

Beyond Endemic Burkitt Lymphoma: Navigating Challenges of Differentiating Childhood Lymphoma Diagnoses Amid Limitations in Pathology Resources in Lilongwe, Malawi

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Abstract

Background. Although Burkitt lymphoma (BL) is the most common childhood lymphoma in sub-Saharan Africa, Hodgkin lymphoma (HL) and other non-Hodgkin lymphomas occur. Diagnosing non-jaw mass presentations is challenging with limited pathology resources. **Procedure.** We retrospectively analyzed 114 pediatric lymphomas in Lilongwe, Malawi, from December 2011 to June 2013 and compared clinical versus pathology-based diagnoses over two time periods. Access to pathology resources became more consistent in 2013 compared with 2011-2012; pathology interpretations were based on morphology only. **Results.** Median age was 8.4 years (2.1-16.3). The most common anatomical sites of presentation were palpable abdominal mass 51%, peripheral lymphadenopathy 35%, and jaw mass 34%. There were 51% jaw masses among clinical diagnoses versus 11% in the pathology-based group ($P < .01$), whereas 62% of pathology diagnoses involved peripheral lymphadenopathy versus 16% in the clinical group ($P < .01$). The breakdown of clinical diagnoses included BL 85%, lymphoblastic lymphoma (LBL) 9%, HL 4%, and diffuse large B-cell lymphoma (DLBCL) 1%, whereas pathology-based diagnoses included HL 38%, BL 36%, LBL 15%, and DLBCL 11% ($P < .01$). Lymphoma diagnosis was pathology confirmed in 19/66 patients (29%) in 2011-2012 and 28/48 (60%) in 2013 ($P < .01$). The percentage of non-BL diagnoses was consistent across time periods (35%); however, 14/23 (61%) non-BL diagnoses were pathology confirmed in 2011-2012 versus 16/17 (94%) in 2013. **Conclusions.** Lymphomas other than Burkitt accounted for 35% of childhood lymphoma diagnoses. Over-reliance on clinical diagnosis for BL was a limitation, but confidence in non-BL diagnoses improved with time as pathology confirmation became standard. Increased awareness of non-BL lymphomas in equatorial Africa is warranted.

Keywords

Burkitt lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma, Africa, low- and middle-income countries, pathology, pediatric oncology, global health

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Introduction

Identified as a lymphoma in Uganda in the 1960s, Burkitt lymphoma (BL) is the most common overall childhood cancer throughout the malaria-endemic regions of

Africa.¹⁻³ Whereas the classical presentation with a rapidly progressing jaw mass is clinically distinct, abdominal mass presentations are impossible to definitively diagnose without pathology evaluation. With a paucity of pathology resources throughout sub-Saharan Africa, it is



evident that childhood malignancies are often diagnosed on clinical grounds or remain undiagnosed.^{4,5}

Over the past 50 years, the majority of endemic BL research studies have relied on clinical or cytology-based diagnoses from fine needle aspiration (FNA).⁶⁻²⁴ Although this is usually sufficient for the classic jaw mass BL presentation, the overlap in similarity of the morphological appearance of BL with the other common non-Hodgkin lymphomas (NHLs) of childhood—lymphoblastic lymphoma (LBL) and diffuse large B-cell lymphoma (DLBCL)—as well as with other small round blue cell solid tumors of childhood, renders this approach fallible.^{25,26} Although the classic cytological appearance of BL with cytoplasmic vacuoles is characteristic, many cases lack these features. In high-income countries, definitive diagnosis of all lymphomas is established with a complete array of diagnostic tools, including morphology, immunohistochemical stains, flow cytometry, and molecular and cytogenetic studies.²⁷

The spectrum of pediatric lymphomas occurring in regions of Africa with high rates of endemic BL is not well described. Data from a multicenter International Network of Cancer Treatment and Research (INCTR) study across sub-Saharan Africa represent the most comprehensive report. Backed by expert international hematopathology review of 132 lymphoma cases, INCTR data demonstrated 72% BL, 13% Hodgkin lymphoma (HL), 7% DLBCL, and 8% other NHL.²⁸ Mutalima et al²⁹ reported 330 lymphomas from Blantyre, Malawi, demonstrating 86% BL, 11% other NHL, and 3% HL—just >60% were pathology confirmed.²⁹

In the United States and Europe, the epidemiological distribution of pediatric lymphoma is well established. HL is the most common overall.^{30,31} Among NHLs, BL is most common (~40%), followed by LBL (~25%), DLBCL (~15%-20%), anaplastic large cell lymphoma (~5%-10%), primary mediastinal B-cell lymphoma (~5%),³¹⁻³⁴ and other rare NHLs (<5%).³⁵ Because clinical presentations and therapeutic strategies for the various lymphomas are distinct, determining the precise histology is critical.

Although there are a few institutions in sub-Saharan Africa attempting to provide comprehensive pediatric oncology treatment, severe limitations in resources remain a critical problem.⁵ Lacking capacity to treat all childhood cancers, several hospitals have attempted to provide single-agent cyclophosphamide regimens aimed at treating low-stage BL (ie, disease limited to the jaws).^{16,17,36-39} This approach was a logical first step toward the provision of care and treatment for children with cancer because of a few factors: (1) the predominance of BL in sub-Saharan Africa, (2) limitations in access to chemotherapy, supportive care, and diagnostic resources, and (3) the established success of curing low-stage BL with cyclophosphamide monotherapy. At Kamuzu Central Hospital (KCH) in Malawi's capital city Lilongwe, this was the treatment paradigm for 20 years.¹⁵

In 2011, the pediatric oncology program at KCH was expanded with the goal of attempting curative treatment of the most common childhood malignancies—lymphomas account for the majority of these curable diseases in Malawi.^{4,29,40,41} The concurrent development of the KCH Pathology Laboratory gradually improved access to pathology services over the study period and greatly enhanced the pediatric oncology program.^{42,43} Acknowledging the challenges of confidently establishing non-BL diagnoses amid severe limitations in resources, our goal was to compare the breakdown of BL versus non-BL diagnoses using clinical and pathology-based methods and describe the evolution of our experience with increasing access to timely pathology evaluations.

Methods

Located in Malawi's central region, KCH is a public tertiary care facility serving a catchment area of approximately 5 to 8 million people. Malawi is endemic for malaria and has an estimated human immunodeficiency virus (HIV) prevalence of 10%.⁴⁴ This study is a retrospective analysis of medical records of children and adolescents (<18 years) newly diagnosed with lymphoma at

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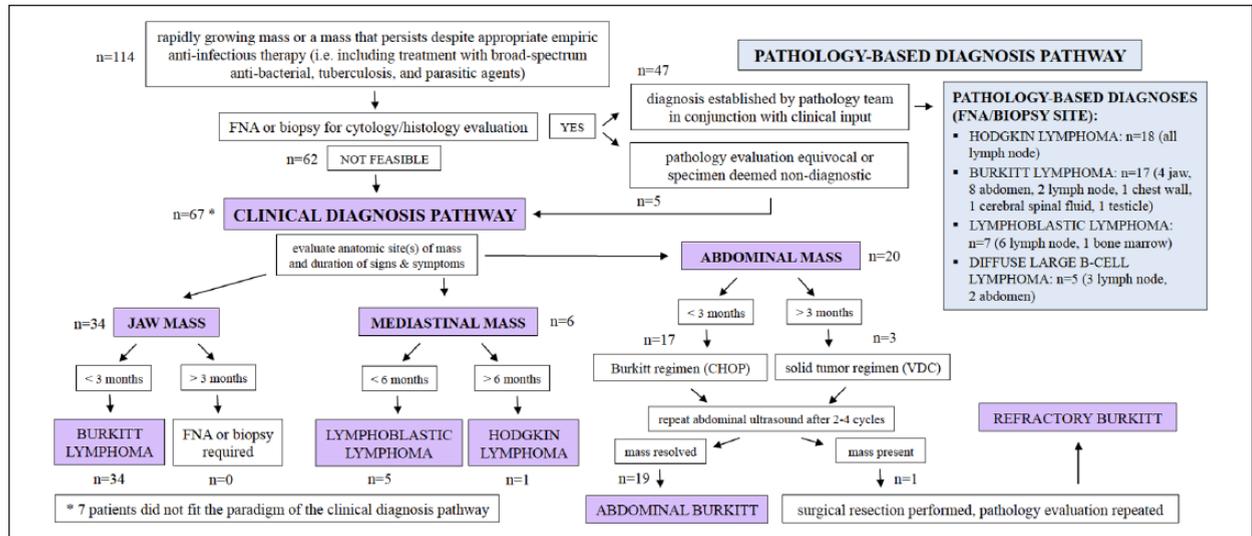
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KCH between December 2011 and June 2013. Data were extracted from medical records and standardized treatment flow sheets; patient health information was de-identified and protected for confidentiality.

Diagnostic and Staging Workup

Standard clinical evaluation included physical exam, complete blood count, point-of-care testing for HIV, chest X-ray (CXR), and abdominal ultrasound. Clinical diagnoses were established based on a constellation of clinical factors, including patterns of anatomical site(s) of presentation, duration of symptoms, and evaluation of treatment response (Figure 1). The well-described phenomenon of a rapidly progressing jaw mass established a clinical diagnosis of BL in the absence of pathology confirmation. Otherwise, clinical diagnoses relied on the established clinical patterns associated with the common pediatric lymphoma entities in high-income countries.

A diagnostic pathology laboratory was opened at KCH in July 2011, and services were gradually increased in subsequent years.^{42,43} In 2011-2012, slide review took place remotely by a pathologist located in Blantyre, Malawi, or through an occasional rotation of volunteers from Pathologists Overseas.⁴² Therefore, although the laboratory was able to process FNA and biopsy specimens, the time required to finalize an interpretation was

dependent on pathologist availability and varied from 1 to several weeks.⁴² Considering this limitation, the clinical utility of delayed pathology evaluation for patients with the aggressive clinical scenarios characteristic of childhood NHL was limited. Bolstered by the addition of a full-time pathologist in late 2012, routine pathology services became incorporated into the pediatric oncology program in January 2013.⁴² From that point onward, except for classic cases of BL or Reed-Sternberg cells (HL), the majority of slides were additionally evaluated at weekly telepathology conferences, including pathologists in Malawi and the United States.⁴² FNA and tissue biopsy specimens were processed and evaluated for morphology only. Sites of FNA/biopsy are delineated for each diagnosis in Figure 1.

A major clinical dilemma surfaced in patients with abdominal masses without other anatomical sites of involvement. In the context of very limited surgical support, intra-abdominal biopsies were not feasible/safe, and those patients who were established as not having solid tumors were clinically diagnosed with BL. Discernment of solid tumor versus abdominal lymphoma was based on (1) pattern of intra-abdominal organ involvement on ultrasound (ie, primary kidney or adrenal masses favored Wilms tumor and neuroblastoma, respectively), (2) reported duration of symptoms (shorter duration of <3 months favored lymphoma), (3) response to initial cycles of chemotherapy (complete

resolution of mass favored lymphoma), and (4) morphological appearance of FNA cytology when available. Upfront surgical resection was not feasible because of the limitations in surgical support; therefore, all patients with abdominal mass received upfront chemotherapy. Some patients who were initially diagnosed as having abdominal lymphoma eventually demonstrated persistence of the abdominal mass after 2 to 4 cycles of chemotherapy and were ultimately identified as having either a refractory lymphoma or a solid tumor on eventual surgical resection. Solid tumors were excluded.

Mediastinal masses, although uncommon as the primary site of presentation in pediatric BL/DLBCL,^{27,45-47} are common in HL, and are the most common anatomical site in LBL.^{33,47,48} Thus, patients presenting with mediastinal masses lacking pathology confirmation were categorized as either HL or LBL based on duration of symptoms (duration >6 months favored HL).

We utilized the St Jude staging classification for NHL and the Ann Arbor classification for HL. Without access to computed tomography (CT) imaging, staging was based on physical exam and CXR only. Abdominal ultrasonography results were inconsistent and often unreliable when used solely for staging assessment; therefore, the presence of abdominal mass was identified by exam only. Mediastinal masses were identified via CXR. Central nervous system (CNS) involvement was based on exam only (ie, cranial nerve palsy, lower-extremity weakness, or bowel/bladder dysfunction). Starting in 2013, routine cytological evaluation of cerebral spinal fluid from the initial lumbar puncture provided additional staging information. Bone marrow aspirations were not routinely performed; bone marrow involvement was determined based on presence of 2 or more cell lines suppressed on peripheral blood count. Bulky disease in HL was defined as mediastinal mass greater than one-third the thoracic diameter on CXR and/or extra-mediastinal nodal aggregates greater than 6 cm in diameter.

Therapeutic and Supportive Care Strategies

Treatment regimens utilized the consistently available chemotherapeutic agents, which included cyclophosphamide, doxorubicin, vincristine, methotrexate, bleomycin, and oral prednisone. The upfront chemotherapy regimen varied according to diagnosis and risk stratification (Table 1). We used a modified INCTR 03-06 BL protocol for patients with stage I/II BL as well as the initial 10 patients with stage III/IV BL.²⁰ After 9 of 10 patients with stage III/IV BL relapsed with INCTR 03-06, and because of the fact that the chemotherapeutic agents (ifosfamide and etoposide) in the INCTR second-line salvage regimen were

unavailable, patients with DLBCL and stage III/IV BL were, thereafter, treated with a modified CHOP regimen (Table 1). We chose not to intensify with high-dose methotrexate because of concerns about its safety in our resource-limited setting.¹⁷ Lacking availability of lymphoblastic leukemia-specific agents (ie, mercaptopurine, cytarabine, asparaginase) and with the challenges of delivering prolonged maintenance phase therapy, patients with LBL received a prolonged CHOP regimen. Patients with HL received a modified ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) protocol without etoposide. Radiation therapy was not available.

General guidelines for chemotherapy included delaying and/or dose-adjusting chemotherapy for absolute neutrophil count $<1.0 \times 10^9/L$ and/or platelet count $<100 \times 10^9/L$. Whole blood transfusions were consistently available; however, access to platelet transfusions was rare. Resources for supportive care have been previously described.⁴⁹ All patients received at least 10 to 14 days of oral allopurinol to treat/prevent tumor lysis syndrome (TLS). Laboratory evaluations of TLS were not available. We generally maintained a low threshold to empirically treat infection/febrile illness with the available antibiotics. Treatment was free of charge, and financial support for transportation was uniformly provided. Definitions of treatment abandonment were according to international guidelines.^{50,51} Only those patients who clinically demonstrated disease progression and subsequently died were defined as having died from disease. All other deaths, where patients died on therapy, were considered treatment-related deaths.

Statistical Analysis and Ethical Considerations

Demographic, disease, and treatment information were described by standard descriptive statistics. Fisher's exact test was used for differences in categorical variables, whereas the Kruskal-Wallis test was used for median values. Survival is reported using standard Kaplan-Meier curves and log-rank test evaluated differences in survivorship functions between groups. Patients who abandoned treatment were presumed to have died and included as deaths in measurements of survival. Statistical significance was considered at a 2-sided α -level of .05. All statistical analyses were done using STATA/IC, version 14 (StataCorp LP, College Station, TX). Ethics committee approval was obtained for this retrospective review from both the Malawi National Health Sciences Research Committee and the Baylor College of Medicine Institutional Review Board for Human Subjects Research. Data were anonymized and de-identified prior to analysis to maintain strict protection of confidentiality. Because of

Table 1. Disease-Specific Chemotherapy Regimens for Pediatric Lymphomas at Kamuzu Central Hospital.^a

Lymphoma	Protocol	Number of Cycles	Frequency
Stage I/II Burkitt lymphoma	Modified INCTR 03-06 protocol Cyclophosphamide 1200 mg/m ² × 1 Vincristine 1.4 mg/m ² × 1 Methotrexate 75 mg/m ² × 1 Prednisone 1-2 mg/kg/d × 5	6	14 Days
DLBCL and Stage III/IV Burkitt lymphoma	Modified CHOP protocol ^b Cyclophosphamide 800 mg/m ² × 1 Doxorubicin 40 mg/m ² × 1 Vincristine 2 mg/m ² × 1 Prednisone 1-2 mg/kg/d × 5	6	21 Days
Lymphoblastic Lymphoma	Modified CHOP protocol ^b Cyclophosphamide 800 mg/m ² × 1 Doxorubicin 40 mg/m ² × 1 Vincristine 2 mg/m ² × 1 Prednisone 1-2 mg/kg/d × 5	8	21 Days
Hodgkin Lymphoma	Modified ABVE-PC protocol Doxorubicin 40 mg/m ² × 1 Bleomycin 10 U/m ² × 1 Vincristine 2 mg/m ² × 1 Etoposide unavailable Cyclophosphamide 800 mg/m ² × 1 Prednisone 1-2 mg/kg/d × 5	6-8	21 Days

Abbreviations: INCTR, International Network for Cancer Treatment and Research; DLBCL, diffuse large B-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

^aAll patients with non-Hodgkin lymphoma received intrathecal methotrexate plus hydrocortisone—2 doses per cycle for patients with central nervous system involvement and 1 dose per cycle otherwise.

^bAn initial 1-week COP reduction prephase (cyclophosphamide 300-400 mg/m², vincristine 2 mg/m², prednisone 1-2 mg/kg for 5 days) was given to mitigate risk for tumor lysis syndrome.

the retrospective nature of this study, informed consent was not obtained for the review of medical records.

Results

Overall, there were 114 patients newly diagnosed with lymphoma, accounting for 44% of all childhood malignancies diagnosed at KCH during the evaluation period (overall n = 258). The median age was 8.4 years (range = 2.1-16.3); there were 41 (36%) girls (Table 2). Pathology confirmation was achieved in 47 (41%) patients: 39 via FNA plus 8 (7 HL, 1 BL) from biopsies. HIV testing was performed in all patients; 4 (4%) were HIV infected (3 BL, 1 HL).

Overall, the most common clinical presentation was palpable abdominal mass (51%) followed by peripheral lymphadenopathy (35%) and jaw mass (34%). There were 51% jaw masses among clinical diagnoses versus 11% in the pathology-based group ($P < .01$) and 62% peripheral lymphadenopathy among pathology-based diagnoses versus 16% in the clinical group ($P < .01$; Table 2). Consequently, the breakdown of diagnoses in

the 2 groups differed significantly. Among 67 clinical diagnoses, there were 57 patients with BL (85%), 6 with LBL (9%), 3 with HL (4%), and 1 with DLBCL (1%). In the pathology-based group (n = 47), there were 18 HLs (38%), 17 BLs (36%), 7 LBLs (15%), and 5 DLBCLs (11%); $P < .01$ (Table 2). Clinical diagnoses of BLs (n = 57) were established by characteristic jaw mass (n = 34) or were diagnoses in patients without jaw mass (20 primary abdominal tumors, 2 periorbital masses, and 1 paraspinal mass with lower-extremity weakness). They all demonstrated rapid improvement with initiation of chemotherapy.

The most common sites of FNA/biopsy were lymph node (n = 29), abdominal mass (n = 11), and jaw mass (n = 4; Figure 1). Five patients had cytology evaluations performed that failed to render a definitive diagnosis, including 1 cervical lymph node FNA, 1 abdominal mass FNA, and 3 evaluations of malignant effusions (2 ascites, 1 pleural).

There were 19 pathology-based diagnoses out of a total of 66 patients (29%) in 2011-2012 compared with 28 pathology-based diagnoses out of 48 patients (60%)

Table 2. Clinical Characteristics and Treatment Outcomes of Children and Adolescents With Lymphoma Categorized by Mode of Diagnosis.

	Overall (n = 114)	Clinical Diagnosis (n = 67)	Pathology Diagnosis (n = 47)	P Value
Median age in years (range)	8.4 (2.1-16.3)	7.6 (2.2-16.3)	9.9 (2.1-15.3)	.01
Female gender, n (%)	41 (36%)	26 (39%)	15 (32%)	.29
Anatomical sites of disease involvement, n (%)				
Abdominal mass	58 (51%)	34 (51%)	24 (51%)	.56
Peripheral LAD	40 (35%)	11 (16%)	29 (62%)	<.01
Jaw mass	39 (34%)	34 (51%)	5 (11%)	<.01
CNS involvement	18 (16%)	12 (18%)	6 (13%)	.61
Periorbital mass	15 (13%)	11 (16%)	4 (9%)	.27
Mediastinal mass	13 (11%)	6 (9%)	7 (15%)	.38
Cytopenias	11 (10%)	4 (6%)	7 (15%)	.20
Lymphoma diagnosis, n (%)				
Burkitt lymphoma	74 (65%)	57 (85%)	17 (36%)	<.01
Diffuse large B-cell lymphoma	6 (5%)	1 (1%)	5 (11%)	
Lymphoblastic lymphoma	13 (11%)	6 (9%)	7 (15%)	
Hodgkin lymphoma	21 (18%)	3 (4%)	18 (38%)	
HIV infected, n (%)	4 (3.5%)	3 (4%)	1 (2%)	.45

Abbreviation: LAD, lymphadenopathy; CNS, central nervous system; HIV, human immunodeficiency virus.

Table 3. Breakdown of Lymphoma Diagnoses Categorized by Time Period.

	Overall (n = 114)	2011-2012 (n = 66)	2013 (n = 48)	P Value
Pathology confirmed, n (%)	47 (41%)	19 (29%)	28 (60%)	.003
Lymphoma diagnosis, n (%)				
Burkitt lymphoma	74 (65%)	43 (65%)	31 (65%)	.21
Diffuse large B-cell lymphoma	6 (5%)	1 (2%)	5 (10%)	
Lymphoblastic lymphoma	13 (11%)	8 (12%)	5 (10%)	
Hodgkin lymphoma	21 (18%)	14 (21%)	7 (15%)	

in 2013 ($P = .003$; Table 3). The percentage of non-BL diagnoses (35%) was consistent across the two time periods (Table 3); however, 14/23 (61%) non-BL diagnoses were pathology confirmed in 2011-2012 versus 16/17 (94%) in 2013 (Table 4). Although the majority of patients with BL were diagnosed clinically, the percentage of pathology-confirmed BLs also increased from 12% (5/43) in 2011-2012 to 39% (12/31) in 2013.

In all, 20 patients (19 BL, 1 DLBCL) received clinical diagnoses in 2013 for the following reasons: having abdominal masses that were not accessible for FNA ($n = 7$), clinical discretion to initiate treatment based on classic presentations of rapidly progressive jaw masses representing BL ($n = 9$), concern over the safety of performing FNA on a periorbital mass ($n = 1$), and 3 patients with cytology evaluations who failed to render a diagnosis.

Table 5 demonstrates clinical characteristics of patients categorized by lymphoma diagnosis. The

abdominal cavity was the predominant anatomical site in patients with BL and DLBCL. Mediastinal mass was most common (77%) in LBL, whereas 95% of patients with HL presented with peripheral lymphadenopathy. Overall, stage I/II BL limited to the jaw/neck represented 22% of all lymphoma diagnoses, and their 18-month overall survival (OS) was 49% (95% CI = 25-68), which trended better than the 18-month OS of 26% (95% CI = 15-40; $P = .09$) for patients with stage III/IV BL and DLBCL. With a median follow-up of 16 months (range = 3-31), 12- and 18-month OS rates for the entire cohort were 36% (95% CI = 27-46) and 29% (95% CI = 18-41), respectively. It is notable that the 18-month OS for patients with LBL was 0% (Table 5).

Discussion

This retrospective observational cohort of children and adolescents with lymphoma in Lilongwe, Malawi,

Table 4. Breakdown of Clinical Versus Pathology-Based Lymphoma Diagnoses Across Time Periods.

Time Period	Clinical Diagnosis	Pathology Diagnosis	Percentage Pathology Confirmed
2011-2012			
BL (n = 43)	38	5	12%
HL (n = 14)	3	11	79%
LBL (n = 8)	6	2	25%
DLBCL (n = 1)	0	1	100%
2013			
BL (n = 31)	19	12	39%
HL (n = 7)	0	7	100%
LBL (n = 5)	0	5	100%
DLBCL (n = 5)	1	4	80%

Abbreviations: BL, Burkitt lymphoma; HL, Hodgkin lymphoma; LBL, lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma.

Table 5. Clinical Characteristics of Children and Adolescents With Lymphoma Categorized by Disease.

	Overall (n = 114)	Burkitt (n = 74)	DLBCL (n = 6)	LBL (n = 13)	Hodgkin (n = 21)	P Value
Median age in years (range)	8.4 (2.1-16.3)	7.6 (2.2-16.3)	11 (2.1-14.1)	9 (4-12.8)	11.5 (3.3-15.3)	.03
Female gender, n (%)	41 (36%)	27 (36%)	2 (33%)	6 (46%)	6 (29%)	.78
Clinical presentation, n (%)						
Abdominal mass	58 (51%)	40 (54%)	4 (67%)	8 (62%)	6 (29%)	.13
Peripheral LAD	40 (35%)	7 (9%)	4 (67%)	9 (69%)	20 (95%)	<.01
Jaw mass	39 (34%)	39 (53%)	0	0	0	<.01
CNS involvement	18 (16%)	16 (22%)	1 (17%)	1 (8%)	0	.06
Periorbital mass	15 (13%)	14 (19%)	1 (17%)	0	0	.04
Mediastinal mass	13 (11%)	0	0	10 (77%)	3 (14%)	<.01
Cytopenias	11 (10%)	4 (5%)	1 (17%)	4 (31%)	2 (10%)	.02
Pathology confirmation, n (%)	47 (41%)	17 (23%)	5 (83%)	7 (54%)	18 (86%)	<.01
HIV infected, n (%)	4 (4%)	3 (4%)	0	0	1 (5%)	1.00
Clinical staging, n (%)						
Stage I/II	37 (32%)	25 (34%)	1 (17%)	0	11 (52%)	
Stage III	46 (40%)	29 (39%)	3 (50%)	8 (62%)	6 (29%)	.03
Stage IV	30 (26%)	20 (27%)	2 (33%)	5 (38%)	3 (14%)	
Median symptom duration, months (range)	2 (0.5-36)	1.5 (0.5-4)	2.5 (1.5-3.5)	2 (1-4)	9 (3-36)	<.01
Overall survival						
12-Month (95% CI)	36% (27-46)	38% (27-49)		15% (2-39)	46% (24-65)	.2
18-Month (95% CI)	29% (20-38)	33% (22-44)		0	38% (17-59)	
Median survivor follow-up, months (range)	16 (3-31)	18 (3-31)		N/A	13 (5-26)	
Treatment abandonment, n (%)	18 (16%)	13 (16%)		1 (8%)	4 (19%)	.72
Number of deaths, n (%)						
Deaths from disease	46 (40%)	28 (35%)		12 (92%)	7 (33%)	.01
Treatment-related deaths	7 (6%)	6 (8%)		0	1 (5%)	.91
Deaths in complete remission	4 (4%)	2 (3%)		0	2 (10%)	.22
Median time to death, months (range)	7 (0.1-26)	5.5 (0.1-26)		9 (1-17)	9 (0.1-23)	.51

Abbreviations: DLBCL, diffuse large B-cell lymphoma; LBL, lymphoblastic lymphoma; LAD, lymphadenopathy; CNS, central nervous system; HIV, human immunodeficiency virus.

^aOne patient with Hodgkin lymphoma abandoned treatment prior to staging, and 8 of 11 stage I/II patients were stage II with bulky disease. Note that for outcome results, Burkitt and DLBCL patients were analyzed as a combined group of patients with mature B-cell non-Hodgkin lymphoma.

demonstrates that approximately one-third of diagnoses are not BL, shifting the lens to focus on increasing the awareness of lymphomas beyond endemic BL. Enhanced by improving pathology services to confirm the non-BL diagnoses over the study period, these data emphasize the importance of not only pathology services, but also collaboration between clinicians and pathologists in this resource-limited setting.

The availability of pathology services evolved over the study period to eventually, in 2013, provide routine diagnostic support for the confirmation of non-BL diagnoses. In comparing the 2 time periods, there were 35% non-BL diagnoses in both 2011-2012 and 2013; the major difference in time periods is that all but one (94%) of the non-BL diagnoses were pathology confirmed in 2013 compared with only 61% in 2011-2012. The 35% non-BL diagnoses in our cohort compares with 28% and 14% non-BL childhood lymphoma diagnoses from data reported by the INCTR and Blantyre, Malawi, respectively.^{28,29} With those proportions of non-BL childhood lymphoma diagnoses occurring throughout the region, we advocate for increased awareness of HL, LBL, and DLBCL with the hope of improving treatment outcomes for all children with lymphoma in sub-Saharan Africa.

In comparing clinical versus pathology-based diagnoses, the breakdown of lymphoma diagnoses contrasted in accordance with the selection bias of clinical presentations in the two groups. There was a significant predominance of peripheral lymphadenopathy in the pathology-based group, primarily because palpable lymphadenopathy is more amenable to FNA and biopsy. That, coupled with the relatively indolent clinical presentation characteristic of HL, theoretically enabled increased uptake of pathologically confirmed diagnoses of HL. In contrast, the distinct nature of a jaw mass that is rapidly growing in size lends itself to an increased overreliance in the clinical confidence in diagnosing BL and decreased numbers of pathology-based BL diagnoses.

With the gradual increase in capacity of the KCH Pathology Laboratory over the study period duration, the uptake of pathology-based diagnoses increased. Although the pathology laboratory was operational starting in July 2011, delays in diagnostic interpretation because of limited availability of pathologists imposed a major limitation on the clinical utility of FNA/biopsy in patients with the aggressive clinical course characteristic of childhood NHL. For that reason, in 2011-2012, there were few pathology-based diagnoses of NHL, and those obtained were mainly by virtue of coincidentally presenting at a time of pathologist availability.

With significant limitations in surgical support for biopsy, a major clinical dilemma surfaced in patients

presenting with primary abdominal tumors. Palpable abdominal mass was the most common anatomical site of presentation in the cohort. Other cohorts have similarly demonstrated high numbers of abdominal BL presentations in Africa, including our more recent prospective cohort of pathologically confirmed BL from KCH.^{22,52} Increased access to more advanced imaging studies (ie, CT or improved ultrasonography), diagnostic laboratory studies (such as lactate dehydrogenase, uric acid, and Epstein-Barr viral load monitoring), and radiology-guided biopsy procedures may improve uptake of pathologically confirmed diagnoses for abdominal lymphomas.^{12,53}

Only 22% of patients presented with stage I/II BL localized to the jaw/neck—the subgroup of patients who historically achieved encouraging outcomes with cyclophosphamide monotherapy.^{6,10,15-17,19,21} Reflecting on the experience at KCH from the previous 20 years, where cyclophosphamide was the only chemotherapy agent available, it appears that a small fraction of lymphoma patients would have had a realistic chance to achieve curative outcomes based on this historical paradigm. The remainder of patients had advanced-stage BL, HL, LBL or DLBCL—and although they received intensified treatment regimens, their long-term outcomes were suboptimal, and there were no survivors among children with LBL. These disappointing results highlight the importance of not only establishing accurate diagnoses, but also providing optimized disease-specific, risk-stratified treatment regimens.^{54,55} It is clear that LBL requires an acute lymphoblastic leukemia-like protocol—a challenge that, to date, has been difficult to surmount in sub-Saharan Africa, however one with successful precedent established in other low-/middle-income countries.⁵⁶⁻⁵⁹

The pattern of pediatric lymphomas in the context of the HIV epidemic in sub-Saharan Africa has not been well described.⁶⁰ Although NHL was the most common HIV-related malignancy in children in the United States and Europe,⁶¹⁻⁶⁶ there does not seem to be an acute increase in pediatric lymphoma incidence in the regions of Africa hardest hit by HIV.^{22,29,67,68} Our data indirectly confirm this observation because HIV-related lymphomas only accounted for 4 cases in the cohort. For contextual comparison, there were 45 children diagnosed with HIV-related Kaposi sarcoma in Lilongwe during the same time period.⁴⁰

Ultimately, the ability to accurately determine pathological diagnoses of lymphoma in sub-Saharan Africa will provide the best opportunity to select the appropriate disease-specific and risk-stratified treatment regimens. The difficulty in making definitive diagnoses of lymphoma based on cell morphology alone is universally

acknowledged; this challenge is more pronounced in sub-Saharan Africa, where the overlap in morphological appearance of BL with LBL and DLBCL can result in diagnostic uncertainty even in centers where cytology is routinely available.^{25,26} In our experience, collaboration between clinicians and pathologists provided increased confidence in pathology-based diagnoses. Prime examples arise in patients with cytology that is suspicious of both BL and LBL; clinical presentation with mediastinal mass and lymphadenopathy will render a diagnosis of LBL, whereas clinical features of an abdominal mass with or without other sites of involvement will render a diagnosis of BL.

Limitations to the study include its retrospective nature, the modest number of pathology-confirmed diagnoses, lack of uniform long-term follow-up, and the limitations of clinical staging information. Recognizing the hardships that populations living in rural poverty endure, delayed presentation to our tertiary care facility occurs and results in encountering extreme clinical presentations that are all included in this retrospective cohort. This may cause a bias toward worse outcomes in comparison with prospective cohorts where such critically ill patients may not meet eligibility criteria. However, this experience captures the reality and scope of challenges encountered in attempting to accurately diagnose and cure childhood lymphoma in sub-Saharan Africa. We hope that it may serve as a foundation on which more sophisticated prospective trials in pediatric lymphoma in Africa can be built. A prospective characterization of lymphoma at KCH is currently under way to more accurately define the spectrum of disease, with a focus on increased access to immunohistochemical stains.⁶⁹ A critical pathology-specific challenge to overcome is the inability to perform immunohistochemical stains on cytology samples. Developing strategies to produce cell blocks from FNA specimens or improve capacity to obtain tissue biopsies has become an important focus.

In conclusion, a variety of childhood lymphomas occur in Malawi beyond endemic BL. Pathology services are essential to definitively confirm the true spectrum of childhood lymphomas in the region. Increased awareness of non-BL lymphomas is warranted, and continued improvements in diagnostic, therapeutic, and supportive care resources are needed to bridge the gap in curative outcomes for pediatric lymphoma in Africa compared with the rest of the world.⁷⁰ With the highest incidence rates of lymphoma worldwide occurring in Africa, we advocate for increased awareness and efforts to implement stronger educational, training, diagnostic, and treatment programs throughout the continent.^{4,41}

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Author Contributions

NKE: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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