ORIGINAL ARTICLE

Pediatric cancer spectrum in Kenya: a histopathologic review

**Franklin C. Margaron · Dan Poenaru ·
Alan Northcutt**

Abstract

Background Pediatric malignancies constitute a unique health care burden especially in resource-poor settings such as Africa, and the use of external epidemiologic data in managing these children may lead to erroneous approaches. *Methods* A retrospective histopathologic analysis of 6,771 pathology reports between March 1992 and August 2006 was undertaken in children under the age of 18. Data were derived from the Kijabe Hospital pathology database, which receives pathologic specimens from 70 different mission hospitals, clinics, and regional hospitals throughout Kenya. *Results* 1,217 of these specimens represented malignancies. The top ten pediatric malignancies were Burkitt's lymphoma (16.6%), non-Hodgkin's lymphoma (8.5%), Hodgkin's lymphoma (7.6%), Kaposi's sarcoma (7.6%), osteosarcoma (7.3%), gonadal germ-cell tumors (5.8%), rhabdomyosarcoma (3.5%), nephroblastoma (3.4%), epithelial carcinoma (2.8%), and chondrosarcoma (1.8%). *Conclusion* Comparison with several previous African and western pediatric cancer databases is undertaken, revealing significant trends useful for the care of children with cancer in the region.

Keywords Cancer · Oncology · Africa · Lymphoma · Sarcoma · Carcinoma · Hodgkin's · Burkitt's · Wilms'

Introduction

In 1964 Drs. Denis Burkitt and MSR Hutt traveled across Uganda, Tanzania, and Kenya to teach histopathologic technique and gather data on cancers endemic to East Africa [1]. They recognized then that the spectrum of cancer across these areas differed greatly from those seen in the West, and even differed from one area to another. Nearly half a century later, the understanding and treatment of pediatric cancer have advanced greatly worldwide—yet the true incidence and outcomes of cancers in East Africa are still largely unknown. Many children in these areas have limited access to diagnosis and therapy, thus affecting negatively both the demographics and outcomes of oncologic disease in the region.

The total incidence of cancer in children under the age of 15 has been shown to be relatively constant from one geographical location to another. This typically ranges between 1 and 2.5 per 1,000 children [2]. However, the actual geographical distribution of the types of cancers represented varies greatly from one area to the next [2]. Childhood cancers represent a diffuse spectrum of disease in which certain types of tumors can present in multiple anatomic locations. Therefore, childhood cancers are subtyped primarily by histology [3, 4].

Survival rates for all children with pediatric solid tumors have risen in developed countries from 27% in 1960 to 70% in 1990 [5]. Survival rates for the non-Hodgkin's lymphomas, including the form that bears Dr. Burkitt's name, have improved greatly in the pediatric population—increasing from 56% in 1975–1984 to 72% in 1985–1994. At the current time the survival for Hodgkin's lymphoma is over 90% [6]. These data derived from Western databases such as the National Cancer Data Base and the Surveillance, Epidemiology, and End-Results (SEER) database give information on age-specific incidence, geographic distribution, risk factors, trends over time, and survival characteristics. The databases have led to knowledge sharing that has facilitated the rapid progress in the fight against pediatric cancer.

F. C. Margaron · D. Poenaru (✉) · A. Northcutt
BethanyKids at Kijabe Hospital, Box 20, Kijabe 00220, Kenya
e-mail: dpoenaru@gmail.com

Several African countries have benefited from national pediatric cancer databases, including Malawi [7] and Tanzania [8]. Other countries have incidence data derived from a single large city or institutional studies such as Uganda [2], Nigeria [9], and Zambia [10, 11]. Kenya currently has no national pediatric cancer database, and information on cancer in the country can only be inferred from a few studies. The first is a prospective study over a 6-month period at Kenyatta National Hospital and seven other centers, examining the distribution of 157 pediatric cancers seen during that time [12]. The second is a histopathologic review from three centers in Western Kenya between 1979 and 1994 covering 600 solid pediatric cancers [13]. Several specific diagnoses have been better explored in Kenya, including Burkitt's lymphoma [14–16] and Hodgkin's disease [17, 18]. Our study was intended to broaden the understanding of the spectrum of pediatric cancers in Kenya.

Materials and methods

The Kijabe Hospital Pathology database is a collection of reports from histopathologic specimens sent to the hospital for diagnosis from 70 different mission hospitals, clinics, and regional hospitals from all over Kenya. Many of these locations can be seen on the map in Fig. 1 as blue squares. 3.6% of the total samples came from locations outside of Kenya—these reports were excluded from the final

Fig. 1 Pathology referral centers in Kenya

analysis. Data available on all reports included patient demographics, details of surgery performed, gross and microscopic description, and final diagnosis. Those patients with incomplete information or unreliable age identifiers were excluded.

All pathology samples were received in formalin saline solution at Kijabe Hospital. These were embedded in paraffin, sectioned, and stained with hematoxylin and eosin under standard technique. Other stains available included periodic acid-Schiff stain and AFB. Histopathologic analysis was performed by the pathology staff at Kijabe Hospital, which was mostly comprised of rotating short-term pathologists from the United States. Pathologic diagnosis was confirmed when necessary through telemedicine consultation with other members of the Kijabe pathology network overseas. When possible, samples requiring further staining and analysis were taken to centers where such testing could be performed.

Results

The total database from March 1992 to August 2006 comprised 65,536 reports. A total of 7,025 pediatric (under age 18) specimens were identified, of which 6,771 came from within Kenya. 1,217 of these samples were identified as malignancies.

The organization of pathology reports is shown in Table 1, using the 12 histopathologic categories established by the International Classification of Childhood Cancers (ICCC) specifications [4], with some expanded sub-typing of the soft-tissue sarcomas and carcinomas for clarity.

The top ten pediatric cancer diagnoses for several databases are presented in Table 2. When comparing the Kijabe database with the American SEER database [6], there are some notable differences. The top three diagnoses on the SEER database, acute lymphoid leukemia (24.5%) astrocytoma (10%), and neuroblastoma (7.5%) are not even represented in the top ten cancers in the Kijabe database. Neither acute myeloid leukemia (4.7%) nor peripheral neuroectodermal tumors (4.5%) are represented, which are number 5 and 6, respectively, on the SEER database. In the Kijabe database the lymphomas, Burkitt's (16.6%), non-Hodgkin's (8.5%), and Hodgkin's (7.6%), make up the top three most frequent diagnoses. The SEER database, on the other side, has only one representative lymphoma, Hodgkin's disease (4.4%), in the top ten. Other pediatric cancers which are more strongly represented in the Kijabe database as compared with SEER include Kaposi's sarcoma (7.5 vs. 0%), osteosarcoma (7.4 vs. 2.4%), gonadal germ-cell tumors (5.8 vs. 1.7%), and epithelial carcinoma (2.7 vs. 0%).

Table 1 Kijabe Hospital pathology database for pediatric cancers

	Cases	Total (%)
Total cancers	1,217	100.0
Leukemia	30	2.5
Acute lymphoid	11	0.9
Acute myeloid	10	0.8
Chronic lymphocytic	3	0.2
Unspecified	6	0.5
Lymphomas and reticuloendothelial neoplasms	420	34.5
Hodgkin's' disease	92	7.6
Non-Hodgkin's lymphoma	103	8.5
Burkitt's lymphoma	202	16.6
Unspecified lymphoma	23	1.9
CNS and intracranial and intraspinal neoplasms	12	1.0
Ependymoma	0	0.0
Astrocytoma	2	0.2
Primitive neuroectodermal tumors	8	0.7
Gliomas	0	0.0
Unspecified CNS tumors	2	0.2
Sympathetic nervous system	21	1.7
Neuroblastoma	19	1.6
Other	2	0.2
Retinoblastoma	16	1.3
Renal tumors	46	3.8
Wilms' tumor	41	3.4
Clear cell carcinoma	2	0.2
Renal carcinoma	2	0.2
Unspecified renal tumors	1	0.1
Hepatic tumors	21	1.7
Hepatoblastoma	4	0.3
Hepatic carcinoma	9	0.7
Unspecified malignant hepatic tumors	8	0.7
Malignant bone tumors	126	10.4
Osteosarcoma	90	7.4
Chondrosarcoma	21	1.7
Ewing's sarcoma	12	1.0
Other specified malignant bone tumors	2	0.2
Unspecified malignant bone tumors	1	0.1
Soft-tissue sarcomas	188	15.4
Rhabdomyosarcoma and embryonal sarcoma	43	3.5
Fibrosarcoma, neurofibrosarcoma, and other fibromatous neoplasms	23	1.9
Kaposi's sarcoma	91	7.5
Other specified soft-tissue sarcomas	18	1.5
Unspecified soft tissue sarcomas	13	1.1
Germ-cell, trophoblastic, and other gonadal neoplasms	117	9.6
Intracranial and intraspinal germ-cell tumors	13	1.1
Other and unspecified non-gonadal germ-cell tumors	7	0.6

Table 1 continued

	Cases	Total (%)
Gonadal germ-cell tumors	71	5.8
Gonadal carcinomas	7	0.6
Trophoblastic tumors	11	0.9
Other and unspecified malignant gonadal tumors	8	0.7
Carcinomas and other epithelial neoplasms	167	13.7
Adrenocortical carcinoma	0	0.0
Thyroid carcinoma	17	1.4
Nasopharyngeal carcinoma	19	1.6
Malignant melanoma	7	0.6
Skin carcinoma	34	2.8
Other and unspecified carcinoma	90	7.4
Other and unspecified malignant neoplasms	53	4.4
Other specified malignant tumors	4	0.3
Other unspecified malignant tumors	49	3.8

When comparing our Kijabe database with several of the other previous African databases—including the Makata database from Kenya [8], Patil's database from Zambia [10], and Mukiibi's database from Malawi [7] there are more similarities. The lymphomas are much more prominent, especially Burkitt's and non-Hodgkin's lymphoma which take up the top two positions on all the African databases. In the Malawi database, Burkitt's lymphoma is included in the non-Hodgkin's lymphomas (54.9%). Kaposi's sarcoma is prominent in all the African databases, being the fourth most common diagnosis in three of them. Epithelial carcinoma is represented on three of the four "top ten" lists. It is more highly represented as the fourth most common diagnosis in Malawi (5.7%), when compared to the two Kenyan databases in which it is number 9 (2.8%, Kijabe) and 8 (2.6%, Makata), respectively.

There are some differences, however, between our spectrum and that of the other African databases. Hodgkin's lymphoma appears in all five databases with slightly higher occurrence in our database (7.6%) as compared with the others, which have roughly equivalent frequency at around 4% each. Osteosarcoma was number 5 in frequency in our database (7.4%) as compared with the other four databases in which it came in 9 or 10 with equal frequency, around 2% of malignancies represented. Gonadal germ-cell tumors (5.6%) and fibrosarcoma (1.9%) only made the "top ten list" in our database alone. Also, the retinoblastomas, which appear prominently as the second or third most common diagnosis in the other African databases (around 11% of the total in each), ranks number 13 in frequency in our database (1.3%).

When examining gender distribution as seen in Table 3, Hodgkin's and non-Hodgkin's lymphomas, chondrosarcoma,

Table 2 Comparison of top ten cancers in several databases

	SEER (USA) [6]	Kijabe (Kenya)	Makata (Kenya) [13]	Zambia [10]	Malawi [7]
1	Acute lymphoid leukemia (24.5%)	Burkitt's lymphoma (16.6%)	Burkitt's lymphoma (33.5%)	Non-Hodgkin's lymphoma (17.5%)	Non-Hodgkin's lymphoma (54.9%)
2	Astrocytoma (10%)	Non-Hodgkin's lymphoma (8.5%)	Non-Hodgkin's lymphoma (21.8%)	Burkitt's lymphoma (13.9%)	Retinoblastoma (11.3%)
3	Neuroblastoma (7.5%)	Hodgkin's disease (7.6%)	Retinoblastoma (11.5%)	Retinoblastoma (11.4%)	Wilms' tumor (6.3%)
4	Wilms' tumor (6.1%)	Kaposi's sarcoma (7.5%)	Kaposi's sarcoma (6.1%)	Kaposi's sarcoma (8.8%)	Epithelial carcinoma (5.7%)
5	Acute myeloid leukemia (4.7%)	Osteosarcoma (7.4%)	Wilms' tumor (4.5%)	Hodgkin's disease (5.9%)	Hodgkin's disease (4.8%)
6	PNET (4.5%)	Gonadal germ-cell tumors (5.8%)	Hodgkin's disease (4.1%)	Wilms' tumor (5.9%)	Soft-tissue sarcoma (4.3%)
7	Hodgkin's disease (4.4%)	RMS (3.5%)	Fibrosarcoma (3.2%)	Acute lymphoid leukemia (4%)	Kaposi's sarcoma (4%)
8	RMS (3.4%)	Wilms' tumor (3.4%)	Epithelial carcinoma (2.6%)	RMS (3.4%)	Unspecified tumors (2.5%)
9	Retinoblastoma (3.1%)	Epithelial carcinoma (2.8%)	Osteosarcoma (2.3%)	Nasopharyngeal carcinoma (2.7%)	Acute leukemia (2.3%)
10	Osteosarcoma (2.4%)	Fibrosarcoma (1.9%)	RMS (1%)	Osteosarcoma (2.1%)	Osteosarcoma (2.0%)

and Kaposi's sarcoma had a strong male predominance—while the gonadal germ-cell tumors had a strong female predominance. There was a slight male predominance in Burkitt's lymphoma and a slight female predominance in rhabdomyosarcoma and nephroblastoma.

As expected, nephroblastoma, neuroblastoma, and retinoblastoma presented at younger ages (<5 years), while Hodgkin's, osteosarcoma, gonadal germ-cell tumors, epithelial carcinoma, and fibrosarcoma presented in older children (>10 years).

Discussion

This analysis is clearly not meant to document the true disease incidence in the Kenyan population—but rather, a cross-sectional analysis of the observed pediatric cancers presenting to mission and other regional hospitals in Kenya. Any inferences to population-based data must be very cautious. Also, no meaningful inferences can be made regarding specific ethnic groups because these are widely mixed in the Kenyan population and most referring hospitals serve multiple groups. Moreover, Kijabe Hospital is not specifically a referral center for the treatment of pediatric cancers, and many of the cases included were referred to cancer centers for further management. Finally, it was not possible to establish a geographic distribution of disease from our database. Although the institution of origin for each specimen was known, each of these institutions draws patients from varied areas of the country, and the regional distribution where each patient lived was not available.

The spectrum of pediatric cancers in our database clearly differs from that observed in western pediatric oncologic databases [5, 6]. Although the database had many similarities with previous African databases, there are some key differences which may help provide greater understanding of the true distribution of disease. Discussion will follow the 12 histopathologic categories specified by the ICCC [4].

First, *leukemias* were underrepresented in our database as compared with the western pediatric databases. This decreased frequency has been previously described in the African population [2], although it is unclear how much of this difference is related to a truly lower disease incidence as opposed to underdiagnosis. Acute leukemias may also be underrepresented in our sample simply because not all children who are diagnosed with leukemia and initiated on therapy in our setting undergo a bone marrow biopsy. Some cases are diagnosed and treated based on clinical suspicion and peripheral blood evaluation, which would not be reflected in our database.

Table 3 Characteristics of top 12 pediatric cancers

	Mean age	Percent male	Most common location
Burkitt's lymphoma	8	53.5	Abdomen
Non-Hodgkin's lymphoma	9	69.9	Abdomen
Hodgkin's lymphoma	11	76.1	Neck node
Kaposi's sarcoma	9	64.1	Neck/neck node
Osteosarcoma	13	49.4	Femur
Gonadal germ-cell tumors	12	18.3	Ovary
Rhabdomyosarcoma	9	44.2	Leg
Wilms' tumor	4	46.3	Kidney
Skin carcinoma	10	50	Head/neck
Fibrosarcoma	11	47.8	Leg
Chondrosarcoma	14	63.6	Leg
Neuroblastoma	5	52.6	Retroperitoneum

The *lymphomas* are strongly represented in all the African databases [7, 10, 13] and took up the three most frequently occurring diagnoses in our database. Burkitt's lymphoma is the most common pediatric cancer in sub-Saharan Africa, with a specific clustering in Western Kenya [13, 16]. Kenya lies within the "lymphoma belt" which stretches across the African continent on both sides of the equator. This cancer has well-established links to the Epstein Barr Virus, holoendemic malaria [16], and HIV infection [19, 20], all of which are highly prevalent in Kenya. Non-Hodgkin's disease has also been linked with HIV infection [19], while Hodgkin's disease has been linked strongly to EBV infection [18]. A male predominance for the lymphomas has likewise been described [2]. The high frequency of lymphoma in the Kenyan population provides the unique opportunity to gain a deeper understanding of this disease group.

Due to cost and lack of availability of three-dimensional imaging techniques, as well as qualified surgeons for biopsy, *central nervous system tumors* are likely underdiagnosed and therefore underrepresented in our database as compared with western statistics [5, 6]. Many of these cases would be referred to larger centers for diagnosis and treatment. However, a truly lower incidence in Africa for brain tumors cannot be ruled out.

Sympathetic nervous system tumors, such as *neuroblastoma*, had a lower incidence in our database as compared with western statistics. This was consistent with the other African databases [7, 10, 13]. The lowest rates in the world for sympathetic tumors have previously been shown to be in sub-Saharan Africa [2]—for reasons that remain unknown.

Retinoblastoma had a significantly lower occurrence in our database compared with the other African databases, including the Makata database from Kenya. This may be a result of sample bias, due to the fact that Kijabe Hospital and its affiliates within the pathology network do not have ophthalmology departments. The true incidence of this diagnosis is likely therefore underrepresented.

Renal tumors such as *Wilms'* were relatively equally represented in the various databases, and no particular trends were elucidated.

Liver tumors are rare in the pediatric population, and subsequently had very little representation on our database. This may be partially due to underdiagnosis in the Kenyan context, due to lack of access to three-dimensional imaging and biopsy. Moreover, some of the harder-to-diagnose hepatoblastomas were likely diagnosed as "unspecified", thus accounting for hepatocellular carcinomas being more prevalent than hepatoblastomas. Patient charts were not available for review in this study, and therefore no correlation can be made to hepatitis or HIV status in these patients.

Bone tumors were strongly represented in our database as compared with the other studies. This increased frequency is partially sample bias, due to a high number of samples coming from the neighboring pediatric orthopedic hospital. Osteosarcoma, for example, had roughly equivalent frequency in all databases but our own. However, previous reports of worldwide incidence of bone tumors at 5% of pediatric cancers are more consistent with our database [2].

Soft tissue sarcomas were strongly represented with rhabdomyosarcoma, fibrosarcoma, and Kaposi's sarcoma all among the top ten most frequent diagnoses. The incidence of Kaposi's sarcoma, which was strongly represented on all four African databases, has increased in recent years due to the AIDS epidemic in Africa [2, 11, 20].

Germ-cell cancers, which typically represent less than 3% of childhood cancers [2], were strongly represented among our data—especially dysgerminomas and teratomas of the ovary. The reasons for the high incidence in our population are unclear.

Epithelial cancers are a varied group in the pediatric population, most commonly dominated by thyroid carcinoma, malignant melanoma, and nasopharyngeal carcinoma [6]. Typically, adult epithelial cancers such as breast, intestinal, and prostate have little representation in the pediatric population and are therefore grouped together as "other" or "unspecified" in the pediatric classification scheme [2, 4]. In our database, however, we had a strong representation of these diagnoses, especially in older children. Although low in numbers, breast (8), esophageal (8), gastric (7), intestinal (1), and prostatic (2) cancers were all present. By far the largest contributor to the 90 patients in the category for "other and unspecified carcinoma" was undifferentiated carcinomas and adenocarcinomas. There

was a trend towards higher incidence of skin carcinomas, especially in older children. This trend was also seen in several of the other African databases [7, 13] and warrants further investigation.

There were some inherent flaws in the database which require specific mention. The database is a collection of pathologic diagnoses, isolated in the majority of cases from patient charts and therefore not offering the availability for chart review to confirm demographic data. Therefore, any errors in data entry could affect the final results. The main result of such errors is likely not incorrect inclusion of a patient, but rather omission of patients because of inability to identify their age.

The spectrum of pediatric cancer in Kenya is unique in the world. Even within the country, cancer incidence varies among tribes and geographic areas [13, 14, 16]. This presents an opportunity for further research and therapeutic advancements for the children in Kenya, many of whom currently have limited access to care. A collaborative effort among mission hospitals, regional hospitals, and major teaching centers through a national pediatric cancer database would greatly benefit such efforts in the future.

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