minimal disease and a combination treatment protocol with advanced and/ or extensive disease.

CHAPTER THREE

Aim

To determine the orofacial manifestations of Burkitt's Lymphoma in Malawi

Objectives

To retrospectively review records of cases of Burkitt's Lymphoma from 2005 to 2007 at Kamuzu Central Hospital (KCH) and Queen Elizabeth Central Hospital (QECH)

To prospectively determine the oro-facial manifestations of Burkitt's Lymphoma at Kamuzu Central Hospital from June 2008 to October 2009.

CHAPTER FOUR

Research Design and Methodology

4.1 Introduction

Malawi, the site for both retrospective and prospective studies, is a landlocked country bordered by Tanzania to its north and north east, Mozambique to its east and southeast and Zambia to its west and southwest. It covers a total land of 118 484 square kilometers one third of which is a lake (Lake Malawi). It has a population of approximately 14 million people. The country has three regions namely northern region, central region and southern region. Each region has its own referral hospital although patients are also transferred from one hospital to another (Figure 1).

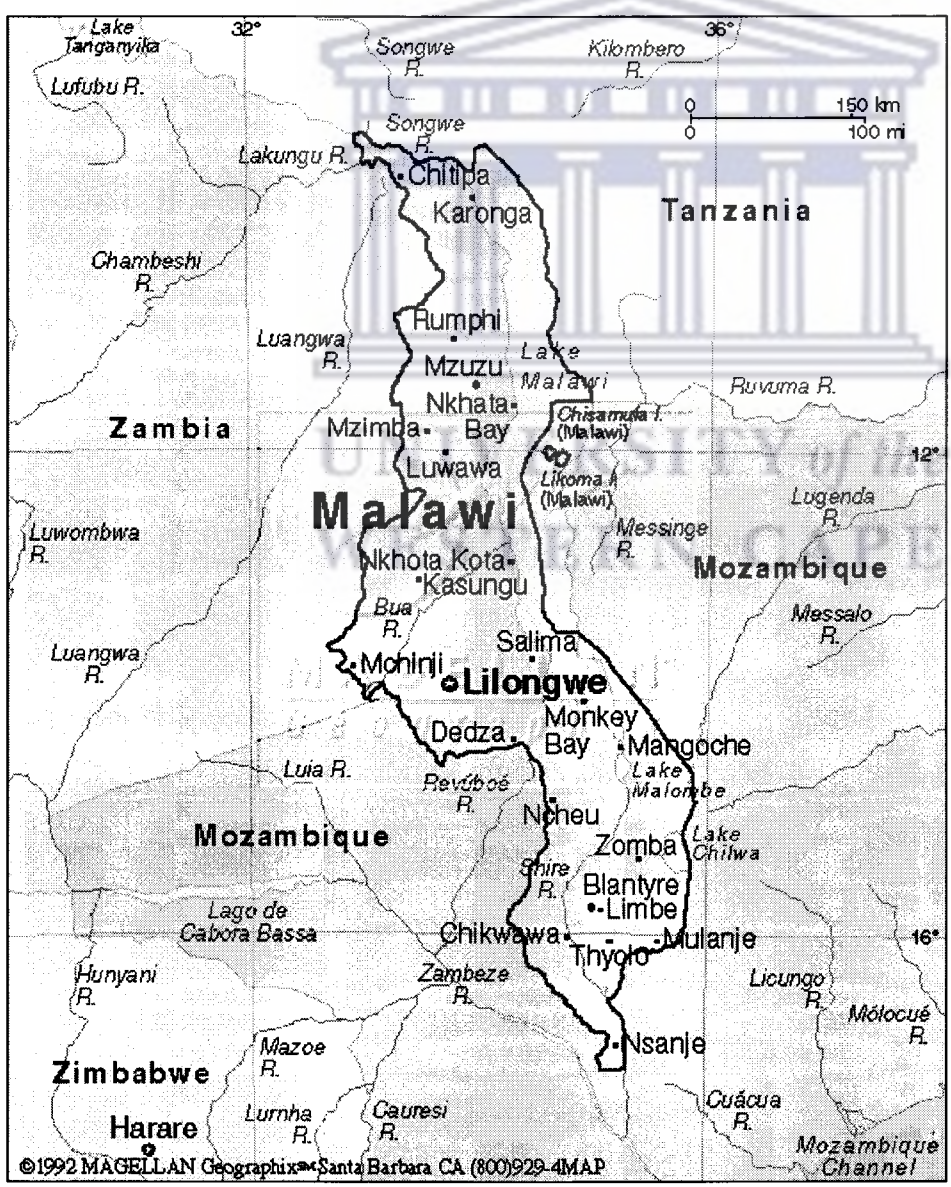


Figure 1: Map of Malawi with districts

4.2 Study Sites

Kamuzu Central Hospital (KCH) is located in Lilongwe in the central region and caters for central and northern region for children with various forms of cancer, Burkitt's lymphoma (BL) inclusive whereas Queen Elizabeth Central Hospital (QECH) is in Blantryre where it caters for the southern region and also receives patients from KCH especially with the most resistant forms of BL. KCH has a bed capacity of 1000. QECH is the biggest referral hospital in Malawi with a bed capacity of 1250. Lilongwe Blantyre which is commercial city in Malawi.

4.3 Study Design

The study was carried out in two parts: One, a retrospective record-based study was carried out on records from 2005 to 2007 at KCH and QECH and two, a prospective study from July 2008 to October 2009 at KCH.

4.4 Study Population: All pediatric cases diagnosed with Burkitt's Lymphoma from KCH and QECH.

4.5 Inclusion Criteria: All children suspected and diagnosed with Burkitt's Lymphoma

Sample Size: In the retrospective study, 661 records were examined from 2005 to 2007 at KCH and QECH whereas 19 patients from KCH were physically and clinically examined with suspected and confirmed BL in the prospective study and then followed-up from June 2008 to October 2009 at KCH.

4.6 Measurements

This study was done in two parts. The first part consisted of extracting relevant information from the records that was recorded in a structured oral health data capture sheet (Appendix 1). The second part was a prospective study which was carried out from June 2008 to October 2009 that consisted of thorough physical and clinical examination of all suspected and known cases of BL. The findings were recorded in the oral health data capture sheet (Appendix 2). Radiology studies were ordered and one clinical photograph of a 9 year old girl with suspected BL was taken at initial diagnosis after obtaining informed consent from the guardian and assent from the child (Figure 7). An informed consent form was obtained from every patient for the oral examination and if any radiological or photographic examinations were carried out (Appendix 3). Consent to access records and to carry out the research was obtained from the Hospital Director at KCH and QECH (Appendix 4). Consent to use clinical photographs for education and publication was obtained from the guardian (Appendix 5).

4.6.1 Design rules for data capture sheet and questionnaire

The same rules of design applied:

- It suited the aim of the study
- It suited the nature of the respondent
- It was clear, simple, unambiguous
- The design minimized potential errors from respondents and coders
- The subject of the questionnaire was of great interest to the respondent, encouraged their co-operation and elicited truthful answers
- Well worded questions were essential, and pitfalls were avoided, for example, 'double-barreled questions' that is, when two questions were included in one- the questions was separated so that the respondent and the researcher distinguished between the two.
- The wording of the questions did not lead the respondent to feel obliged to answer in a particular way, which may not have been truthful
- Questions did not alienate either the respondent or the researcher
- Efficient and meaningful analysis of the acquired data was possible.

4.6.2 Instruments used

Data capture sheets (Appendix 1 and 2) with open and close ended questions was the instrument used to collect the data in this study. It was designed to ensure that it suited the aim and objectives of the study and was simple, clearly understood and unambiguous.

4.6.3 The development of the oral health data capture sheets

Planning of the oral health data capture sheet began in March 2008 in consultation with professionals working in the field and dental colleagues. After a thorough review of the literature, the questions were formulated. The data were grouped into the following categories:

Demographics

The demographic information included name of the facility, name and record number of the patient, the referral person, district of residency, age in years and gender.

Medical History

Information was collected on the following conditions: Malnutrition, Malaria, Tuberculosis, HIV, Anaemia, Fever and full description of other conditions

Family History of Burkitt's Lymphoma

The patient and/or guardian were asked if anybody in the family had the same disease. If yes, they had to say who and when they had it (Appendix 4).

Presentation of lesions

Orofacial presentation and other sites of the lesion were recorded into the data capture sheet for the retrospective study. Details and the extent of the orofacial presentation was recorded directly into the data capture sheet and patient's record immediately after the oral examination was conducted in the Prospective study. Additional relevant information was entered into the data capture sheet after examination by the Pediatrician and other health workers.

Site of the Orofacial lesions

The location of the Burkitts lesion was recorded with regard to the following sites: mandible, maxilla, mandible/maxilla, palate, tongue, lip, cheek, parotid gland, not specified or other.

Orofacial presentation at initial diagnosis

The presentation on their first visit or initial visit at diagnosis was recorded in regards to: cervical lymphadenopathy, enlargement of tonsils, nasal blockage, facial swelling (including saliva), numbness/paraesthesia of lip, face, intra-oral swelling (palatal, gingival, tongue, salivary gland), intraosseus mass, mobile/ loose teeth, displaced teeth or description of other presentation

Other sites of presentation

For both studies, other sites of the presentation of the Burkitts lesion were ticked off from the list as yes or no. The list consisted of abdomen, liver, Brain, CNS, spleen, lungs, spine, breast, ovaries and kidney and a full description of other sites not included in the list (Appendix 1 & 2).

History of Oral Problems

The patient was asked if they had symptoms of pain or any discomfort in relation to their disease causing difficulties with any of the following: eating, drinking liquids, swallowing solid food, speaking, breathing, playing, sleeping or resting and description of other difficulty (Appendix 2).

Detailed Description of Burkitts Lesion

The full description of Burkitts lesion in terms of size, texture, colour and extent (lip, palate etc) was recorded in the data capture sheet (Appendix 2)

Orofacial or intraoral pathology

All the orofacial conditions present were recorded using codes 1-16 and specific location using codes 11-29) and full description of other conditions not included (Appendix 2)

Previous treatment for Burkitts lesion

The patient was asked if they were previously treated for Burkitts lesion, by whom and what they did in order to establish treatment failure and recurrence/ relapse.

Hospitalisation

For the Retrospective study, data was gathered from the record to find about the patient's previous admission and their duration of stay in the ward. The information was recorded in the data capture sheet (Appendix 1). For the Prospective study, information was collected as the patient presents to the hospital about their previous hospitalisation if any, duration and what for. The patient's present hospitalization was also recorded in the data capture sheet (Appendix 2).

Tests or Investigations

For both studies, all the tests and/ or investigations conducted were ticked off from the list and then recorded in the data capture sheet. The list included the following: Fine needle biopsy (FNA), chest X-rays (CXR), bone scan, skull X-rays, intra-oral x-rays, lumbar puncture (LP) Bone marrow biopsy, ultrasound scan (USS), CT scans (head, spine, abdominal), HIV, Malaria film and a full description of other tests done (Appendix 1 and 2).

Referral

For the prospective study, information about whether the patient was referred following the diagnosis of Burkitts and to whom that referral was made (Appendix 2).

Treatment

For the Retrospective study, data regarding the treatment provided was extracted from the records to the data capture sheet (Appendix 1). For the Prospective study, information was recorded directly into the data capture sheet on the treatment they were receiving (Appendix 2).

Outcomes

Information from both Retrospective and Prospective study about whether the patient was cured and discharged from the hospital, absconded or defaulted, had complications, died or had relapse, lost to follow up (Appendix 1and 2).

4.6.7 Piloting the oral health data capture sheet

In June 2008, the completed oral health data capture sheet was tested on 10-records. The pilot study was carried out to:

- Test the suitability of the method of collecting the data
- Check the adequacy of the data capture sheet
- Check that all questions were clear and unambiguous
- Remove any items that did not yield usable data.

4.6.8 Preparation for the final draft

After the pilot study, irrelevant and ambiguous questions were identified and either reformulated or deleted. It was hoped that this would result in an improvement of the data capture sheet and increase in the efficiency of the enquiry. The final draft of the questionnaire was printed and copied for the larger study.

4.7 Establishing contacts

All researchers are dependant upon the goodwill and availability of their subjects. During initial meetings with the core-management of KCH and head of the pediatric department of the two hospitals at KCH and QECH, it was anticipated that co-operation of the hospital director of KCH and QECH and the relevant health authorities would be obtained. Permission was sought for patients to participate in the prospective study and also to access patient records. Once permission was granted, all participants were required to sign the consent forms to participate in the study.

4.8 Data collection

A consultative meeting with other professional colleagues from the children's Burkitts ward and dental therapists in the oral surgery section of the dental department was conducted whereby the reasons of the Burkitt's lymphoma study was emphasized and the Surveillance of Burkitts form was discussed and how it would be used to completely fill the oral health data capture sheet. Following that meeting, the structured oral health data capture sheet was distributed to the dental therapists and one medical officer in the Burkitts ward to start capturing all the necessary information from the records and patient examination for the Prospective, while the principal investigator would capture data from the records for 2005-2007 (Retrospective) and prospectively from oral examination and answers from the participant.

4.9 Data capture and Statistical analysis

Microsoft excel software was used for data analysis and statistical analysis from the oral health data capture sheet. Chi-square tests and p-values were used to test statistical significance and associations between different variables e.g, age group and occurrence of variant forms of cancers, HIV sero-status and occurrence of Burkitts lesions, gender and frequency of BL, frequency of BL and district, or age and frequency of BL.

4.10 Validity and reliability

All relevant information from the patient's record was entered into the data capture sheet and interpretation of data was done by the principal investigator (JM) thereby assuring confidentiality and uniformity in recording of information. Furthermore to ensure validity, the triangulation method was used, whereby an independent person was asked to review ten per cent of the data to check for bias. The principal investigator, JM (fluent in English, Chichewa and Tumbuka) was the only person involved in conducting clinical examination, investigations and treatment. For the prospective study, the records were kept in the children's Burkitts ward where patients were admitted. Only 19 children were enrolled into the prospective study because they were enrolled as they reported to the dental department and then followed up for the duration of the study.

4.11 Ethical considerations

The participants in the study were required to complete a consent form (Appendix 3) if they were willing to participate in the study. Participation was voluntary and that each individual was given the right to refuse to be included in the study or to withdraw from the study at any time. Furthermore, it was re-iterated that their decision to participate or not, would not affect their management or care in any way whatsoever. The participants were assured of confidentiality regarding the information they provided should they decide to take part. Ethical clearance to carry out the study was obtained from the Senate Research Committee, University of the Western Cape and management of the two hospitals; KCH and QECH. For the clinical photograph, the UWC consent form was adopted so that the photograph could be used for education and publication purposes (Appendix 5).

4.12 Images

One clinical photograph was used to show Burkitts lesions as they presented in the prospective study in a 9 year old girl. A clinical photograph was taken only after the consent form was signed by the guardian/ parent and used to show one of the different orofacial manifestations of BL (Appendix 5).

CHAPTER FIVE

Results

In this chapter, the findings will be reported in two parts - Part I will report on the retrospective record-based review while Part II on the prospective study findings.

PART 1: Retrospective Record-based review (2005-2007)

5.1 Demography

A total of 661 cases were observed of which 253 (38.3%) were females and 408 (61.7%) were males. The number of cases showed a decline from 2005 to 2007. KCH saw more cases in all the three years than QECH. In Table 9a a total of 192 (72.7%), 146 (70.9%) and 131 (68.6%) in 2005, 2006 and 2007 presented at KCH respectively. Figure 2 is a bar graph of Table 9a showing the summary total of cases against gender per year.

Table 9a: Total admission in the pediatric oncology ward

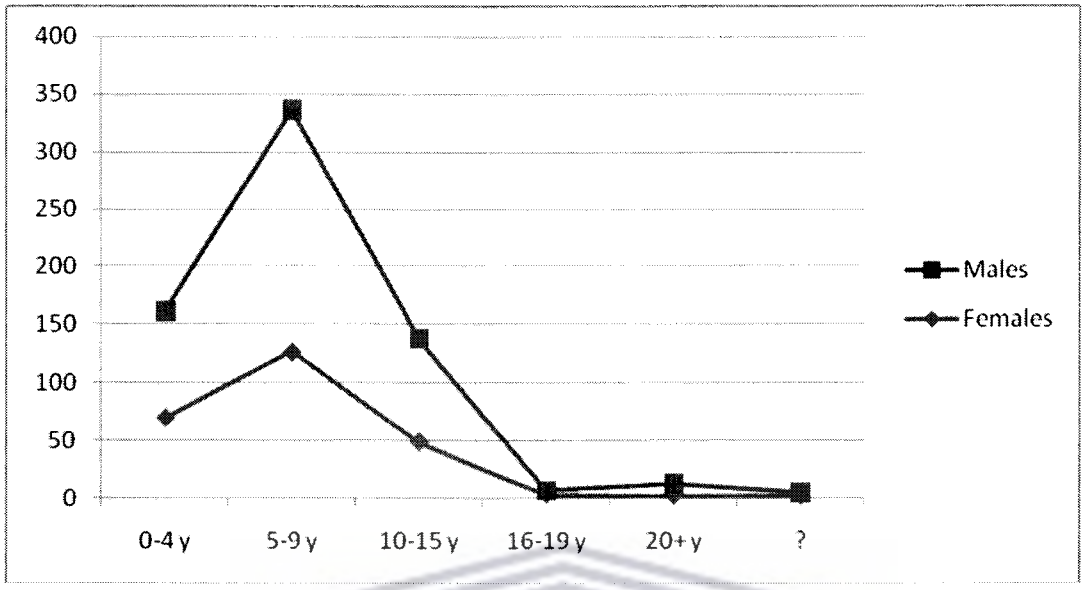
	KCH 2005	QECH 2005	KCH 2006	QECH 2006	KCH 2007	QECH 2007	TOTAL
Female	72 (27.3%)	26 (9.8%)	55 (26.7%)	23 (11.2%)	48 (25.1%)	29 (15.2%)	253 (38.3%)
Male	120 (45.5%)	46 (17.4%)	91 (44.2%)	37 (18.0%)	83 (43.5%)	31 (16.2%)	408 (61.7%)
Total	192 (72.7%)	72 (27.3%)	146 (70.9%)	60 (29.1%)	131 (68.6	60 (29.1%)	661

Table 9b: Summary of Table 9a showing total cases according to gender and year of admission

Gender	2005	2006	2007	Total
Female	98 (14.8%)	78 (11.8%)	77 (11.6%)	253 (38.3%)
Male	166 (25.1%)	128 (19.4%)	114 (17.2%)	408 (61.7%)
Total	264 (39.9%)	206 (31.2%)	191 (28.9%)	661 (100.0%)

Figure 2 is a linear graph that depicts well the distribution of age and gender of all patients in regards to the occurrence of various cancers that attended or that were admitted to the children's oncology wards of the two hospitals, KCH and QECH. The 5-9 year olds (51%) were the age group most affected by the various cancers including Burkitt's lymphoma, followed by 0-4yrs (24.4%) and 10-15yrs (20.9%). In Figure 2 below is a linear graph of Table 10 that depicts well the age groups, gender and the occurrence of cancer.

Figure 2: All suspected cases against age groups



Since all the patients admitted in the children's oncology unit are considered Burkitt's suspects until proven otherwise, open biopsy, bone marrow aspiration and fine needle biopsy are used to confirm diagnosis by histology and further by flow cytometry by looking at immunophenotypes e.g., CD20. The flow cytometry is commonly done with KCH samples which are sent to the United Kingdom. On the other hand, bone marrow aspirations are done at QECH for histology. However of the 661 suspects, a total of 502 biopsies were conducted whilst others were diagnosed based on clinical presentation.

Not all biopsies were conclusive because some of the samples were either unsatisfactory, had blood in them or inadequate especially with the CD20. The results indicated that 397 (60.1%) had BL either by histology, flow cytometry (immunophenotyping) or based on clinical presentation; 15 (2.6%) had Neuroblastoma; 9 (1.5%) had Wilm's tumour; 7 (1.2%) had Retinoblastoma; 28 (4.8%) had different forms of Lymphomas (large B-cell lymphoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, lymphoblastic leukaemia; 15 (2.6%) had kaposi's sarcoma; 83 (14.2%) had other tumours not specified in the table like Rhabdomyosarcoma, Small round cell tumour, Yolk sac tumour, Hepatoblastoma, Reparative giant cell granuloma and Fibrosarcoma; 32 (5.5%) had non-tumour conditions such as infection, cystic swelling and abscesses. Refer to Tables 10a and 10b below for distribution of these cancers according to age groups.

Table 10a: Cancer type according to age group (2005-2007)

Cancer	0-4yrs	5-9yrs	10-15yrs	16-19yrs	20+yrs	?	Total
Burkitt's lymphoma	78	238	72	3	3	3	397
Neuroblastoma	8	3	4	0	0	0	15
Wilm's Tumour	4	3	2	0	0	0	9
Retinoblastoma	6	1	0	0	0	0	7
Lymphomas	3	9	11	1	3	1	28
Kaposi's sarcoma	5	8	2	0	0	0	15
Other Tumours	30	25	19	1	8	0	83
Non-Tumours	13	10	9	0	0	0	32
Total	147	297	119	5	14	4	586

Table 10a above shows different forms of cancer according to age group. Burkitt's lymphoma is the largest component affecting children 0-15 years of age.

Table 10b: BL diagnosis according to age groups

Type	0-4yrs	5-9yrs	10-15yrs	16-19yrs	20+yrs	Unknown	Total
BLc	24 (6.0%)	97 (24.4%)	22 (5.5%)	0	0	1 (0.3%)	144 (36.3%)
BLp/l	11 (2.8%)	22 (5.5%)	8 (2.0%)	0	0	0	41 (10.3%)
CBL	43 (10.8%)	119 (30.0%)	42 (10.6%)	3 (0.8%)	3 (0.8%)	2 (0.5%)	212 (53.4%)
Total	78 (19.6%)	238 (59.9%)	72 (18.1%)	3 (0.8%)	3 (0.8%)	3 (0.8%)	397 (100%)

In the Table 10b, 53.4% depicted as CBL, were diagnosed based on clinical presentation and history, 10.3% indicated by BLp/l, were based on histology whereas 'certainly' BL (BLc) represented 36.3% of all BL cases. Those that had 'possibly' or 'likely' BL (BLp/l) could have been differentials of BL. Also in the Tables 10a and 10b, the 5-9 year age group predominated with BL representing 60% of all the cases with BL. BL represented 60.1% of all the tumours in the paediatric ward. Based on Table 10b, the average peak is (5+9) divided by 2 to give 7 years of age for Burkitt's lymphoma. On the site of BL lesion, abdomen was the most common site representing 20.3% of 881 sites established for the study followed by Maxilla accounting for 13.7% of all the sites; Orbits 10.2%; Mandible 7.2%; Spleen involvement 6.02%; cheeks 5.7%; Maxilla and mandible 4.5%; lymph nodes 4.1%; lower limbs 3.9%; spine 2.7%; brain involvement 2.5%; liver involvement 2.4%; palate 1.8%, face 1.6%, kidney 1.5% and other sites as indicated in Table 11 below in descending order.

Table 11: Total BL cases according to site(s) and age groups

Site of Lesion	0-4 y	5-9 y	10-15 y	16-19 y	20+y	Unknown	Totals
Abdomen	29	109	43	0	1	1	183
Maxilla	37	71	11	1	1	0	121
Orbit	23	56	10	1	0	0	90
Mandible	17	34	11	0	1	0	63
Spleen	10	35	7	1	0	0	53
Cheeks	12	32	6	0	0	1	50
Maxilla & Mandible	3	29	8	0	0	0	40
Lymph nodes	6	21	5	3	1	0	36
Lower Limbs	3	20	11	0	0	0	34
Spine	2	18	3	1	0	0	24
Brain	2	14	6	0	0	0	22
Liver	6	13	2	0	0	0	21
Palate	6	10	0	0	0	0	16
Face	4	7	3	0	0	0	14
Kidney	2	7	4	0	0	0	13
Neck	2	4	5	1	0	0	12
Upper limbs	1	6	3	0	0	0	10
Temporal	3	6	1	0	0	0	10
CNS	0	6	2	0	0	0	8
Parotid	3	2	0	0	1	1	5
Nose	1	3	1	0	0	0	5
Ear	0	3	2	0	0	0	5
Skin/Scalp	0	3	2	0	0	0	5
Frontal	0	3	2	0	0	0	5
Scrotum/ Testis	1	2	1	0	0	0	4
Pubic bone	1	2	0	0	0	0	3
Thyroid	0	3	0	0	0	0	3
Jaws	1	2	0	0	0	0	3
Zygoma	0	2	0	0	0	0	2
Occiput	0	1	1	0	0	0	2
Chest	0	1	1	0	0	0	2
Head	0	2	0	0	0	0	2
Back	0	1	1	0	0	0	2
Urinary bladder	0	2	0	0	0	0	2
Clavicle	1	1	0	0	0	0	2
Knees	0	2	0	0	0	0	2
Ovaries	1	1	0	0	0	0	2
Mastoid	0	1	0	0	0	0	1
Breast	0	0	1	0	0	0	1
Lungs	0	1	0	0	0	0	1
Gluteal/ Buttock	1	0	0	0	0	0	1
Totals	178	536	154	8	5	3	881

In Table 11, the maxilla was the most common orofacial site for BL followed by the mandible, cheeks, maxillomandible, lymph nodes, palate, face, nose, parotid, zygoma, jaws and lips in that descending order.

Table 12: Orofacial BL involving other site(s) per age groups

Age Groups	0-4yrs	5-9yrs	10-15yrs	16-19yrs	20+yrs
Other sites	29 (32.2%)	106 (49.8%)	23 (50.0%)	2 (50.0%)	0
BL Orofacial	90	213	46	4	4

Of the 357 BL patients with orofacial manifestation, 44.8% involved other site(s) which included the abdomen, orbit, spleen, CNS, brain, spine and others. Among the 0-4yrs with orofacial BL, 32.2% presented with other sites, 49.8% among 5-9yrs, 50.0% among 10-15yrs and 50.0% among 16-19yrs presented with sites other than the orofacial region. The presentations included eye proptosis, ptosis, paraplegia, paraparesis, weakness in the lower extremeties, distended abdomen, splenomegaly, hepatomegaly, abdominal pain and/ or discomfort.

Table 13: Orofacial findings at initial diagnosis of BL

Features	0-4yrs	5-9yrs	10-15yrs	16-19yrs	20+yrs	Unknown	Total
Intraosseous mass	52	131	27	0	2	0	212
Loose teeth	23	65	9	0	2	0	99
Pain, discomfort	4	35	7	0	0	0	46
Displaced teeth	4	18	4	0	0	0	26
Cervical lymphadenopathy	1	16	3	0	0	0	20
Infected tumour	7	7	4	0	2	0	20
Palatal infiltration	4	9	1	0	0	2	14
Gingival enlargement	1	12	1	0	0	0	14
Difficulties breathing	5	9	0	0	0	0	14
Oral ulceration	3	10	1	0	0	0	14
Gingival bleeding	2	9	1	0	0	1	12
Intra-oral swelling	1	6	0	0	1	2	10
Firm, fixed swelling	3	5	2	0	0	0	10
Caries	3	1	1	0	0	0	5
Nasal growth	0	2	0	0	0	1	2
Trismus	0	1	0	0	0	0	2
Bone/ soft tissue deformity	3	8	3	0	0	1	14
Submandibular lymphadenopathy	2	8	1	0	0	0	11
Fungating/ lobulated mass	0	2	0	0	0	0	2
Salivation +++	1	0	0	0	0	0	1
Difficult speech	1	0	0	0	0	0	1
Jaw deviation	0	1	0	0	0	0	1
Unable to close the mouth	0	1	0	0	0	0	1
Cellulitis	0	1	0	0	0	0	1

Apart from the usual maxillary or mandibular swellings, orofacial findings at initial diagnosis of BL are an important aspect of the orofacial manifestation of BL in Malawi. The common findings in the Table 13 in the descending order are as follows: intraosseous mass (212); loose teeth (99); pain and/ or discomfort (46); displaced teeth (26); cervical lymphadenopathy (20); infected tumour (20); palatal infiltration (14); gingival enlargement (14); bone/ soft tissue deformity (14); ulceration (14); difficulties breathing (14); gingival bleeding (12), submandibular lymphadenopathy (11); intraoral swelling (10); halitosis (9); caries (5) and others.

Table 14: HIV test and outcomes according to age groups in orofacial BL

Age	HIV-NR (n= 233)	HIV-R (n= 33)	HIV tested (n= 266)
0-4 years	22 (8.27%)	3 (1.13%)	25 (9.4%)
5-9 years	65 (24.44%)	3 (1.13%)	68 (25.56%)
10-15 years	12 (4.51%)	2 (0.75%)	14 (5.26%)
16-19 years	0	0	0
20+ years	1 (0.38%)	1 (0.38%)	1 (0.38%)
Unknown	2 (0.75%)	0	2 (0.75%)
Total	**102 (38.34%)**	**9 (3.38%)**	**110 (41.35%)**

According to Table 14, 40.2% of the 661 patients were tested for HIV. Of those that got tested, 35.2% were HIV negative (HIV-NR) whilst 5.0% were HIV positive (HIV-R). Of the 266 that got tested for HIV, 110 were BL patients with orofacial manifestation. However, 101 patients were non-reactive and constituted 37.97% of those with orofacial BL; 3.38% with orofacial BL were HIV positive or reactive. HIV status and the occurrence of BL in this study were independent.

On treatment and treatment outcomes, 88.4% of all the patients received chemotherapy ranging from monotherapy with cyclophosphamide (CTX) to combination therapies such as CTX plus IT dose(s) Methotrexate (MTX) and Hydrocortisone (HC) or CTX plus Vincristine (VCR) and MTX (COM). 4.8% of those with orofacial BL sought traditional medicine before visiting their respective health facilities; thus delaying tactics. See Table 15 for details on treatment outcomes and complications.

Table 15: Management and treatment outcomes for orofacial BL

Features	0-4yrs	5-9yrs	10-15yrs	16-19yrs	20+yrs	Unknown	Total
CTX (+/- VCR)	14	60	8	0	0	0	82 (12.4%)
CTX + IT MTX & HC	29	82	16	0	2	1	130 (19.7%)
COM (P)	10	14	5	0	0	0	29 (4.4%)
Medical conditions	22	65	17	0	1	0	105 (15.9%)
Complication (s)	20	51	9	0	1	0	81 (12.3%)
Defaulted	17	23	6	0	0	0	46 (6.96%)
Recurrence	7	18	1	0	0	0	26 (3.9%)
Died	4	9	5	0	0	0	18 (2.7%)
Biopsy done	44	128	28	0	2	2	204 (30.9%)
Traditional medicine	0	8	3	0	0	0	11 (1.7%)

The total number of patients that defaulted was 97 (14.7%), total deaths were 54 (8.2%), total complications of chemotherapy were 194 (29.4%), total medical conditions were 314 (47.5%), total recurrence was 53 (8.01%). Of these totals, 26 (3.93% had recurrent orofacial BL, 105 (33.4%) had medical conditions on either initial presentation of BL or throughout the course of the treatment. Some of the presentations included fever, jaundice, septicaemia, pneumonia, malaria, diarrhoea, headache, dehydration, weight loss, anemia and cough. Of the 194 that had complications to chemotherapy, 81 patients with orofacial BL had complications accounting for 41.8% of all patients with complications. The complications included vomiting after administration of chemotherapy, neutropenia and anemia in some of the patients. Regarding abscondment, at least half (46) of those that defaulted had orofacial BL.

The abscondment was done during the treatment phase and in most cases abscondment led to recurrences/ relapses. In a few cases, the patients did not return for the repeat dose nor the review examinations. Eight patients with orofacial BL died during their course of treatment, not necessarily because of the tumour but other medical conditions that they presented with. The causes of death were mainly dehydration, hypoglycaemia, severe sepsis, pneumonia, respiratory distress syndrome, severe anemia and in one case, the advanced tumour.

On the relationship between district of residence and occurrence of orofacial BL, all the patients came from the rural area. Lilongwe, a district in the central region had more cases than any other district within the same region and also compared to the northern and southern region. Lilongwe had 65 orofacial BL cases, Dedza had 22 orofacial BL, Salima had 18 orofacial BL, Mchinji had 15 orofacial BL, Dowa and Kasungu had 13 orofacial BL each, Nsanje from the southern region had 12 orofacial BL, Zomba from the south had 11 orofacial BL while Nkhotakota in the centre had 10 orofacial BL. For the rest of the figures, see Table 16 below:

Table 16: Orofacial BL according to district of residence and age groups

District	0-4yrs	5-9yrs	10-15yrs	16-19yrs	20+yrs	Unknown	Totals
Lilongwe	10	40	13	2	0	0	65
Dedza	9	7	6	0	0	0	22
Salima	4	12	2	0	0	0	18
Mchinji	2	13	0	0	0	0	15
Dowa	3	7	2	0	0	1	13
Kasungu	3	7	2	0	0	1	13
Mangochi	1	8	3	0	0	0	12
Zomba	1	9	1	0	0	0	11
Nkhotakota	2	7	1	0	0	0	10
Ntchisi	1	5	1	0	0	0	7
Thyolo	1	4	1	0	0	1	7
Ntcheu	2	4	0	0	0	0	6
Machinga	3	1	1	0	0	0	5
Blantyre	1	4	0	0	0	0	5
Mulanje	1	4	0	0	0	0	5
Mozambique	1	4	0	0	0	0	5
Mzimba	0	2	2	0	0	0	4
Chikwawa	1	2	0	0	0	0	3
Mwanza	1	2	0	0	0	0	3
Phalombe	2	1	1	0	0	0	3
Balaka	1	1	0	0	0	0	2
Nsanje	0	2	0	0	0	0	2
Rumphi	1	1	0	0	0	0	2
Nkhatabay	0	2	0	0	0	0	2
Chitipa	0	0	1	0	0	0	1
Unknown	0	1	0	0	0	0	1
Totals	**51**	**149**	**37**	**2**	**0**	**3**	**242**

PART 2: Prospective study

Demography

A total of nineteen patients from KCH, Lilongwe were examined after being diagnosed with BL. There were 9 (47.4%) males and 10 (52.6%) females. More than two thirds were in the 5-9 year age group (Table 17).

Table 17: Demography

Gender	0-4yrs	5-9yrs	10-15yrs	Total
Male	1 (5.3 %)	5 (26.3 %)	3 (15.8 %)	9 (47.4 %)
Female	2 (10.5 %)	8 (42.1 %)	0	10 (52.6 %)
Total	**3 (15.8 %)**	**13 (68.4 %)**	**3 (15.8 %)**	**19 (100%)**

Table 18 shows the sites of the BL lesion and the age groups affected.

Table 18: Site(s) of BL lesion by age group

Site	0-4yrs	5-9yrs	10-15yrs	Total
Mandible	1 (2.4%)	7 (16.7%)	0	8 (19.0%)
Abdomen	2	3 (7.1%)	0	5 (11.9%)
Cheek	0	4 (9.5%)	0	4 (9.5%)
Maxilla	0	2 (4.8%)	2 (4.8%)	4 (9.5%)
Orbits	0	3 (7.1%)	1 (2.4%)	4 (9.5%)
Spine	1 (2.4%)	3 (7.1%)	0	4 (9.5%)
Palate	0	1 (2.4%)	1 (2.4%)	2 (4.8 %)
Maxillo-mandible	0	2 (4.8%)	0	2 (4.8%)
Zygoma	0	1 (2.4%)	1 (2.4%)	2 (4.8%)
Legs	1 (2.4%)	1 (2.4%)	0	2 (4.8%)
Lymph node (s)	0	0	1 (2.4%)	1 (2.4%)
Spleen	1 (2.4%)	0	0	1 (2.4%)
Face	0	1 (2.4%)	0	1 (2.4%)
Liver	1 (2.4%)	0	0	1 (2.4%)
Neck	0	0	1 (2.4%)	1 (2.4%)
Total	**7 (16.7%)**	**28 (66.7%)**	**7 (16.7%)**	**42 (100%)**

Medical conditions at initial diagnosis of BL were malaria (6), cough (3), anemia (1), fever (3), haematuria (1), oliguria (1), dehydration (1), vomiting and very ill presentation (1).

Orofacial presentation included maxillary swelling (4), mandibular swelling (8), palatal infiltration (2), cheek swelling (4), dental abscess (1), dental caries (1), trismus (2), intraosseous mass (2), loose teeth (2), cervical lymphadenopathy (1), maxillary or mandibular pain (4), gingival enlargement (2), geographic tongue (1), infected tumour (2), distended abdomen (3), splenomegaly (1), abdominal pain (3), eye proptosis (3), paraplegia (2), weight loss (1), swollen eye (1), hepatomegaly (1), sore legs (2), numbness of a big toe (1) and constipation (1).

Table 19: Management and treatment outcomes for Prospective BL

Features	0-4yrs	5-9yrs	10-15yrs	Total
CTX	3	12	3	18
CTX + IT MTX + HC	0	1	0	1
COM	1	1	1	3
HIV-Test	2	14	3	19
Recurrence on admission	0	3	0	3
Died	0	2	0	2
Defaulted	0	1	0	1
Relapse(s)	0	1	0	1
Abdominal tapping	0	1	0	1
Total	**6**	**36**	**7**	**49**

Table 19 above is self- explanatory. It includes various outcomes such as type of treatment, chemotherapy protocol, relapses, abdominal tapping, death, defaulted, HIV test and recurrences on admission.18 received CTX monotherapy, 1 received CTX + IT dose MTX + HC, 3 received COM therapy.

Case Report

A 9 year old female presented to the dental clinic - oral surgery section with a huge and rapidly growing mass on the left mandible of 3 weeks duration, a distended abdomen and pain. On examination, the swelling was huge, diffuse and tender on palpation, facial asymmetry and had trismus (Figure 3). Intraorally, the mandibular gingiva was erythematous with lingual and buccal growth displacing the newly erupted first premolar (34) lingually with an intraosseous mass and anterior mandibular crowding. Oral hygiene was poor.

Investigations included a full blood count (FBC), malaria parasites to rule out malaria, HIV pre-test counseling and testing, abdominal ultrasound and skull x-rays. She tested positive for malaria, her full blood count was normal, ultrasound of the abdomen revealed an enlarged spleen (splenomegaly). Skull x-rays did not reveal any pathology hence a clinical diagnosis of Burkitt's lymphoma was made. She was referred to the children's oncology ward for further investigation and chemotherapy. In the ward, a fine needle biopsy was carried out and she was treated with 7 doses of cyclophosphamide intravenously. Her last visit was at the end of July 2009 and there was no swelling and she was well.

Figure 3: 9 year old girl with orofacial BL

CHAPTER SIX

Discussion and concluding remarks

Part I: Retrospective study

In this study, BL accounted for 60.1% of all childhood malignancies in the two hospitals namely KCH and QECH. This is in agreement with other findings by Kalyanyama et al. (2002) who described it as one of the commonest malignancies of the orofacial region whereby their study found BL to constitute 88.2% of all malignancies in children. Similarly, Sinfield et al. (2007), Banda et al. (2001) and Banda (1995) found that BL constituted 50% of all paediatric cancers in Malawi. Consequently, BL has remained the commonest paediatric tumour in Malawi.

In terms of gender predilection for BL, this study showed a male preponderance at a ratio of male to female 1.6:1. Ajayi et al. (2007a, b) showed a male to female ratio of 8:1 and that BL occurred mostly in the first decade of life with maxilla as the most predominant site. The 5-9 year age group predominated BL accounting for 59.9% of all BL cases giving an average age of 7 years. This simply conforms to the endemic form of BL of Africa. According to Ferry (2006), endemic BL are cases that occur in children usually 4-7 years old with a male: female ratio of 2:1, involving the bones of the jaws and other facial bones, as well as kidneys, gastrointestinal tract, ovaries, breast and other extranodal sites. In agreement with Ferry (2006), Tsui et al. (2000) indicated that the incidence of jaw involvement is highest at the age of 3 years and drops steadily thereafter, and the maxilla is affected more often than the mandible in a ratio of 2:1, while in sporadic areas, the mandible is more commonly affected. Surprisingly, abdomen in this study was the most common site accounting for 20.3% whereas the maxilla followed with 13.7%, mandible constituting 7.2% while orbit constituted 10.2%.

From Table 9b it is obvious that there was male preponderance with a male to female ratio of 1.6 to 1, but its statistical significance was measured using chi-square test [(Observed-Expected frequency)^2 divided by Expected frequency]. The null hypothesis H_0 stated that there was no difference between gender and occurrence of cancers in this study. The degree of freedom given by (r-1)(c-1) is (2-1)(3-1) = 2. Chi square test = 0.5568. However at the degree of freedom = 2, the p-value (0.05) was 5.99. The observed frequency between males and females was due to chance alone. Therefore the null hypothesis is valid and it can be deduced that both males and females had equal chances for the occurrence of cancer in this study while clinically, there was a male preponderance.

Similarly with Table 10a, the chi square test was used to test the null hypothesis, H_0, which stated that there is no difference between age groups and various forms of cancer in this study. At the degree of freedom (r-1)(c-1) = (8-1)(6-1) = (7)(5) = 35, and chi square test (X^2) = 99.34. The p-value (0.05) at df = 35 is 49.80. The null hypothesis was therefore rejected because the difference was quite significant.

Therefore there is an association between various age groups and various forms of cancer. BL constituted a majority of the cases affecting children from 0-15 years old.

Orofacial signs and symptoms of BL depend on the site of the lesion. For instance, bilateral maxilla and mandible may cause discomfort and/ or pain, difficulties with speech, breathing, eating, opening and even closing of the mouth. Apart from the usual presentation of maxillary, mandible or cheek swellings, orofacial findings included intraoseous mass, intraoral swelling, bouncy loose teeth, displaced mobile teeth, ulceration, gingival enlargement or growths, gingival bleeding and/ or bleeding tumour, submandibular and cervical lymphadenopathy, halitosis, infected tumour with necrotic tissues in one of the prospective BL cases, palatal infiltration, nasal blockage due to growth, dental caries, jaw deviation, trismus, salivation, cellulitis and facial swelling. Pain in this study was not a prominent feature and this is in agreement with Tsui et al. (2000 p10).

The trend of BL cancers from both KCH and QECH has decreased from 2005 to 2007 probably due to better access to health services by the public and use of treated bed nets against mosquitoes with the aim of preventing malaria, a disease that causes high mortality and morbidity in Malawi. Malaria accounts for most of the hospital admissions and out-patient attendances countrywide.

Overall, HIV serostatus did not seem to contribute much to the occurrence of BL such that only 3.38% of the patients with orofacial BL were HIV seropositive whereas 38.4% were HIV seronegative in the retrospective study. While HIV is known to be associated with BL in Europe and North America, the same cannot be said in Malawi where it has been demonstrated that BL is independent of HIV and site of presentation. NHL was one of the first cancers identified as being AIDS-related (Beral et al. 1998) but African studies suggest that the risk associated with HIV is very much lower than in Europe and North America (Newton et al. 1995). However, the incidence of NHL is not high at least in comparison with the US, and a substantial proportion of NHL is BL, which is largely confined to childhood age groups. Also in agreement to this is a recent study in Uganda which indicated that the risk of this cancer is not influenced by HIV infection (Parkin et al. 2000). In addition to this, Malawi has long been known to be an area of endemic BL since the late 1960s (Banda et al. 2001; McGlashan, 1969).

Part II: ***Prospective study***

With the prospective BL study, the mandible was the most common site whereas the females dominated accounting for more than half of all the cases. There was no statistical significance between males and females in the occurrences of BL.

All the nineteen (19) were tested for HIV and only one 9 year old female patient was HIV positive. This one patient was very ill with pallor, jaundice and severe dehydration when she first presented at KCH dental department. While in the dental department, she was resuscitated with half darrows just to keep her hydrated. She presented with bilateral maxillary and mandibular swellings. She also complained of abdominal pain and lower left leg pain. On examination, she was very pale, jaundiced, febrile and had trismus. Intraorally, she had bilateral and pedunculated swellings on both mandibles that were purplish. Because of trismus, the mouth could not be properly examined and she was admitted into the general paediatric ward to be stabilized first before the oncology unit. Unfortunately, she died two days after her being admitted to the ward. This is a typical example of patients whereby health care workers could not adequately diagnose cancers including BL. She was severely dehydrated and anemic and could hardly move her lips. She possibly had a tumour lysis syndrome.

The second death in the prospective BL study was an 8 year old female that presented with a huge recurrent mandibular swelling and swollen left eye. The tumour recurred six months after remission. On examination, she was a wasting, unhappy ill child with facial asymmetry and halitosis. The swelling was hot to touch and very tender on palpation. Intraorally, there was necrosis in the left mandible. She was given high doses intravenous antibiotics and daily irrigation with diluted hydrogen peroxide and normal saline after debridement of necrotic tissues was complete. The child improved for a week, but deteriorated thereafter. The swelling was fluctuant and extremely tender on palpation, requiring incision and drainage. Unfortunately the mother absconded when she saw that the child was deteriorating by the day. The guardian then decided to discharge the child from hospital so that the child should die at their home in Nkhatabay, in the northern region. On the way there, the child died. Hesseling et al. (2003) reported that guardians had a tendency to abscond with their children if treatment appeared to make their children sick. Furthermore, parents and guardians often live far away, have large families to support and have to support themselves away from home during the child's hospital stay. In the present retrospective BL study, some guardians absconded with their children at the time when hospitals had a shortage of drugs. Sustainability of drugs is very crucial considering that BL constitutes 60.1% of all childhood malignancies in Malawi.

These cases highlight the importance of patient education and support. Huang et al. (2005) suggested that patient education should include information about the disease and adverse effects of the drugs used to treat the diseases; however, they further emphasized the need for emotional support. Educating health care workers directly involved in patient care and family members about the need for emotional support for the patient is very important. To date the remainder of the prospective BL study patients are alive, some still receiving chemotherapy while two have completed treatment with no recurrence.

The fact that Lilongwe had more cases than any other districts may indicate an association between the environment and the occurrence of BL. Generally, there were more BL cases in the central region than the north and south combined. Could it be the cultural practices that predispose these children to BL? Further research in this area is worth pursuing.

In conclusion, BL continues to dominate childhood malignancies in Malawi and therefore needs urgent attention from all corners of the society. The community needs to be encouraged to continue using treated mosquito bed nets for malaria prevention since malaria is thought to be one of the causes of BL. The University of North Calorina (Chapel Hill) Project together with KCH and Lilongwe district health office have already initiated the malaria vaccine with an effort to prevent incidences of malaria which at the moment is the number one killer disease.

Dentists and dental auxiliaries need to recognize BL as quickly as possible for prompt referral if they are in the rural or remote area. It should also be the dental staff's responsibility to educate the community in their catchment area so that they present early as soon as their children start noticing loose teeth and acute swellings without any obvious cause.

BL remains the most common childhood malignancy and orofacial manifestation need to be understood by all health personnel involved in the care of the patients so that prompt referral is made for a better prognosis. Some of the orofacial manifestation could be life threatening causing obstructed airways.

The present study has demonstrated that BL responds better to chemotherapy and it is curable. Best management of BL involves having knowledgeable people on the ground to necessitate prompt referral at all health facility levels. Secondly, there has to be trained staff on management and administration of chemotherapy. KCH has one trained nurse in chemotherapy administration while QECH has more than one nurse. Each hospital has a clinical staff that is committed to the oncology ward.

CHAPTER SEVEN

Recommendations

1. Each hospital needs to train its health care workers directly dealing with the cancer patients on various forms of cancer, diagnosis and management, possible complications, and patient care for emotional support.
2. All health care workers in the rural areas and those working in the private sector should undergo training in the early detection and prompt referral of BL cases.
3. Oral health care workers need to be trained on the orofacial manifestations of BL so that referral and treatment are promptly made.
4. Intensive campaigns to encourage mothers to use bed treated mosquito nets for prevention of malaria and to access health services (which is free) rather than utilising traditional healers for an initial diagnosis.
5. Further research to establish why Lilongwe is a BL prone district with more BL cases than any other districts in the central region and the other two districts.
6. Government need to make chemotherapy readily available in optimal doses rather than sub-optimal doses that encourage recurrences.
7. Government needs to include BL as one of the priority diseases so that chemotherapy should be part of the essential health package for the referral hospitals.
8. The malaria vaccine, if successful, must be included in the EPI (expanded programme of immunization) package so that the rural areas can benefit directly.
9. Orofacial manifestation of BL should be included in the training curriculum for dental therapists.

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Appendix 1: Oral health data capture sheet (Retrospective study)

BURKITTS Retrospective Data Collection Form (to be collected with the attached leaflet)

1	Name of Facility						
2	Name & Record number						
3	Who referred the patient	Self	Dental	Medical Assistants	Nurse	Other (specify):	
4	Where does the patient live (district)?						
5	Age (in years)						
6	Gender					M	F

Medical History

Condition		**Yes**	**No**	**Not recorded**
7	Malnutrition			
8	Malaria			
9	Tuberculosis			
10	HIV			
11	Anaemia			
12	Fever			
13	Other: please describe fully:			

14. Other sites of Presentation

	Condition	Yes	No
	Abdomen		
	Liver		
	Brain, CNS		
	Spleen		
	Lungs		
	Spine		
	Breast, Ovaries		
	Kidney		
	Other: please describe fully:		

15. Site of Oro-facial Burkitts Lesion

1	Mandible	
2	Maxilla	
3	Mandible/Maxilla	
4	Palate	
5	Tongue	
6	Lip	
7	Cheek	
8	Parotid	
9	Not specified	
10	Other (please describe):	

16. Oro-facial Presentation at initial diagnosis

1	Cervical lymphadenopathy	
2	Enlargement of tonsils	
3	Nasal blockage	
4	Facial swelling (incl. salivary gland)	
5	Numbness/parasthesia of lip, face	
6	Intra-oral swelling (palatal, gingival, tongue, salivary gland)	
7	Intraosseus mass	
8	Mobile/loose teeth	
9	Displaced	
10	Other (please describe):	

17. Detailed Description of Burkitts Lesion

Size, Extent (lip, cheek, palate etc), Texture, Colour

18.	**Was treatment provided?**		**Yes**	**No**
	If yes, what, please describe fully?			

19.	**Was the patient hospitalised following your diagnosis of Burkitts**	**Yes**	**No**
	If yes, for how long?		
	If yes, what was done? Describe fully		

20. Tests done

Tests		**Yes**	**No**
	Fine needle biopsy		
	Blood tests (CBC, platelet etc)		
	Chest X-rays		
	Skull X-rays		
	Intra-oral X-rays		
	Lumbar puncture		
	Bone marrow		

	Ultrasound		
	CT scans (head, spinal, abdominal)		
	Bone scan		
	HIV		
	Malaria		
	Other: please describe fully:		

21. Outcomes

	Outcome	**Yes**	**No**	**Not recorded**
	Cured, Survived and in remission			
	Recurrence			
	Complications (specify):			
	Treatment Failed			
	Referred			
	Transferred			
	Lost to follow up			
	Defaulted			
	Died			
	Other:			

Appendix 2: Oral health data capture sheet (Prospective study)

BURKITTS Prospective Data Collection Form (to be collected with the attached leaflet)

1	Name of Facility					
2	Name & Record number					
3	Who referred the patient	Self	Dental	Medical Assistants	Nurse	Other (specify):
4	Where does the patient live (district)?					
5	Age (in years)					
6	*Gender*				M	F

Medical History

	Condition	**Yes**	**No**	**Not recorded**
7	Malnutrition			
8	Malaria			
9	Tuberculosis			
10	HIV			
11	Anaemia			
12	Fever			
13	Other: please describe fully:			

14	**Family/sibling history of Burkitts?**	Yes	No	Don't know
	If yes, who and when did they have it?			

15. Other sites of Presentation

	Condition	**Yes**	**No**
	Abdomen		
	Liver		
	Brain, CNS		
	Spleen		
	Lungs		
	Spine		
	Breast, Ovaries		
	Kidney		
	Other: please describe fully:		

16. Site of Oro-facial Burkitts Lesion

1	Mandible	
2	Maxilla	
3	Mandible/Maxilla	
4	Palate	
5	Tongue	

6	Lip	
7	Cheek	
8	Parotid	
9	Not specified	
10	Other (please describe):	

17. Oro-facial Presentation at initial diagnosis

1	Cervical lymphadenopathy	
2	Enlargement of tonsils	
3	Nasal blockage	
4	Facial swelling (incl. salivary gland)	
5	Numbness/parasthesia of lip, face	
6	Intra-oral swelling (palatal, gingival, tongue, salivary gland)	
7	Intraosseus mass	
8	Mobile/loose teeth	
9	Displaced	
10	Other (please describe):	

History of Oral Problems

18	Are you having any pain or discomfort with your mouth now?	**Yes**	**No**
	If yes, please describe		
19	If yes, is this pain /discomfort causing difficulty with:	**Yes**	**No**
	Eating		
	Drinking liquids		
	Swallowing solid food		
	Speaking		
	Breathing		
	Playing		
	Sleeping or resting		
	Other (please describe)		

20. Detailed Description of Burkitts Lesion

Size, Extent (lip, cheek, palate etc), Texture, Colour

21. Oro-facial or intra-oral pathology (please describe fully)

CODE	CONDITION	CODE	LOCATION
1	**No abnormal condition**	11	upper lip
2	Pseudomembraneous Candidiasis	12	lower lip
3	Erythematous Candidiasis	13	mucosa of upper lip
4	Hyperplastic Candidiasis	14	mucosa of lower lip
5	Angular Cheilitis	15	mucosa around corner of mouth on R side
6	Herpetic Ulceration	16	mucosa around corner of mouth on L side
7	Apthous Ulceration	17	cheek mucosa on R side of patient
8	Infective (TB, STDs) Ulceration	18	cheek mucosa on L side of patient
9	Atypical Oral Ulceration	19	mucosa of upper jaw, bet lip/cheek & gums
10	Erythema Multiforme	20	mucosa of lower jaw, bet lip/cheek & gums
11	Oral Hairy Leukoplakia	21	mucosa of gums of upper teeth
12	Kaposi's Sarcoma	22	mucosa of gums of lower teeth
13	Sarcoma	23	top surface of tongue
14	Carcinoma	24	Sides of tongue
15	HPV-related lesions	25	under surface of tongue
16	Leukoplakia	26	mucosa bet undersurface tongue & gums of L teeth
		27	mucosa of hard palate
		28	mucosa of soft palate
		29	mucosa behind last molar of U & L jaws

Other lesions (please describe in full):

.....

.....

.....

CONDITION	LOCATION

22.	**Did the patient have any treatment for the Burkitts lesion previously?**		**Yes**	**No**
	If yes, by whom?			
	What did they do?			

23.	**Was the patient previously hospitalised?**		**Yes**	**No**
	If yes, for how long?			
	If yes, what for?			
	Other (please describe):			
24.	**Was treatment provided at this present visit?**		**Yes**	**No**
	If yes, what, please describe fully?			

25.	**Was the patient hospitalised following your diagnosis of Burkitts**		**Yes**	**No**
	If yes, for how long?			
	If yes, what was done? Describe fully			

26. Tests done

Tests		Yes	No
	Fine needle biopsy		
	Blood tests (CBC, platelet etc)		
	Chest X-rays		
	Skull X-rays		
	Intra-oral X-rays		
	Lumbar puncture		
	Bone marrow		
	Ultrasound		
	CT scans (head, spinal, abdominal)		
	Bone scan		
	HIV		
	Malaria		
	Other: please describe fully:		

27.	Was the patient referred following your diagnosis of Burkitts	Yes	No
	If yes, to whom?		

Ref: a:/Burkitts/datacapt.wpd

25/02/08

Appendix 3: Informed consent

Date:

Dear Parent of ……..,

I am a Masters Student in the Department of Community Oral Health at University of the Western Cape. We are interested in examining your child's face, mouth and teeth to look for any problems related to cancer (Burkitt's lymphoma). We are doing this to see if we can come up with signs that can help clinicians to rapidly diagnose this cancer and refer the child promptly for management.

The oral examination will take about 10 minutes. We may take photographs, but we will only take photographs of your teeth and no one will be able to identify the child or see the face on the photographs. There are no risks in participating and there should be no more discomfort than in a routine dental check up examination.

All information gathered in the study will be treated as strictly confidential. No one will have access to this information except the researcher. Neither your name nor anything that identifies you will be used in any reports of this study. All information collected will be maintained and stored in such a way as to keep it as confidential as possible.

If you would like your child to take part in the study, please sign the bottom of this letter. Please contact Dr J Mlotha at 08842858 (C) or 09252921 (C) or 01 756900 (w) for any further enquiries.

Thanking you in advance for your co-operation
Yours sincerely

Dr J Mlotha

I ……..understand what will be required of my child to take part in the study. I agree to allow my child to participate in the research being undertaken by Dr J Mlotha. I understand that at any time I may withdraw my child from this study without giving a reason and without affecting his/her normal care, management or schooling.

Name: ……. ……

(print in block letters) (Signature)

Date: …… Witness: ……

INFORMATION LETTER

Dear Participant,

I am a Masters student from the department of Community Oral Health, Faculty of Dentistry, University of the Western Cape and I am investigating the orofacial manifestations in children with cancer (Burkitt's lymphoma). This is a rapidly growing tumour and a major public health problem. I am hoping that this research outcome will assist dental staff and other health workers involved in the chain of referral to rapidly diagnose and refer the patient promptly for treatment of Burkitt's lymphoma.

Your child has been chosen to represent a group of the population, therefore your collaboration in having your child to participate in this study is very crucial.

The survival rate of a child with BL depends on rapid diagnosis and treatment. In order to achieve early rapid diagnosis, knowledge of the orofacial presentations of BL is essential for prompt referral. In this respect, your child's participation is crucial for the success of this study, and thus improving oral and general health of the population.

Thank you in advance for your cooperation.

Yours sincerely

Dr. J. Mlotha

Appendix 4: Consent to access records and to carry out research study

TO: THE HOSPITAL DIRECTOR

Kamuzu Central Hospital
P.O. Box 149
Lilongwe
ATTN: DR. HADGE JUMA

Queen Elizabeth Central Hospital
P.O. Box 95
Blantyre
ATTN: DR. GERALD MSUKU

I, Dr J Mlotha, am a Dentist at Kamuzu Central Hospital. At present I am a part-time Masters student at the Department of Community Dentistry, University of the Western Cape.

Malawi, like other African countries in the central and eastern region, has high prevalence of childhood malignancies of which BL constitutes 40-50% (Banda, 2001; Banda, 1995). Concomitant with the malignancies are other features such as low birth weight, high infant and under-five mortality rates due to malaria, severe anemia, malnutrition, neonatal sepsis, HIV/AIDS, meningitis and pneumonia (WHO, 2006). The large majority of children with BL come from the rural areas where there are no facilities for its management. In this regard, it is necessary that all health care workers become familiar with the orofacial manifestations of BL for early detection and prompt referral to central hospitals (tertiary level care) for management, considering the aggressive nature of the tumour.

The purpose of this study is to document the orofacial manifestations in children with BL. It is anticipated that the findings may assist in the education of oral and other health care workers in the early recognition of BL for prompt referral. Oral health workers are a critical component of the referral chain since these lesions can be life threatening.

For my research project, I have undertaken to do a retrospective patient record-based study to document orofacial manifestations of BL, demographic data, the tests that were conducted, treatment provided and whether they survived or died and had relapse. For the prospective study, I will conduct routine oral examination, take clinical photographs of the lesion only with a signed consent and order radiology studies.

In order to be able to carry out this study I will need access to patient records and the patients. All information gathered in the study will be treated as strictly confidential. No one will have access to this information except me, the principal investigator. No names will be used in the reports of this study. All information collected will be maintained and stored in such a way as to keep it as confidential as possible.

If you have any questions or queries regarding the proposed study please do not hesitate to contact me, Dr J Mlotha on tel: 08842858 (C) or 09252921 (C) and work; 01 756900.

Thanking you in advance for your co-operation.

Yours sincerely

Dr J Mlotha

CHIEF DENTAL SURGEON/ MSC (DENT) DPH STUDENT

Appendix 5: Ethical Consideration for photography

UNIVERSITY OF THE WESTERN CAPE
FACULTY OF DENTISTRY

Patient Consent to Clinical Photography and Video Recordings	Surname: Name: Date of Birth: Gender:

I, ... consent to photographs or video recordings being taken of me/my child as requested, I understand that these photographs and recordings will be stored appropriately, treated with the utmost confidentiality and be part of my dental record. I hereby give consent for the images or recordings to be used ONLY for the boxes I have indicated with a tick (√):

□ **Record purposes and for my/my child's future management**
The photographic images and recordings will form part of the information collected for you or your child's care and treatment. This information is handled in accordance with the HPCSA Booklet 14: Guidelines on the keeping of patient records.

□ **Education and training purposes**
The photographic images and recordings may be used for teaching purposes and viewed by health professionals outside of the UWC Faculty of Dentistry. The images may be used for example, in talks, conference presentations, posters or on the Internet to help train other health professionals in the management of dental and oral diseases

□ **Approved research purposes & publication**
This may involve the photographic images and recordings being used for example in medical or dental publications, journals, textbooks, conference material, e-publications and on the Internet. Images will be seen by health professionals and researchers who use the publications in their professional education. The images may be seen by the general public. Images will not be used with identifying information such as name, however, full confidentiality is not guaranteed.

□ **Other purposes** (please specify): .....

- I understand that all efforts will be made to conceal my/my child's identity but that full confidentiality cannot be guaranteed.
- I understand that my consent or refusal will in no way affect my /my child's dental care.

Patient Signature: ..... Date: .....

Parent/Guardian (if patient under 18 years) Name: .....

Signature..... Date: .....

Child assent (7-17 years): ..... Date: .....

Witness Name & Signature..... Date: .....

Requesting Clinician Name (print): .....

Date: .....

Department: ..... Phone: .....

Patient Name (print): .....

Views required.....

Required for: **Records** **Teaching/Lectures** **Research** **Publication**

Images taken by: .....

Date.....

Location where copies stored: .....