The changing clinical pattern of endemic Burkitt lymphoma in Western Africa? - Experience from a tertiary center in Ghana

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Abbreviations	Full Term
BL	Burkitt lymphoma
BTP	Burkitt Tumor Project
eBL	Endemic Burkitt lymphoma
EBV	Ebstein-Barr Virus
CI	Confidence Interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
FNAC	Fine Needle Aspirate Cytology
IT	Intra-thecal
ITN	Insecticide Treated Nets
IV	Intravenous
KATH	Komfo Ankoye Teaching Hospital
KBTH	Korle Bu Teaching Hospital
NHIS	National Health Insurance Scheme
NIH	National Institutes of Health
POND	Pediatric Oncology Network Database
RR	Relative risk
sBL	Sporadic Burkitt lymphoma
SES	Socioeconomic status
WHO	World Health Organization

ABSTRACT

Background: Burkitt lymphoma (BL) is the commonest childhood cancer in Ghana, where the endemic variant is the predominant subtype and historically presents as a highly chemo-sensitive jaw tumor. This study aimed to update the current epidemiological characteristics of childhood BL in our institution.

Procedure: Patient data for all children diagnosed with BL and seen at Korle Bu Teaching Hospital between January 2007 and December 2012 were retrospectively analyzed.

Results: BL was diagnosed in 173 children (< 13 years) during the study period, with the abdomen as the most common tumor site (46%) followed by the jaw (31%). Abdominal tumors were associated with advanced/disseminated disease (p=0.002), and were more likely to occur in females irrespective of tumor stage (Relative risk= 1.56 [95% CI; 1.1–12.3]). Twenty-five percent (43/173) of the study cohort died and mortality was influenced by increasing age (p=0.02) and advanced disease (p=0.03). Treatment delay was experienced by 9 in 10 patients primarily due to familial financial constraint (75%). Treatment abandonment was observed as a first event in 94% of patients and two-thirds of children in the study were eventually lost to follow up.

Conclusion: The predominance of primary abdominal tumors in our study cohort may indicate a changing epidemiological pattern of BL in Ghana. High rates of treatment delay and abandonment were evident and are likely to be contributing factors to the poor childhood cancer survival outcomes seen in resource limited countries in Africa.

INTRODUCTION

Burkitt lymphoma (BL) is a highly aggressive B-cell malignancy characterized by its hallmark *c-myc* oncogene translocations [1-2], and classified broadly into 3 subtypes based on distinct variations seen in malaria-endemic and non-endemic regions: endemic (African), sporadic (non-endemic) and immunodeficiency-associated BL [3-4]. The endemic variant is found within the "lymphoma belt" of equatorial Africa, an area extending 10–15^{o} north and south of the equator, which corresponds to regions where malaria is holoendemic [5–6].

Epstein-Barr Virus (EBV) and plasmodium falciparum malaria infection are known to be important co-factors in the pathogenesis of endemic BL [3,7-8]. In countries within the lymphoma belt, EBV infection is documented to occur much earlier in childhood [9], and the virus genome isolated in almost 100% of tumor cells unlike the sporadic and immunodeficiency-associated variants, where EBV is detected in approximately 15-40% of cases [8, 10]. Although a causal association between EBV and endemic BL is recognized, the precise mechanism by which malaria infection and EBV reactivation interact to promote oncogenesis remains poorly understood. Malaria-induced lytic EBV reactivation and polyclonal B-cell proliferation has been linked to an increased likelihood of chromosomal translocations that deregulate the *c-myc* oncogene and predispose to tumorigenesis. It has also been proposed that malaria co-infection impairs EBV-specific T-cell immunity as a cause or outcome of enhanced EBV replication, leading to a loss of viral control [11].

Endemic BL (eBL) represents 50-75% of all childhood malignancies in sub-Saharan Africa [12], classically presenting as facial tumor(s) that involve either the jaw or retro-orbital space, while primary abdominal disease is less common [2,13].

The current epidemiology of eBL in Ghana is based on historical data collected during the Burkitt Tumor Project (BTP) from 1968-1996. This was a collaborative research endeavor between the Ghanaian government and the National Institutes of Health (NIH), USA, with its head office located at the department of child health in Korle Bu Teaching Hospital (KBTH), Accra, Ghana. Initial findings of the project suggested a male predominance with a peak age at presentation of 6-8 years, similar to Uganda and Malawi [3,12]. A ten-year prospective study (1969-1979) revealed facial tumors to be the most common clinical presentation in the country followed by abdominal tumors [14]. However, this clinical pattern demonstrated an unexplained reversal in incidence by the early 1980s [15]. Assessment of the geographical distribution of childhood BL in Ghana indicated a non-random temporal pattern, with the majority of cases residing in the southern-most parts of the country. This was attributed to variability in access to medical care as well as physician interest in diagnosis of BL [16].

Recent case reviews have shown eBL to still be the most common childhood cancer in Ghana, though its proportion in relation to other pediatric cancers has steadily declined over time. In the 1990s, two-thirds of all childhood cancers seen at our institution were lymphomas with BL making up over 90% of them [17]. In the past 10 years there has been a decline in the prevalence of childhood lymphomas, dropping to 31% and BL making up 22% of all childhood cancers [18].

Little information exists in either local or international literature about the current clinical pattern of childhood BL in West African countries such as Ghana. We therefore aimed to retrospectively review all children with BL seen at the pediatric oncology unit of our institution over a 6-year period to evaluate its epidemiological characteristics.

METHODS

Study setting

Ghana is a lower middle-income country in West Africa with a population of 25 million and approximately 40% of its inhabitants are aged 0-14 years. Although there is a government-administered National Health Insurance Scheme (NHIS) available to the general population, it does not cover childhood cancers and families are required to pay "out-of-pocket" for chemotherapy and other treatment related expenses.

KBTH is the largest government-funded hospital in Ghana. It is located in the national capital of Accra and serves as a major tertiary referral center for cases from all regions of the country. It is also home to one of only two pediatric oncology units in Ghana. Approximately 125 new oncology cases are seen per year at the unit, encompassing a wide array of solid tumors and hematological malignancies [18]. There is no national cancer registry for the country, making it difficult to accurately estimate national pediatric cancer incidence.

Basic laboratory tests for cancer diagnostic work up are readily available at KBTH. However, most of these tests are not covered by the NHIS and pose a serious financial burden for many patients. Immunophenotyping and cytogenetic studies are currently unavailable in KBTH and EBV serology is not routinely performed as part of the BL diagnostic workup in our unit.

Subject selection criteria and Data collection

All children (< 13 years) with BL confirmed by histology/cytology and diagnosed between January 1st, 2007 and December 31st, 2012 were included.

Patient demographic and clinical information were obtained from their medical records and the Pediatric Oncology Network Database (POND) archive, which is a free access

online database located in the unit and designed by St. Jude's Children's Research Hospital in Memphis, Tennessee, USA, to facilitate hospital-based cancer registration in resource limited countries [19]. Information on age, gender, place of residence, primary caregiver/guardian occupation and educational attainment, HIV status, tumor site, baseline disease staging, and disease outcome were obtained. Both educational attainment and occupation of the primary caregiver/guardian were used as proxy measures for socioeconomic status (SES) and have previously been validated as reliable surrogates for SES in neighboring west African countries [20]. Treatment abandonment was defined as the failure to attend hospital for prescribed chemotherapy within 28 days or a post-treatment follow up appointment within 3 months while treatment delay was said to have occurred if chemotherapy was not initiated within 48 hours of a diagnostic confirmation of BL. Patients who had missing data on abandonment and cause of treatment delay were excluded from the final analysis.

Staging of disease was done using the St. Jude/Murphy classification [21]. Stages I & II constituted localized disease with stages III & IV representing advanced disease. Chemotherapy treatment was administered based on local protocol and staging (Supplemental Table S1).

Statistical analysis

Data were summarized and expressed as means and standard deviations for continuous variables and percentages for categorical variables. Chi-square and Fisher's exact test were used to evaluate proportional differences while student t-test and ANOVA were used to assess differences in means. Relative risk was calculated using the Mantel Haenszel method. All level of significance was considered as $p<0.05$. Data analysis was performed using SPSS version 20.0.

RESULTS

Patient Characteristics

There were 173 children in the study cohort [Table 1] with a mean age of 6.9 (± 2.7) years at diagnosis. No significant gender difference was observed in age at diagnosis [Table 2], though males presented at a slightly older age than females (7.2 years vs 6.4 years, p= 0.09). Only 29% of primary caregivers/guardians had attained a secondary level education or above while almost 50% had no formal education [Table 1]. The majority of parents were employed in low income jobs such as subsistence farming and petty trading [Table 1].

A large proportion of patients (139/173) resided outside of the Greater Accra region – where our pediatric oncology unit is located – and some families from the Northern region had to travel up to 600 kilometers (373 miles) to receive treatment at our institution [Supplemental Figure S1]. All 104 patients with available information on HIV serology tested negative.

Tumor Characteristics

Primary abdominal tumor was the most common clinical presentation [Table 1]. There was a male predominance for jaw tumors [Fig. 1], and males aged 0-4 years were more likely to present with a jaw tumor compared to other sites (Relative Risk = 1.32 [95% CI; 1.10 – 15.33]) while females were more likely to present with an abdominal tumor even after adjusting for age and tumor stage (Relative Risk = 1.56 [95% CI; 1.07 – 12.28]). Facial tumors were most common in the 5–9 years group [Table 2]. The majority of patients presented with advanced/disseminated disease [Table 1], which was strongly associated with abdominal disease (p = 0.002).

Outcomes

Table 3 outlines the factors contributing to delays and abandonment of treatment. Treatment delay was marginally longer for advanced disease compared to localized tumors with lack of funds being the most significant contributor. Abandonment of treatment was nearly universal and abandonment rate did not differ by disease stage. Two-thirds of children in the study were lost to follow up during treatment and 44 (25%) were confirmed to have died during the study period. There was no significant difference in mortality between males and females (p= 0.54). All deaths occurred in children with advanced/disseminated disease and mortality was found to be influenced by increasing age and advanced disease [Table 4].

DISCUSSION

This study updates the clinical pattern of childhood BL in Ghana first described in our institution over 40 years ago and highlights some of the challenges faced by resource limited countries in achieving good treatment outcomes for common childhood cancers. Some limitations to our study findings are centered on its retrospective analysis of historical hospital-based records which had some missing or incomplete data. Furthermore, due to a lack of appropriate patient contact information, we were unable to trace children who had defaulted treatment to determine their disease progression or survival status. This limited our ability to accurately comment on BL-associated survival rates for our cohort. Data were not collected on children who subsequently resumed treatment after initial attrition and so the true impact of treatment abandonment on disease outcome(s) in our study is unknown. The relatively small sample size did not permit more robust statistical analysis and there is a possibility that some of our study findings may be due to chance.

Despite these limitations, it is of interest to note that while the patient demographics for childhood BL in our institution has remained mostly unchanged since the 1960s, there has been a striking transformation in the clinical presentation of disease from the characteristic facial tumor to a predominantly abdominal tumor pattern.

This change has corresponded with a reduction in BL incidence. Approximately 29 cases of BL per year were diagnosed during the study period, representing a 30% reduction compared to figures from the BTP three decades ago [22]. This decline could be due to a reduced exposure of Ghanaian children to malaria as a result of enhanced control measures with Insecticide Treated Nets (ITNs) combined with improved urbanization and socioeconomic status of the average Ghanaian [23-24]. Malaria prevention measures within the lymphoma belt have already been shown to significantly

lower the risk of BL [25]. However, a possible artefact explanation for this decline is the failure to capture undiagnosed cases of BL in the community due to poor parental health-seeking behavior for childhood cancers in Ghana [26]. In addition, the establishment of a second pediatric oncology unit in the country at the Komfo Anokye Teaching Hospital (KATH) in Kumasi has likely led to a reduction in the case referral rate to our hospital. An 8-year retrospective study from KATH estimated their annual BL case rate at 78 cases per year, although this represented both clinically suspected and histologically proven BL [27]. Our study highlights the necessity of a national cancer registry in Ghana for accurate estimation of cancer incidence.

Though facial/jaw tumors are the hallmark feature of eBL, we observed a shift towards predominantly abdominal tumors in patients seen at our hospital. This mirrors findings documented by the BTP in the 1970s, when a sudden and unexplained rise in the proportion of children presenting with abdominal tumors was noticed [15]. The advent of routine radiological imaging as part of the diagnostic workup for children presenting with solid tumors to our unit may offer a plausible explanation for this change as historical cases were not systematically subjected to the same rigorous investigations for tumor localization and autopsies were not regularly performed on children who died from BL prior to treatment [14]. It is possible that the historical burden of abdominal tumors has been underestimated. However, it would be expected that the introduction of routine imaging at our hospital as a standard procedure for tumor staging would correspond to an increase in the proportion of children diagnosed with combined facial/jaw and abdominal tumors and not just solitary abdominal disease. Similarly, while the predominance of advanced disease in our cohort may also offer an alternative explanation due to extensive tumors involving the abdomen, a higher proportion of cases with both abdominal and facial/jaw tumors should also have been noted. We

hypothesize that there has been a reduction in the incidence of BL from an endemic pattern to a level intermediate between endemic and sporadic BL (sBL). Though this cannot be definitively concluded from this study, similar findings have been observed in east and west African regions previously considered to have a predominantly endemic variant of disease [7, 28]. Our study finding raises an issue of the necessity for an accurate and globally accepted definition of endemic versus sporadic BL. While these terms were historically used to describe the epidemiological distribution of BL, the solitary use of geographic location and/or clinicopathological features as descriptive delineators for these variants has been called into question [29]. The longstanding association of endemic and sporadic BL with jaw/facial and abdominal tumors respectively has led to these variants being considered synonymous with these tumor patterns. This is especially true in the lymphoma belt, where diagnosis often relies on clinical presentation with a jaw tumor and findings from fine needle aspirate cytology (FNAC) [30]. The risk of diagnostic misclassification becomes even more acute in cases of abdominal tumors due to the overlapping similarities in the morphological appearance of endemic and sporadic BL on FNAC. [31] While recent advances in molecular studies have led to the identification of subtle but distinct differences in the breakpoint pattern of *c-myc*/IgH gene translocation for eBL and sBL [32], the lack of cytogenetic studies, genomic sequencing and tests for EBV detection in tumor samples in resource limited countries within the lymphoma belt impedes diagnostic certainty. The question of whether all childhood BL within the lymphoma belt should be considered endemic and if not, what specific feature(s) should define it, remains to be addressed for us to fully interpret the implications of our study finding.

We observed similarities with the historical pattern of geographic distribution for children with BL first observed at our hospital in the 1970s [16]. Our findings

underscore previous observations that most children with BL reside in the southern half of the country, with most cases dwelling in the Eastern region. This sharply contrasts with a recent study at KATH in the Ashanti region of Ghana, which found that majority of cases seen at their facility were residents of the Ashanti and Western regions of the country [27]. This discrepancy in geographic distribution of cases is most likely due to bias in proximity and access to medical facilities. Previously, all cases of childhood BL were referred to our hospital from other regions in the country due to health worker awareness of the BTP, which was known to cover all medical costs pertaining to treatment and transportation of patients to and from their home villages [16]. The conclusion of the project, together with the establishment of an alternative oncology treatment center has probably led to significant reduction in the referral rate of BL cases to our hospital from regions that are closer in proximity to the Ashanti region. As seen in other countries [25, 33-34], the incidence and distribution of malaria in Ghana might offer a clue to the possible spatial dispersion of childhood BL. However, available data on geographic variations of malaria transmission in Ghana are conflicting making it difficult to draw any conclusions to this regard.

Occupational status and educational attainment of the parents/guardians were used as proxies for socioeconomic status (SES) in this study and most patients belonged to a low SES. Though the impact of SES on the distribution and clinical characteristics of BL is still unclear, poverty is associated with an early age at primary EBV infection [28, 35], and is likely to influence health-seeking practices, affordability of treatment and compliance. SES should be considered as a surrogate indicator for exposure to factors believed to play an etiological role in BL. It may also be associated with a poor defense response toward environmental exposures due to poor nutrition, poor hygienic conditions, and an increased risk of malaria as a result of poor housing [12].

The strong association between facial/jaw tumors and males aged 0-4 years has also been observed in numerous studies [7, 34-36], suggesting gender differences in exposure to factors that influence tumorigenesis which likely wane with increasing age [7].

Our study highlights the multifactorial influence on outcomes of cancer treatment often observed in resource-limited countries. Many studies have outlined the risk factors for poor prognosis of BL, such as advanced disease and abdominal tumors [37-38]. Approximately 90% of children in our study presented with advanced/disseminated disease, which was strongly associated with abdominal tumors.

Factors known to adversely affect BL treatment outcome such as low SES, distance of residence from referral hospital, inadequate treatment support measures, and poor patient compliance [26, 39] were all present in our study. Although treatment abandonment in our study cohort was much higher than rates of up to 67% documented for childhood cancers in other resource limited countries [40], the fact that 76% of children managed for BL at our hospital did not reside in the Greater Accra region, where our facility is located, might explain why a significant proportion abandoned treatment and were eventually lost to follow up. Low SES was observed to be a predictor of treatment delay for our study cohort which corroborates previous findings that high treatment abandonment rates in developing countries are a major cause of therapeutic failure and adverse outcomes in childhood cancers [40].

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LEGENDS

TABLE 1 Characteristics of children (< 13 years) diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

TABLE 2 Gender and primary tumor site categorized by age group at diagnosis for children diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

TABLE 3 Treatment delays and abandonment rates for children diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

TABLE 4 Survival outcomes for all children (< 13 years) diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

FIGURE 1 Graph of the gender distribution of BL by tumor site for children diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

SUPPLEMENTAL TABLE S1 Local chemotherapy protocol for treatment of endemic BL at KBTH

SUPPLEMENTAL FIGURE S1 Map of Ghana illustrating the geographic distribution of children diagnosed with BL at the pediatric

oncology unit, KBTH (2007 – 2012) by region of residence

TABLE 1: Characteristics of children (< 13 years) diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

Study Co-variates		**N (%)**
Gender	Male	105 (61)
	Female	68 (39)
Age group	0 – 4	32 (19)
	5 – 9	104 (60)
	≥ 10	37 (21)
Parental Occupation	Professional/Managerial	17 (10)
	Subsistence farmer	54 (31)
	Petty trader	52 (30)
	Artisan	34 (20)
	Unemployed	16 (9)
Education of primary caregiver	None	75 (43)
	Primary	50 (29)
	Secondary	31 (18)
	Tertiary	17 (10)
Tumor site	Jaw	54 (31)
	Abdomen	79 (46)
	Jaw & Abdomen	37 (21)
	Systemic	3 (2)
Disease stage	Localized (stages I – II)	20 (12)
	Disseminated/Advanced (stages III – IV)	153 (88)
Survival outcome	Alive	11 (6)
	Dead	44 (25)
	Lost to follow up	118 (69)

TABLE 2: Gender and site of primary tumor for the study cohort categorized by age group at diagnosis.

	0 – 4 years (n = 32)	**5 – 9 years (n = 104)**	**≥ 10 years (n = 37)**	***P***
Gender				
Boys	16	67	22	0.34
Girls	16	37	15	
Tumour site				
Jaw	14	31	9	0.40
Abdomen	10	48	21	
Jaw + Abdomen	7	24	6	
Systemic	1	1	1	

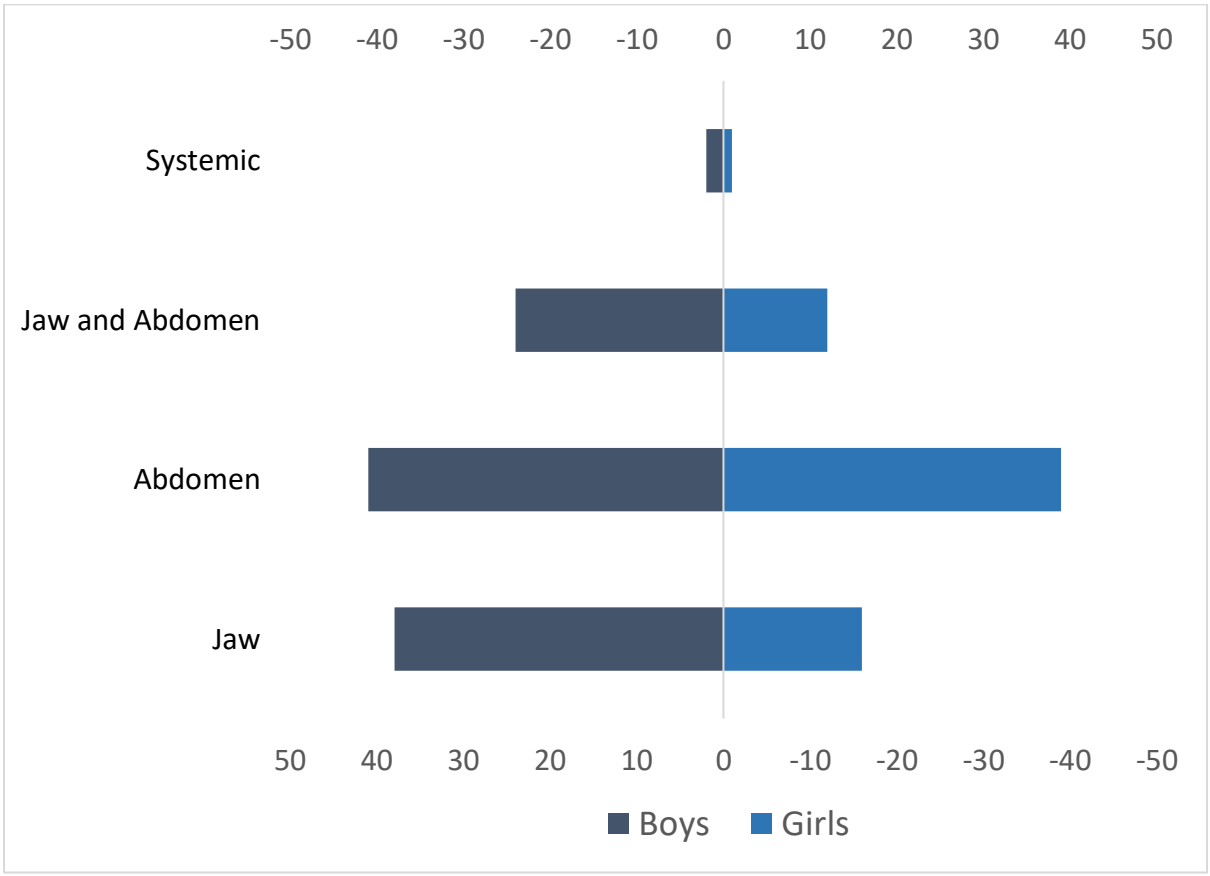
TABLE 3: Treatment delays and abandonment rates for children diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

	All (N = 147)	Localized (n = 20)	Advanced (n = 127)	p-value
Treatment delay (%)				
Febrile Neutropenia	37 (25)	7 (35)	30 (24)	0.28†
Lack of funds	110 (75)	13 (65)	97 (76)	
Days of treatment delay (± SD)				
All	7.0 ± 2.7	7.1 ± 1.8	7.5 ± 2.2	
Febrile Neutropenia	7.2 ± 2.7	7.0 ± 1.9	7.3 ± 2.4	0.89¶
Lack of funds	7.8 ± 2.0	6.9 ± 1.5		
			7.7 ± 2.2	
Other	6.0 ± 1.0			
Abandoned treatment (%)	138 (94)	20 (100)	118 (93)	0.24†

Keys: ¶ = ANOVA test; † = Chi-square test; SD = standard deviation

TABLE 4: Survival outcomes for all children (< 13 years) diagnosed with BL at the pediatric oncology unit, KBTH (2007 – 2012)

	Alive (n = 11)	**Died (n = 44)**	**Lost to follow up (n = 118)**	***P***
Age (in years)				
0 - 4	-	4	28	
5 - 9	3	35	66	0.02
≥ 10	8	5	24	
Gender				
Boys	8	25	72	0.54
Girls	3	19	46	
Disease stage				
Localized (stages I-II)	9	-	11	0.03
Advanced (stages III-IV)	2	44	107	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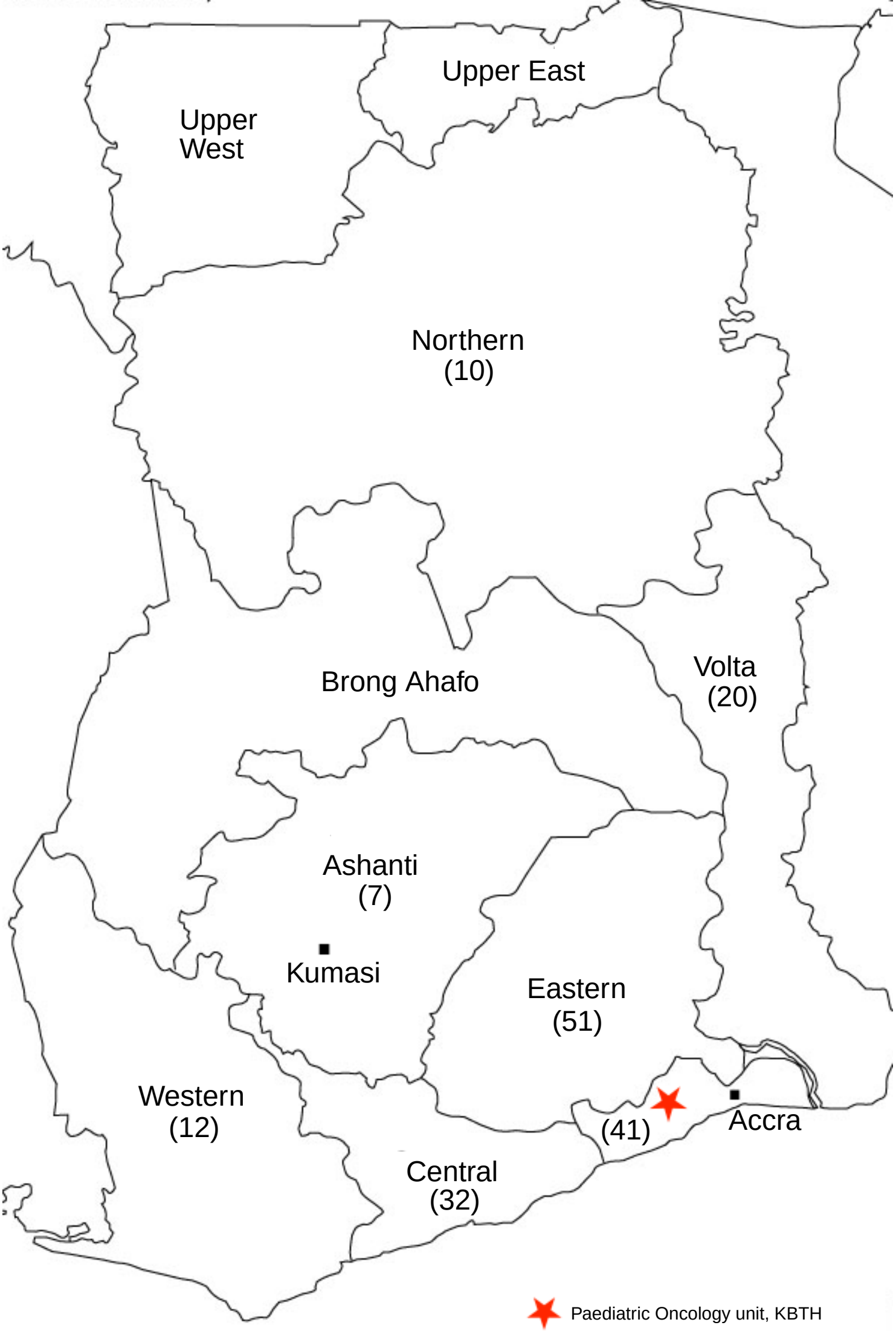
Boys
Girls


Upper East
Upper West
Northern (10)
Brong Ahafo
Volta (20)
Ashanti (7)
Kumasi
Eastern (51)
Western (12)
(41)
Accra
Central (32)
Paediatric Oncology unit, KBTH

LOCAL CHEMOTHERAPY PROTOCOL FOR TREATMENT OF ENDEMIC BURKITT LYMPHOMA ACCORDING TO TUMOUR STAGING AT KORLE BU TEACHING HOSPITAL, ACCRA, GHANA.

Tumor Stage	Course of Treatment
Stage I & II	4 courses of IV Cyclophosphamide 40mg/kg every 2 weeks with intrathecal (IT) Methotrexate for central nervous system (CNS) prophylaxis during courses 1-3.
Stage III	A pre-phase dose of IV Cyclophosphamide 1400mg/m2 with IT Methotrexate, followed by a combination chemotherapy consisting of 6 cycles (Cyclophosphamide, Vincristine and Doxorubicin alternating with Cyclophosphamide, Vincristine and Cytarabine every 2 weeks) with IT Methotrexate given during the first 3 courses
Stage IV	For bone marrow involvement a modified version of a mature B-cell protocol for high income countries without Rituximab is used, and inclusive of four cycles of maintenance therapy, following reduction, induction and consolidation phases of therapy. For CNS disease, additional intrathecal therapy is included until cerebrospinal fluid (CSF) cytology is negative