Transactions of the Royal Society of Tropical Medicine and Hygiene 105 (2011) 717–726

Contents lists available at SciVerse ScienceDirect

Transactions of the Royal Society of Tropical Medicine and Hygiene

journal homepage: http://www.elsevier.com/locate/trstmh

Clinical characteristics, treatment and outcome of childhood Burkitt's lymphoma at the Uganda Cancer Institute

Jackson Orem[a,b], Yusuf Mulumba[a], Sara Algeri[c], Rino Bellocco[b,c], Fred Wabwire Mangen[d], Edward Katongole Mbidde[a,e], Elisabete Weiderpass[b,f,g,h,*]

[a] Uganda Cancer Institute, Mulago Hospital and the Makerere University School of Medicine, P.O. Box 3935, Kampala, Uganda
[b] Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, P.O. Box 371, SE-171 77, Stockholm, Sweden
[c] Department of Statistics, University of Milano-Bicocca, Via Bicocca degli Arcimboldi 8, 20126 Milan, Italy
[d] Makerere University School of Public Health, Department of Epidemiology and Biostatistics, P.O. Box 7072, Kampala, Uganda
[e] Uganda Virus Research Institute, P.O. Box 49, Entebbe, Uganda
[f] Department of Etiological Research, Cancer Registry of Norway, Pb 5313 Majorstuen, 0304 Oslo, Norway
[g] Department of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway
[h] Department of Genetic Epidemiology, Samfundet Folkhälsan, Pb 211, 00250 Helsinki, Finland

ARTICLE INFO

Article history:
Received 3 September 2009
Received in revised form 2 August 2011
Accepted 16 August 2011
Available online 1 November 2011

Keywords:
Burkitt's lymphoma
Mortality
HIV
Cancer
Pediatrics
Uganda

ABSTRACT

Burkitt's lymphoma (BL) is a major cause of death among Ugandan children. We studied clinical characteristics and outcomes of childhood BL over time at the Uganda Cancer Institute (UCI). A total of 1217 children (766 boys, 451 girls, mean age 6.69 years) diagnosed with BL between 1985 and 2005 were included. There were no significant changes in the proportion of boys and girls diagnosed, or in mean age at diagnosis. Facial tumor ($n = 945$, 77.65%) and abdominal disease ($n = 842$, 69.19%) were the most common presentations. The proportion of children presenting with hepatic mass, malignant pleocytosis, and advanced-stage (stage C and D) BL increased during the study period ($P < 0.01$). A total of 1085 children out of 1206 (89.97%) received at least one cycle of chemotherapy, and 832 of 1099 (75.71%) demonstrated objective response (i.e. complete or partial remission). The most common symptoms at BL diagnosis were fever ($n = 621$, 51.03%), anemia ($n = 593$, 48.73%), and weight loss ($n = 588$, 48.32%). Significant increases in the proportion of children with fever, and significant changes in the proportion of children with anemia, night sweats and severe infection were observed. HIV positivity was 3.87%, but no substantial differences in the proportion of HIV-positive children were observed. Mortality was not significantly different over time: it was similar in boys and girls, higher in older children (compared with younger ones), in those with advanced-stage BL, and HIV-positive children, but lower in children with facial tumors compared with other tumor presentations, and among those who received chemotherapy.

1. Introduction

Burkitt's lymphoma (BL) is the most common childhood cancer in sub-Saharan Africa.[1,2] A recent increase in incidence has been observed in Uganda and many other parts of sub-Saharan Africa in the BL belt.[1,3,4] BL is a major cause of death and misery among children in this region, and although it is easily recognizable, treatable and potentially curable,[5] the outcome of BL in sub-Saharan Africa remains poor. This is mainly attributable to socioeconomic factors such as poverty and lack of access to specialized health care.

* Corresponding author. Tel.: +35 8 40 845 340; fax: +35 8 93 155 116.
E-mail address: eliwei@ki.se (E. Weiderpass).

0035-9203/$ – see front matter © 2011 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.trstmh.2011.08.008

The clinical characteristics of BL may be influenced by immunodeficiency and geographical setting. For example, endemic BL is common in areas with high malaria incidence, such as equatorial Africa and Papua New Guinea, and is etiologically linked to Epstein–Barr virus (EBV). The main clinical characteristic of endemic BL is facial tumors.[2] Sporadic BL on the other hand, is common in the developed world, where presentation with abdominal disease is most often seen. The description of HIV-associated BL has illustrated the influence of immunodeficiency on the clinical characteristics of BL, especially systemic characteristics such as generalized lymphadenopathy.[6] Although it has been previously suggested that the HIV epidemic in sub-Saharan Africa may adversely affect BL prognosis, at present only a few studies have examined this association.[7,8]

The clinical characteristics of BL in African children are thought to be largely unchanged compared with their initial description more than 50 years ago.[9] However, changes in the clinical characteristics of childhood BL may very well have occurred in many sub-Saharan African countries. Given the high incidence of the disease in Uganda, the existence and significance of changes in the clinical characteristics of BL over time are of great importance. Indeed, there is a need to understand the causes of these changes and their impact on disease outcome. Therefore we conducted a study to assess the frequency distribution of the clinical characteristics, treatment and outcome of childhood BL over time at the Uganda Cancer Institute (UCI).

2. Materials and methods

2.1. Study setting

Uganda is a country in East Africa with a population of 30 million, and a per capita income of US$300. The health care system in Uganda is organized into national, regional, district and sub-district levels. Primary health care units are present in different villages and serve a population of about 1000 persons. Institutions on the national level undertake specific health functions, and the UCI is one of them. It was established in 1967 with a mandate of cancer research, training and clinical care.[10]

Patients with suspected cancers detected in primary health care units or sub-district level heath care centers are referred to district hospitals for diagnostic procedures. All tissue samples are sent to regional hospitals for histological diagnosis, and when histological diagnosis cannot be established at the regional hospitals, the samples are sent either to the national hospitals, or to the UCI in Kampala. Turnaround time for histological diagnosis is usually about 2 weeks. If the diagnosis of cancer is confirmed by histology, or if the diagnosis by histology is inconclusive, patients are referred directly to the UCI, the only dedicated cancer treatment center in the country.

Cancer is not a disease that is mandatorily reported to public health authorities in Uganda, thus it is impossible to know the exact number of cases that occur every year countrywide. However, information on incidence rates of BL in Uganda is available from the three regional population-based cancer registries currently functioning in the country. The Kyadondo Cancer Registry in Kampala, the capital city, is the oldest cancer registry in Africa, and has been in operation since 1945. It has a high completeness (90%) and accuracy of cancer reporting for cases in Kyadondo county[11] and has been included in the last 10 editions of *Cancer Incidence in Five Continents* [http://www.iacr.com.fr/statist.htm]. The UCI is within the catchment area of the Kyadondo Cancer Registry. There has been no change in the cancer reporting system in Uganda in the last 25 years. However, since the 1980s, the HIV epidemic and the emergence of HIV-related malignancies, a major one being BL, have changed the epidemiology of cancer in Uganda.[1] Although BL is more common in HIV-positive people, there has not been a dramatic increase in the number of BL cases in Uganda in the last decades, and information on the characteristics of the subset of HIV-positive individuals with BL is scanty.

2.2. Children included and information retrieved

The primary selection criteria for inclusion in the present study were: age less than 18 years; clinical, histological or cytological diagnosis of BL; and first admission to the UCI between 28 September 1985 and 21 February 2005 (beginning and end of enrollment period for newly diagnosed patients). Thus this study comprises nearly 20 years of observation. The start date for inclusion was chosen as this was the time when standardized comparable medical records became available. Indeed, before the 1985 war and political instability in Uganda caused several medical doctors to flee the country. As a consequence, the management of patients and their medical records at the UCI was of poor quality, and unsuitable for data analysis.[12]

Follow-up time was defined as the date of first admission to the UCI with a BL diagnosis until 29 October 2006, which was the last date of reported admission or visit to the UCI considered for this study. Children were considered lost to follow-up if no clinical information was available in the medical records 6 months after the last expected follow-up visit.

Medical records from the UCI were retrieved and reviewed for demographic and clinical characteristics, as well as vital status (as no reliable mortality registry exists in the country). Information on sex, age, symptoms, tumor presentation and disease stage at baseline, HIV status (by ELISA test, which is the most common for HIV diagnosis in Uganda), chemotherapy treatment administered, response to chemotherapy and vital status were abstracted. The staging work-up, UCI treatment protocol, and criteria for response to chemotherapy have been described in detail elsewhere.[8] Briefly, the staging work-up includes an evaluation of clinical history, physical examination and tumor measurements supplemented by basic imaging (X-rays of the jaw or chest, or abdominal ultrasound). The work-up also includes laboratory testing: complete blood counts, bone marrow aspirate, blood chemistry (liver and renal function tests), lactic acid dehydrogenase, uric acid and electrolytes (Na^+, K^+, Ca^{++}, Cl^-, bicarbonates), and whenever necessary, biopsy and cerebrospinal fluid analysis. BL is then staged as follows: A: solitary extra-abdominal site; B: multiple extra-abdominal sites; C: intra-abdominal

tumor with or without facial tumor; D: intra-abdominal tumor; AR: resected intra-abdominal tumor.[13–15] In some analyses stages C and D were grouped together as advanced disease.

The only effective treatment for BL is chemotherapy. Children with BL at the UCI receive cycles of chemotherapy every 2 weeks, for a total of four to six cycles over 2 or 3 months. A minimum of three cycles are required to achieve complete remission. The first line of chemotherapy, irrespective of disease stage, comprises a combination of cyclophosphamide, vincristine and methotraxate. Intrathecal methotraxate or cytosine arabinoside were used for central nervous system prophylaxis and treatment. After the first line of chemotherapy, a re-staging work-up is done to determine response to chemotherapy. Those who achieve complete remission are followed up every 2 months for 6 months. After the first 6-month follow-up period, subsequent follow-up is carried out as follows: every 4 months for 1 year, then every 6 months for a further year, and subsequently yearly. Children with BL who achieve only partial remission, or who relapse, are further treated with another chemotherapy combination as a second line of treatment.

In the analysis presented here, response to chemotherapy was categorized as complete remission (i.e. no evidence of disease), partial remission (i.e. 50% or greater decrease in tumor size), stable disease (i.e. neither decrease nor increase in disease noted), no response (i.e. progressive disease with new disease appearance despite chemotherapy, or recurrent disease with appearance of tumor following documentation of remission), or not assessed (i.e. child died before any response to chemotherapy could be observed, or the child left the hospital at the decision of his/her caretakers). Objective response was defined as complete remission (i.e. no evidence of disease) or partial remission (i.e. 50% or greater decrease in tumor size).

2.3. Statistical methods

Data on the characteristics of children with BL were summarized by means and standard deviations, or with proportions; differences in proportions and means were tested by the χ^2 test, *t*-test, *z*-test or ANOVA procedures.

Time since BL diagnosis was used as the temporal scale in the survival analysis. Death due to BL was used to define the failure status, whereas all other means of leaving the study were considered to censor the observed survival. The Kaplan–Meier technique was used to calculate 5-year survival rates, and the log-rank test was used to analyze differences between survival curves. Next, the Cox proportional hazards model[16] was fitted to estimate the hazard ratio (HR), reflecting the effect of the covariates on survival.

Odds is defined as the ratio of the probability that the event of interest will occur, in this case presenting with an advanced stage of disease, divided by the probability that the same event will not occur (i.e. [risk/1−risk]). For the analysis of disease stage, logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals to compare stages of disease at baseline by sex and presence of ovarian mass.

Both Wald and likelihood ratio tests were used to assess the statistical significance of the variables of interest. All *P*-values were derived from two-sided tests and $P < 0.05$ (assuming a 95% confidence level) was considered statistically significant. Cox assumptions of proportionality were evaluated both graphically and analytically, using a test based on Martingales and Schoenfeld residuals.[17] Data analyses were performed with the Stata statistical package version 11.2 (StataCorp. LP, College Station, TX, USA).

3. Results

Of 1237 children diagnosed with BL with available medical records at the UCI during the study period, 20 were excluded as they were over 18 years of age on the date of diagnosis, or due to lack of date of first or last admission or visit to the UCI. Therefore 1217 children aged 0.4–17 years [766 (62.94%) boys and 451 (37.06%) girls] fulfilled the inclusion criteria for the study and were included in all subsequent analyses. The mean age at diagnosis and first admission to the UCI was 6.69 years (SD = 2.89). The proportion of boys and girls, and the mean age at diagnosis remained similar throughout the study period.

Most children (59.57%) were aged between 5 and 9 years at BL diagnosis, though boys were slightly younger than girls at diagnosis (*t*-test for the difference in mean age, $P = 0.026$). The minimum follow-up time was 1 day (17 children left the UCI the same day they were admitted) and the maximum was 175.86 months (13.49 years), with a mean follow-up of 10.44 months (SD = 23.64 months). Follow-up time was similar between boys and girls ($P = 0.980$) (Table 1).

While most children had a clinical diagnosis of BL, only 50.53% had a histological confirmation and 9.37% had a cytological confirmation of the disease. The proportion of histologically confirmed BL increased significantly in the last period of diagnosis (58.12%). The most common symptoms at diagnosis were fever, anemia, weight loss, night sweats, severe infection and history of severe or recurrent malaria. Significant increases in the proportion of children presenting with fever were observed during the study period, as well as differences over time in the proportion of children presenting with anemia, night sweats and severe infection. The most common tumor presentations were facial tumor and abdominal disease. Among girls, one-third presented with ovarian mass. Presentation with hepatic mass and malignant pleocytosis increased during the study period, whereas other types of tumor presentations remained similar. HIV positivity was 3.87%, and did not differ substantially between different periods of diagnosis. Most children presented with advanced stages of BL (stage C, 32.12% and stage D, 26.67%), and there was an increase in the overall proportion of children presenting with advanced stages during the study period, although girls presented more frequently with advanced stages than boys. Girls presenting with ovarian mass were overwhelmingly diagnosed at advanced stages. About half of the children in the present study received at least three cycles of chemotherapy. There was a small but significant increase in the proportion of children receiving zero or only one cycle of chemotherapy during the study period

Table 1
Demographic characteristics of children aged <18 years diagnosed with Burkitt's lymphoma at the Uganda Cancer Institute by period of diagnosis

	All (n = 1217)	1985–1990 (n = 59)	1991–1995 (n = 258)	1996–2000 (n = 432)	2001–2005 (n = 468)	P-value
Sex						0.250[a]
Boys	766 (62.94)	35 (59.32)	156 (60.47)	264 (61.11)	311 (66.45)	
Girls	451 (37.06)	24 (40.68)	102 (39.53)	168 (38.89)	157 (33.55)	
Mean age at diagnosis (years)						
All	6.69 ± 2.89	6.92 ± 2.65	6.79 ± 3.19	6.59 ± 2.92	6.71 ± 2.72	0.756[b]
Boys	6.55 ± 2.82	6.94 ± 2.75	6.67 ± 3.06	6.55 ± 2.91	6.45 ± 2.64	0.723[b]
Girls	6.93 ± 2.98	6.88 ± 2.54	6.97 ± 3.38	6.66 ± 2.95	7.21 ± 2.80	0.417[b]
t-test difference between boys and girls	P = 0.026					
Age at diagnosis (years)						0.109[a]
0–4	290 (23.83)	13 (22.03)	62 (24.03)	113 (26.16)	102 (21.79)	
5–9	725 (59.57)	35 (59.32)	146 (56.59)	251 (58.10)	293 (62.61)	
10–14	187 (15.37)	11 (18.64)	42 (16.28)	63 (14.58)	71 (15.17)	
15–17	15 (1.23)	0	8 (3.10)	5 (1.16)	2 (0.43)	
Mean follow-up time (days)						<0.001[a]
All[c]	292.19 ± 661.86	610.42 ± 1185.18	588.62 ± 1052.62	268.57 ± 503.53	110.44 ± 165.75	
Boys	291.83 ± 660.85	497.20 ± 1106.70	611.56 ± 1093.55	285.93 ± 516.40	113.34 ± 176.14	<0.001[b]
Girls	292.80 ± 664.31	775.54 ± 1297.56	553.55 ± 991.02	241.30 ± 482.86	104.70 ± 143.32	<0.001[b]
t-test difference between boys and girls	P = 0.980					

Data are number (%) or mean ± SD, unless otherwise indicated.
[a] P-value refers to Pearson's χ^2 test for association between demographic characteristics and period of diagnosis.
[b] P-value refers to ANOVA model for age or follow-up time (overall, for girls and for boys) and period of diagnosis.
[c] Range 1–4924 days.

(P < 0.001). Overall, 89.97% of children received at least one cycle of chemotherapy; the proportion was similar in boys and girls, and in HIV-positive and HIV-negative children. Most children achieved either complete or partial remission, yielding an objective response of 75.71%, which was similar in boys and girls, and increased during the study period (Table 2).

In total, 191 children died during follow-up (15.69% of 1217); among the 1206 children with information on chemotherapy, 46 died without receiving any chemotherapy, and 145 died despite having received at least one cycle of chemotherapy (Table 3). Cox model-derived HRs for mortality indicated that there was no statistically significant difference between boys and girls, nor in relation to type of diagnosis (clinical, histological or cytological). Children aged 15–17 years at diagnosis had a higher mortality rate (HR 3.81, 95% CI 1.81–8.01) compared with children diagnosed at ages 0–4 years. There was a significant increase in mortality rate among children with symptoms of fever, weight loss, night sweats, or severe infection at BL diagnosis, compared with children without these symptoms. Children with symptoms of anemia and severe or recurrent malaria at BL diagnosis had a decreased mortality rate compared with children without these symptoms. Children presenting with facial tumor had a relatively decreased mortality rate (HR 0.33, 95% CI 0.25–0.45) compared with children with other tumor presentations. HIV-positive children had an increased overall mortality rate compared with HIV-negative children (HR 2.50, 95% CI 1.47–4.26). A decreased mortality rate was revealed with increasing cycles of chemotherapy (P < 0.001). Children treated with at least one cycle of chemotherapy had a 90% reduction in mortality rate (HR 0.10, 95% CI 0.07–0.14). Children who achieved complete or partial remission after chemotherapy also had a lower mortality rate (HR 0.04, 95% CI 0.01–0.12; HR 0.16, 95% CI 0.05–0.53, respectively) compared with those with no response to chemotherapy. Disease stage was associated with mortality rate (P < 0.001); children diagnosed at advanced stages had an increased mortality rate (HR 4.04, 95% CI 2.72–5.99) compared with those diagnosed at stage A, B and AR combined. Period of BL diagnosis was not associated with mortality rate (Table 3).

Boys and girls had no significant difference in odds for advanced stage of disease at baseline (Table 4). However, when we analyzed girls according to tumor presentation, we found that girls without an ovarian mass had a lower odds to present with advanced disease stages compared with boys (OR 0.67, 95% CI 0.52–0.88), while girls with an ovarian mass had a particularly high odds to present with a late stage of disease compared with boys (OR 13.69, 95% CI 6.31–29.72), as well as compared with girls without an ovarian mass (OR 19.73, 95% CI 8.88–43.85) (Table 4).

The Kaplan–Meier survival estimates indicated that there was no overall survival difference between boys and girls (P = 0.091) (Supplementary Figure 1), nor by period of diagnosis (P = 0.126) (Supplementary Figure 2). HIV-negative children had a higher survival than HIV-positive children (P < 0.001) (Supplementary Figure 3). The proportion of children who died during follow-up, regardless of HIV status, decreased from 21.77% before antiretrovirals (ARV) became available in Uganda, to 13.56% after the introduction of ARVs in 1996, whereas the proportion of deaths among HIV-positive children was 61.54% before the introduction of ARV and 21.88% afterwards (data not shown). Although, the survival of HIV-positive children with BL in the periods before and after the introduction of ARVs in Uganda was higher in the first year after diagnosis, this difference leveled off in subsequent years (P = 0.061) (Supplementary Figure 4).

Table 2
Clinical characteristics of children aged <18 years diagnosed with Burkitt's lymphoma at the Uganda Cancer Institute by period of diagnosis

	All (*n* = 1217)	1985–1990 (*n* = 59)	1991–1995 (*n* = 258)	1996–2000 (*n* = 432)	2001–2005 (*n* = 468)	*P*-value[a]
Clinical diagnosis						0.221
No	213 (17.50)	11 (18.64)	43 (16.67)	88 (20.37)	71 (15.17)	
Yes	1004 (82.50)	48 (81.36)	215 (83.33)	344 (79.63)	397 (84.83)	
Tissue diagnosis						<0. 001
No (clinical diagnosis only)	488 (40.10)	6 (10.17)	106 (41.09)	205 (47.45)	171 (36.54)	
Histology	615 (50.53)	33 (55.93)	109 (42.25)	201 (46.53)	272 (58.12)	
Cytology	114 (9.37)	20 (33.90)	43 (16.67)	26 (6.02)	25 (5.34)	
Symptoms or concomitant diseases at BL diagnosis						
Fever[b]	621 (51.03)	28 (47.46)	124 (48.06)	201 (46.53)	268 (57.26)	0.007
Anemia	593 (48.73)	35 (59.32)	148 (57.36)	219 (50.69)	191 (40.81)	<0.001
Weight loss[c]	588 (48.32)	31 (52.54)	125 (48.45)	200 (46.30)	232 (49.57)	0.700
Night sweats	318 (26.13)	17 (28.81)	43 (16.67)	75 (17.36)	183 (39.10)	<0.001
Severe infection	192 (15.78)	12 (20.34)	58 (22.48)	65 (15.05)	57 (12.18)	0.002
Malaria (severe or recurrent)	58 (4.77)	2 (3.39)	15 (5.81)	21 (4.86)	20 (4.27)	0.770
Tumor presentation						
Facial tumor	945 (77.65)	42 (71.19)	202 (78.29)	326 (75.46)	375 (80.13)	0.228
Abdominal disease	842 (69.19)	40 (67.80)	180 (69.77)	282 (65.28)	340 (72.65)	0.121
Generalized lymphadenopathy	512 (42.07)	31 (52.54)	120 (46.51)	180 (41.67)	181 (38.68)	0.072
Hepatic mass	460 (37.80)	23 (38.98)	111 (43.02)	130 (30.09)	196 (41.88)	0.001
Ovarian mass (*n* = 451 girls)	145 (32.15)	10 (41.67)	31 (30.39)	47 (27.98)	57 (36.31)	0.293
Testicular tumor (*n* = 766 boys)	32 (4.18)	0	11 (7.05)	9 (3.41)	12 (3.86)	0.157
Renal mass	193 (15.86)	9 (15.25)	35 (13.57)	64 (14.81)	85 (18.16)	0.355
Malignant pleocytosis	147 (12.08)	3 (5.08)	9 (3.49)	50 (11.57)	85 (18.16)	<0.001
Spinal cord compression	132 (10.85)	7 (11.86)	29 (11.24)	42 (9.72)	54 (11.54)	0.825
Thoracic involvement	60 (4.93)	3 (5.08)	13 (5.04)	22 (5.09)	22 (4.70)	0.993
Bone involvement	58 (4.77)	1 (1.69)	15 (5.81)	15 (3.47)	27 (5.77)	0.214
Pleural disease including effusion	44 (3.62)	1 (1.69)	10 (3.88)	16 (3.70)	17 (3.63)	0.877
Mediastinal tumor	13 (1.07)	1 (1.69)	3 (1.16)	4 (0.93)	5 (1.07)	0.955
Breast mass	11 (0.90)	1 (1.69)	4 (1.55)	5 (1.16)	1 (0.21)	0.220
Lung parenchymal involvement	11 (0.90)	0	1 (0.39)	6 (1.39)	4 (0.85)	0.484
HIV status (*n* = 1163)						
Positive	45 (3.87)	1 (1.69)	12 (4.71)	11 (2.57)	21 (4.99)	0.205
Disease stage at baseline (*n* = 1211)						0.007
A	302 (24.94)	14 (23.73)	58 (22.48)	134 (31.16)	96 (20.69)	
B	192 (15.85)	10 (16.95)	57 (22.09)	60 (13.95)	65 (14.01)	
C	389 (32.12)	18 (30.51)	80 (31.01)	133 (30.93)	158 (34.05)	
D	323 (26.67)	17 (28.81)	62 (24.03)	100 (23.26)	144 (31.03)	
AR	5 (0.41)	0	1 (0.39)	3 (0.70)	1 (0.22)	
Advanced stage (C and D)						
Among all children	712 (58.79)	35 (59.32)	142 (55.04)	233 (54.19)	302 (65.09)	0.005
Among girls	279 (62.28)	15 (62.50)	65 (63.73)	88 (52.69)	111 (71.61)	0.006
Girls without ovarian mass	142 (46.71)	5 (35.71)	35 (49.30)	47 (38.84)	56 (56.12)	0.061
Girls with ovarian mass	137 (95.14)	10 (100)	30 (96.77)	41 (89.13)	56 (98.25)	0.140
Among boys	433 (56.75)	20 (57.14)	77 (49.36)	145 (55.13)	191 (61.81)	0.073
z-test difference of proportions between boys and girls	*P* = 0.059					
Chemotherapy, cycles completed (*n* = 1206)						<0.001
0	121 (10.03)	3 (5.08)	18 (7.03)	43 (10.05)	57 (12.31)	
1	225 (18.66)	7 (11.86)	47 (18.36)	74 (17.29)	97 (20.95)	
2	186 (15.42)	14 (23.73)	48 (18.75)	58 (13.55)	66 (14.25)	
3	138 (11.44)	10 (16.95)	31 (12.11)	44 (10.28)	53 (11.45)	
4–5	206 (17.08)	17 (28.81)	55 (21.48)	60 (14.02)	74 (15.98)	
6	238 (19.73)	5 (8.47)	38 (14.84)	105 (24.53)	90 (19.44)	
≤7	92 (7.63)	3 (5.08)	19 (7.42)	44 (10.28)	26 (5.62)	
At least 1 cycle (*n* = 1206)						
Among all children	1085 (89.97)	56 (94.92)	238 (92.97)	385 (89.95)	406 (87.69)	0.078
Among girls	397 (88.42)	23 (95.83)	93 (91.18)	143 (86.14)	138 (87.90)	0.403
Among boys	688 (90.89)	33 (94.29)	145 (94.16)	242 (92.37)	268 (87.58)	0.066
z-test difference of proportions between boys and girls	*P* = 0.168					
At least 1 cycle by HIV status (*n* = 1152)						
Among all children	1034 (89.76)	56 (94.92)	235 (92.89)	381 (89.86)	362 (87.02)	0.050
Among HIV-positive	37 (84.09)	1 (100.00)	11 (91.67)	8 (72.73)	17 (85.00)	0.620
Among HIV-negative	997 (89.98)	55 (94.83)	224 (92.95)	373 (90.31)	345 (87.12)	0.057
z-test difference of proportions between HIV-positive and HIV-negative	*P* = 0.206					

Table 2 (*Continued*)

	All (n = 1217)	1985–1990 (n = 59)	1991–1995 (n = 258)	1996–2000 (n = 432)	2001–2005 (n = 468)	P-value[a]
Response to chemotherapy (n = 1099)						0.025
Complete remission	489 (44.49)	32 (57.14)	118 (48.76)	175 (44.64)	164 (40.10)	
Partial remission	343 (31.21)	14 (25.00)	75 (30.99)	131 (33.42)	123 (30.07)	
Stable disease	48 (4.37)	1 (1.79)	13 (5.37)	18 (4.59)	16 (3.91)	
No response	8 (0.73)	1 (1.79)	1 (0.41)	4 (1.02)	2 (0.49)	
Not assessed	211 (19.20)	8 (14.29)	35 (14.46)	64 (16.33)	104 (25.43)	
Objective response[d] (n = 1099)						
Among all children	832 (75.71)	46 (82.14)	193 (79.75)	306 (78.06)	287 (70.17)	0.010
Among girls	296 (73.82)	20 (86.96)	72 (76.60)	108 (73.97)	96 (69.57)	0.293
Among boys	536 (76.79)	26 (78.79)	121 (81.76)	198 (80.49)	191 (70.48)	0.018
z-test difference of proportions between boys and girls	P = 0.268					

Data are number (%), unless otherwise indicated.

[a] P-value refers to Pearson's χ^2 test for association between clinical characteristics and period of diagnosis.

[b] Defined as axillary temperature >37.5 °C.

[c] Progressive loss in body weight of more than 10% of ideal body weight for the age and sex of the child.

[d] Objective response was defined as complete remission (i.e. no evidence of disease) or partial remission (i.e. 50% or greater decrease in tumor size).

4. Discussion

This study is the first comprehensive description of clinical characteristics, treatment and outcome of childhood BL in the UCI during the last two decades. Our study has a number of strengths, including the large sample size, long observation period, and the unique position of the study site, as the UCI is the only national cancer treatment center in Uganda. Because this was a retrospective study that analyzed routine data from a single cancer institute, the potential for selection bias is a major weakness, especially since children with better family support are more likely to go to the hospital for diagnosis and treatment. Thus, our results cannot be considered truly representative of the entire country, although most suspected cancer patients, in particular children, are indeed referred to the UCI. In the absence of routine mechanisms for tracing children who do not return for additional treatment or routine follow-up, it is not surprising that there was a substantial number of children in our study that were censored in the data analysis at the last admission or visit to the UCI.

Our study indicated that the major clinical characteristics of BL remained the same over this study's 20-year observation period: age distribution, sex distribution, the proportion of children with a clinical diagnosis only, presentation with facial tumors or abdominal disease, girls presenting with ovarian mass being diagnosed at advanced stages, HIV positivity, and presenting with symptoms of severe or recurrent malaria at BL diagnosis remained unchanged. However, we did find increases in the proportion of children presenting with malignant pleocytosis and hepatic mass, and with symptoms at diagnosis such as fever and night sweats. There were also other significant differences over time in the proportion of children presenting with anemia and severe infection.

Changes in BL tumor presentation have been suggested in other parts of Africa.[18–21] In the 1980s, changes in BL tumor presentation were noted in Ghana,[18] where more children presented with abdominal disease rather than facial tumors. In Nigeria, similar changes in tumor presentation were reported.[19] More recent observational studies in Kenya suggested that the clinical manifestations of BL vary according to the regions of the country.[20,21] However in all these instances no clear explanations were given for the observations. Moreover, as we did not confirm these findings in our study, it is possible that the changes in tumor presentation reported elsewhere were due to random variations.

There was no clear decrease in mortality among children diagnosed more recently compared with those diagnosed in earlier periods; thus the period of diagnosis was not, per se, associated with mortality. This was unexpected if we accept the assumption that the health care system in Uganda had improved over time. Nevertheless, as expected, mortality was associated with a number of other clinical characteristics, including tumor presentation, with facial tumors being associated with lower mortality as compared with other presentations; and disease stage, with advanced stage at diagnosis (stages C and D) being increasingly common, and associated with a four-fold higher mortality rate compared with children presenting with less-advanced stages. Girls presenting with ovarian mass in particular had a much higher odds of having advanced-stage BL than boys, or girls without ovarian mass. Symptoms of fever, weight loss, night sweats, or severe infection at BL diagnosis were associated with higher mortality as was HIV infection, with HIV-positive children having a higher mortality compared with HIV-negative children both before and after ARV introduction; and age, with older children (15–17 years) having a four-fold higher mortality rate than children diagnosed at younger ages.

As expected, chemotherapy, and evidence of response to chemotherapy, decreased mortality dramatically. Indeed, children receiving chemotherapy had overwhelmingly better survival, and most deaths occurred among children who did not receive any chemotherapy or received only one cycle of chemotherapy. Response to chemotherapy also seemed to increase over time. Although most of the children received at least one cycle of chemotherapy, there was a small significant increase during the study period in the proportion of children not receiving any treatment at all. Given that BL is highly curable when properly treated with

Table 3
Hazard ratios (HR) and 95% confidence intervals for the association between demographic and clinical characteristics and mortality among 1217 children aged <18 years diagnosed with Burkitt's lymphoma at the Uganda Cancer Institute, 1985–2005

	Deceased (n = 191) (15.69%)	Alive (n = 1013) (83.24%)	Lost to follow-up (n = 13) (1.07%)	HR (crude)	95% CI	P-value[a]	HR (adjusted for sex and age)	95% CI	P-value[b]
Sex						0.092			0.101
Girls	81 (42.41)	362 (35.74)	8 (61.54)	1	Ref.		1	Ref.	
Boys	110 (57.59)	651 (64.26)	5 (38.46)	0.78	0.59–1.04		0.79	0.59–1.05	
Age at diagnosis (years)						0.001			<0.001
0–4	55 (28.80)	234 (23.10)	1 (7.69)	1	Ref.		1	Ref.	
5–9	102 (53.40)	614 (60.61)	9 (69.23)	0.73	0.53–1.02		0.73	0.53–1.01	
10–14	26 (13.61)	158 (15.60)	3 (23.08)	0.69	0.44–1.11		0.68	0.42–1.08	
15–17	8 (4.19)	7 (0.69)	0	3.77	1.79–7.93		3.81	1.81–8.01	
Clinical diagnosis						0.485			0.398
No	34 (17.80)	175 (17.28)	4 (30.77)	1	Ref.		1	Ref.	
Yes	157 (82.20)	838 (82.72)	9 (69.23)	1.14	0.79–1.65		1.18	0.81–1.71	
Tissue diagnosis						0.041			0.068
No (clinical diagnosis only)	59 (30.89)	425 (41.95)	4 (30.77)	1	Ref.		1	Ref.	
Histology	105 (54.97)	501 (49.46)	9 (69.23)	1.09	0.79–1.50		1.08	0.78–1.49	
Cytology	27 (14.14)	87 (8.59)	0	1.83	1.16–2.88		1.74	1.10–2.76	
Symptoms or concomitant diseases at diagnosis[c]									
Fever	118 (61.78)	499 (49.26)	4 (30.77)	1.70	1.27–2.27	<0.001	1.69	1.26–2.27	<0.001
Anemia	71 (37.17)	517 (51.04)	5 (38.46)	0.43	0.32–0.57	<0.001	0.43	0.32–0.57	<0.001
Weight loss	137 (71.73)	443 (43.73)	8 (61.54)	3.13	2.28–4.28	<0.001	3.11	2.27–4.28	<0.001
Night sweats	76 (39.79)	240 (23.69)	2 (15.38)	2.31	1.73–3.09	<0.001	2.30	1.72–3.08	<0.001
Severe infection	56 (29.32)	136 (13.43)	0	1.91	1.40–2.61	<0.001	1.91	1.40–2.61	<0.001
Malaria (severe or recurrent)	5 (2.62)	52 (5.13)	1 (7.69)	0.39	0.16–0.96	0.040	0.40	0.17–0.98	0.045
Tumor presentation[d]									
Facial tumor	106 (55.50)	831 (82.03)	8 (61.54)	0.34	0.26–0.46	<0.001	0.33	0.25–0.45	<0.001
Abdominal disease	169 (88.48)	665 (65.65)	8 (61.54)	3.85	2.47–6.00	<0.001	3.78	2.42–5.90	<0.001
Generalized lymphadenopathy	89 (46.60)	420 (41.46)	3 (23.08)	1.22	0.92–1.62	0.170	1.24	0.94–1.66	0.133
Hepatic mass	109 (57.07)	348 (34.35)	3 (23.08)	2.44	1.83–3.25	<0.001	2.43	1.82–3.24	<0.001
Ovarian mass (n = 451 girls)	40 (49.38)	100 (27.62)	5 (62.50)	2.09	1.35–3.23	0.001	2.17	1.36–3.47	<0.001
Testicular tumor (n = 766 boys)	6 (5.45)	26 (3.99)	0	1.26	0.55–2.86	0.589	1.26	0.55–2.87	0.582
Renal mass	51 (26.70)	139 (13.72)	3 (23.08)	2.20	1.60–3.03	<0.001	2.21	1.60–3.05	<0.001
Malignant pleocytosis	25 (13.09)	120 (11.85)	2 (15.38)	1.13	0.74–1.73	0.556	1.15	0.76–1.76	0.509
Spinal cord compression	36 (18.85)	95 (9.38)	1 (7.69)	1.95	1.36–2.81	<0.001	1.98	1.37–2.85	<0.001
Thoracic involvement	23 (12.04)	37 (3.65)	0	3.17	2.05–4.91	<0.001	3.03	1.94–4.74	<0.001
Bone involvement	14 (7.33)	42 (4.15)	2 (15.38)	1.77	1.02–3.05	0.041	1.77	1.02–3.06	0.042
Pleural disease including effusion	19 (9.95)	25 (2.47)	0	3.61	2.25–5.81	<0.001	3.39	2.07–5.53	<0.001
Mediastinal tumor	5 (2.62)	8 (0.79)	0	2.94	1.21–7.15	0.017	3.36	1.37–8.24	0.008
Breast mass	7 (3.66)	3 (0.30)	1 (7.69)	4.52	2.12–9.62	<0.001	4.52	2.12–9.64	<0.001
Lung parenchymal involvement	7 (3.66)	4 (0.39)	0	5.92	2.77–12.63	<0.001	5.55	2.59–11.91	<0.001
HIV status (n = 1163)									
Negative	161 (91.48)	944 (96.92)	13 (100)	1	Ref.		1	Ref.	
Positive	15 (8.52)	30 (3.08)	0	2.52	1.49–4.29	0.001	2.50	1.47–4.26	0.001

Table 3 (*Continued*)

	Deceased (*n* = 191) (15.69%)	Alive (*n* = 1013) (83.24%)	Lost to follow-up (*n* = 13) (1.07%)	HR (crude)	95% CI	*P*-value[a]	HR (adjusted for sex and age)	95% CI	*P*-value[b]
Chemotherapy, cycles completed (*n* = 1206)						<0.001			<0.001
0	46 (24.08)	72 (7.19)	3 (23.08)	1	Ref.		1	Ref.	–
1	70 (36.65)	154 (15.37)	1 (7.69)	0.52	0.35–0.75		0.52	0.35–0.76	
2	17 (8.90)	168 (16.77)	1 (7.69)	0.07	0.04–0.13		0.07	0.04–0.13	
3	10 (5.24)	125 (12.48)	3 (23.08)	0.05	0.02–0.10		0.05	0.02–0.10	
4–5	14 (7.33)	189 (18.86)	3 (23.08)	0.03	0.02–0.06		0.03	0.02–0.06	
6	20 (10.47)	216 (21.56)	2 (15.38)	0.03	0.02–0.06		0.03	0.02–0.06	
≤7	14 (7.33)	78 (7.78)	0	0.06	0.03–0.10		0.06	0.03–0.10	
At least 1 cycle (*n* = 1206)	145 (75.92)	930 (91.81)	10 (76.92)	0.10	0.07–0.14	<0.001	0.10	0.07–0.14	<0.001
Response to chemotherapy (*n* = 1099)						<0.001			<0.001
No response	3 (2.04)	5 (0.53)	0	1	Ref.		1	Ref.	
Complete remission	30 (20.41)	455 (48.30)	4 (40.00)	0.04	0.01–0.12		0.04	0.01–0.12	
Partial remission	36 (24.49)	306(32.48)	1 (10.00)	0.16	0.05–0.53		0.16	0.05–0.53	
Stable disease	15 (10.20)	33 (3.50)	0	0.39	0.11–1.36		0.38	0.11–1.31	
Not assessed	63 (42.86)	143 (15.18)	5 (50.00)	0.90	0.28–2.89		0.92	0.29–2.94	
Disease stage at baseline (*n* = 1211)						<0.001			<0.001
A	10 (5.26)	287 (28.47)	5 (38.46)	1	Ref.		1	Ref.	
B	19 (10.00)	173 (17.16)	0	3.39	1.58–7.30		3.43	1.59–7.39	
C	84 (44.21)	300 (29.76)	5 (38.46)	7.31	3.79–14.09		7.24	3.75–13.98	
D	76 (40.00)	244 (24.21)	3 (23.08)	8.08	4.18–15.64		8.18	4.22–15.86	
AR	1 (0.53)	4 (0.40)	0	4.30	0.55–33.61		3.77	0.48–29.81	
Advanced stage (C and D)[e]	160 (84.21)	544 (53.97)	8 (61.54)	4.04	2.73–5.96	<0.001	4.04	2.72–5.99	<0.001
Period of diagnosis						0.114			0.173
1985–1990	18 (9.42)	41 (4.05)	0	1	Ref.		1	Ref.	
1991–1995	51 (26.70)	207 (20.43)	0	0.69	0.40–1.18		0.71	0.42–1.22	
1996–2000	57 (29.84)	370 (36.53)	5 (38.46)	0.55	0.33–0.94		0.58	0.34–0.99	
2001–2005	65 (34.03)	395 (38.99)	8 (61.54)	0.75	0.44–1.27		0.78	0.46–1.33	

Data are number (%), unless otherwise indicated.

[a] *P*-value refers to crude HR obtained using Cox model.

[b] *P*-value refers to HR adjusted for both sex and age obtained using Cox model and likelihood-ratio test (except for the analysis of testicular cancer or ovarian mass, sex and age themselves, where sex, testicular cancer and ovarian mass were adjusted for age, and age was adjusted for sex).

[c] Compared with children without the specific symptoms, regardless of whether they had other symptoms.

[d] Each presentation compared with all other tumor presentations combined.

[e] Compared with all other stages combined.

Table 4
Odds ratios (OR) and 95% confidence intervals for advanced disease stage at baseline (C and D versus all other categories combined) by sex and ovarian mass, among 1211 children aged <18 years diagnosed with Burkitt's lymphoma at the Uganda Cancer Institute, 1985–2005

	OR (crude)	95% CI	*P*-value[a]	OR (adjusted for age)	95% CI	*P*-value[b]
Boys compared with girls	0.79	0.63–1.01	0.059	0.82	0.64–1.04	0.106
Girls without ovarian mass compared with boys	0.67	0.51–0.87	0.003	0.67	0.52–0.88	0.004
Girls with ovarian mass compared with boys	14.92	6.89–32.31	<0.001	13.69	6.31–29.72	<0.001
Girls with ovarian mass compared with girls without ovarian mass	22.33	10.11–49.31	<0.001	19.73	8.88–43.85	<0.001

[a] *P*-value refers to crude OR obtained using logistic regression model.
[b] *P*-value refers to OR adjusted for age obtained using logistic regression model.

chemotherapy, it is of great concern that many children are still not benefiting from adequate treatment in Uganda. Boys and girls, and HIV-positive and HIV-negative children received a similar number of cycles of chemotherapy, indicating that there is no preferential treatment according to gender or HIV status.

Nevertheless, HIV-positive children had more than twice the mortality rate of HIV-negative children. The mortality among HIV-positive children was dramatically reduced in our study population after the introduction of ARV in Uganda, but HIV-positive children still had a higher mortality rate than HIV-negative children throughout the study period. Information on ARV use among HIV-positive children in our study was unfortunately not available, as HIV treatment is usually administered in general pediatric HIV clinics, and therefore not readily available when children are referred to the UCI for cancer treatment.

Endemic BL is strongly linked to EBV and malaria, and characteristically presents with facial tumor. There is an equally strong association between EBV and HIV in HIV-associated BL, which characteristically presents with systemic manifestations such as those described in our study.[21–25] In an earlier study at the UCI we compared the clinical characteristics of BL in HIV-positive and HIV-negative children in Uganda and noted presentation with facial tumor, systemic manifestations, advanced stage of disease and poor prognosis to be significantly associated with HIV positivity. We also noted a similarity in response to chemotherapy between HIV-positive and HIV-negative children.[8] It is unclear whether EBV infection has an impact on the clinical characteristics of BL, but this is a subject of interest given the observations in nasopharyngeal carcinoma, another EBV-related cancer, where subtype changes in EBV have been put forth as a cause of changes in the clinical features and prognosis of the disease.[26] In our study children with anemia and severe or recurrent malaria had a reduced mortality compared with children without these concomitant co-morbidities, due to the fact that these co-morbidities are associated with each other, and presentation with facial tumors (which have a lower mortality) were most common in children with history of severe and recurrent malaria.

The lack of clear decrease in mortality among children diagnosed more recently compared with those diagnosed in earlier periods, the sustained significant increase in the proportion of children presenting with advanced disease stages (C and D), and the proportion of children still not receiving chemotherapy, could be a result of socioeconomic factors leading to an inability to reach hospital care, or to initiate or complete treatment, which has been shown in this study to be of fundamental importance for good outcome. Improvements in the health care system in Uganda, including facilities for early cancer diagnosis, increasing access to histological confirmation and rapid referral to the UCI for specialized cancer care, would improve the chances of children with BL to be diagnosed at earlier stages and properly treated, resulting in lower mortality.

Authors' contributions: JO conceived and designed the study; JO, YM, SA, RB and EW drew the analysis plan; YM prepared the database; YM, SA and RB analyzed the data; all authors contributed to data interpretation; JO drafted the initial manuscript and EW the final version. All authors critically reviewed the subsequent drafts and read and approved the final manuscript. EW is guarantor of the manuscript.

Acknowledgements: The authors thank Dr Fred Okuku, Dr Agrey Dabangi and Twalib Olega for data abstraction, Ms Carol Nankabirwa and Mr David Sentongo for record retrieval, Mr Albert Maganda and Ms Josephine Maganda for data entry, Mrs Pouran Almsted for data auditing, and Ms Trudy Perdrix-Thoma for language review and editorial assistance.

Funding: Financial support was provided by the Swedish International Development Cooperation agency (SIDA), Makerere University and Mulago Hospital Kampala, Uganda. The work reported in this paper was partially undertaken during the tenure of an Expertise Transfer Fellowship awarded by the International Agency for Research on Cancer (IARC) to Dr Weiderpass.

Conflicts of interest: None declared.

Ethical approval: Ethical approval for the study was obtained from the Makerere University College of Health Sciences Ethical Committee (Kampala, Uganda) and the Uganda National Council for Science and Technology.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.trstmh.2011.08.008.

References

1. Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S. Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997. *Br J Cancer* 2000;**82**:1585–92.
2. Stiller CA, Parkin DM. International variations in the incidence of childhood lymphomas. *Paediatr Perinat Epidemiol* 1990;**4**:303–24.
3. Parkin DM, Garcia-Giannoli H, Raphael M, Martin A, Katangole-Mbidde E, Wabinga H, et al. Non-Hodgkin lymphoma in Uganda: a case-control study. *AIDS* 2000;**14**:2929–36.
4. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull* 1996;**52**:682–703.
5. Meremikwu MM, Ehiri JE, Nkanga DG, Udoh EE, Ikpatt OF, Alaje EO. Socioeconomic constraints to effective management of Burkitt's lymphoma in south-eastern Nigeria. *Trop Med Int Health* 2005;**10**:92–8.
6. Ziegler JL, Drew WL, Miner RC, Mintz L, Rosenbaum E, Gershow J, et al. Outbreak of Burkitt's-like lymphoma in homosexual men. *Lancet* 1982;**2**:631–3.
7. Kagu BM, Durosinmi, Adeodu OO, Akinola NO, Adediran IA, Salawu L. Determinants of survival in Nigerians with Burkitt's lymphoma. *Afr J Med Med Sci* 2004;**33**:195–200.
8. Orem J, Maganda A, Mbidde EK, Weiderpass E. Clinical characteristics and outcome of children with Burkitt lymphoma in Uganda according to HIV infection. *Pediatr Blood Cancer* 2009;**52**:455–8.
9. Burkitt D. A sarcoma involving the jaws in African children. *Br J Surg* 1958;**46**:218–23.
10. Orem J, Wabinga H. The roles of national cancer research institutions in evolving a comprehensive cancer control program in a developing country: experience from Uganda. *Oncology* 2009;**77**:272–80.
11. Parkin DM, Wabinga H, Nambooze S. Completeness in an African cancer registry. *Cancer Causes Control* 2001;**12**:147–52.
12. Savage L. Former African cancer research powerhouse makes plans for a return to greatness. *J Natl Cancer Inst* 2007;**99**:1144–5.
13. Magrath IT. African Burkitt's lymphoma. History, biology, clinical features, and treatment. *Am J Pediatr Hematol Oncol* 1991;**13**:222–46.
14. Ziegler JL, Magrathi T. In: Ioachin HL, editor. *Pathology annual*. New York: Appleton-Century Croft; 1974. p. 19.
15. Ziegler JL. Burkitt's lymphoma. *Med Clin North Am* 1977;**61**:1073–82.
16. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. 2nd ed. New York: Wiley; 2002.
17. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;**81**:515–26.
18. Biggar RJ, Nkrumah FK, Perkins IV. Presenting clinical features of Burkitt's lymphoma in Ghana, West Africa. *J Trop Pediatr Environ Child Health* 1979;**25**:157–61.
19. Oguonu T, Emodi I, Kaine W. Epidemiology of Burkitt's lymphoma in Enugu, Nigeria. *Ann Trop Paediatr* 2002;**22**:369–74.
20. Mwanda OW. Clinical characteristics of Burkitt's lymphoma seen in Kenyan patients. *East Afr Med J* 2004;**8**(Suppl):S78–89.
21. Otieno MW, Remick SC, Whalen C. Adult Burkitt's lymphoma in patients with and without human immunodeficiency virus infection in Kenya. *Int J Cancer* 2001;**92**:687–91.
22. Lazzi S, Ferrari F, Nyongo A, Palummo N, de Milito A, Zazzi M, et al. HIV-associated malignant lymphomas in Kenya (Equatorial Africa). *Hum Pathol* 1998;**29**:1285–9.
23. Bellan C, Lazzi S, Hummel M, Palummo N, de Santi M, Amato T, et al. Immunoglobulin gene analysis reveals 2 distinct cells of origin for EBV-positive and EBV-negative Burkitt lymphomas. *Blood* 2005;**106**:1031–6.
24. Goldschmidts WL, Bhatia K, Johnson JF, Akar N, Gutierrez MI, Shibata D, et al. Epstein-Barr virus genotypes in AIDS-associated lymphomas are similar to those in endemic Burkitt's lymphomas. *Leukemia* 1992;**6**:875–8.
25. Mutalima N, Molyneux E, Jaffe H, Kamiza S, Borgstein E, Mkandawire N, et al. Associations between Burkitt lymphoma among children in Malawi and infection with HIV, EBV and malaria: results from a case-control study. *PLoS ONE* 2008;**3**:e2505.
26. Kian TC, Miriam T, Richard Q, Peng YS, Li LE, Ivy S, et al. Clinical characteristics, prognostic factors and outcomes of Burkitt lymphoma in adult Asians. *Leuk Lymphoma* 2008;**49**:824–7.