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Research Paper

Therapeutic Radiation Needs in Pediatric Oncology

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Abstract

Most new pediatric cancer diagnoses are in LMICs, where survival rates range from 5-25%, compared with 80% in high-resource countries. Access to radiotherapy, a key component of cancer treatment, is extremely limited in East Africa. The objective of this study was to assess and describe the need for radiation therapy for pediatric oncology patients at a tertiary referral center in Tanzania. This study conducted a retrospective review of pediatric oncology patients treated at BMC from 2010-2014. The indication for radiation therapy was deduced from contemporary SIOP and COG protocols. Two radiation oncologists estimated the potential benefits of radiotherapy, both for curative and palliative intent, based on age, diagnosis, and stage at presentation. A total of 221 pediatric patients were included. The most common diagnoses were Burkitt lymphoma (n = 36), other non-Hodgkin lymphoma (n = 33), Wilms tumor (n = 32), acute leukemia (n = 28) and retinoblastoma (n = 23). Treatment regimens included chemotherapy only (74%), surgery only (2%), and both (14%). No patients received radiotherapy due to lack of availability. Of the 144 evaluable cases, radiation therapy was found to have been included in the treatment plan for 34% of patients (95% CI: 26-42%). Of these, 84% (95% CI: 74-94%) would have been treated with curative intent and 16% (95% CI: 6-26%) would have benefited from palliative radiotherapy. One-third of the evaluated patients were deemed to benefit from radiation as part of their treatment, with most regarded for curative intent. Introducing radiotherapy has the potential to improve pediatric cancer outcomes in this region.

Keywords: Pediatric oncology, radiotherapy, global oncology, LMIC.

Introduction

Advances in chemotherapy, surgery, and radiotherapy techniques have significantly improved outcomes for pediatric cancer patients. From 1970-2011, the death rate for pediatric cancer decreased 67% in the United States with overall survival rates now exceeding 83% [1]. Unfortunately, these improvements in high-resource countries have not been realized in low- and middle-income countries (LMICs) where nearly two-thirds of all cancer diagnoses are made [2]. This is likely due to a lack of infrastructure and access to these therapeutic

advances.

Radiation therapy plays an integral role in the management of many pediatric cancers, administered with curative or palliative intent [3-5]. As early as the 1960s, investigators at St. Jude Children's Hospital pioneered its use in pediatric Acute Lymphoblastic Leukemia and showed significantly increased five-year survival rates. In the 1970s, the benefit of radiation therapy for advanced stage Wilms' tumor was demonstrated in a series of seminal randomized trials. Radiation therapy access can be particularly beneficial in low- and middle-income countries (LMICs) due to lack of a reliable chemotherapy supply, limited surgical capacity, and a more advanced stage of presentation. However, of the 139 LMICs, 55 countries, including 358 million people, have no access to radiation therapy [6]. In Africa, it is estimated that the current radiotherapy infrastructure covers only 34% of adult and pediatric radiotherapy needs, compared to 198% in North America [7]. Although recognizing the multiple challenges that present in establishing a radiotherapy program in a LMIC, it is both a clinically and economically rewarding pursuit. The global expansion of radiation therapy for equalizing disparate outcomes should be addressed on a geographical- and cultural-specific basis to maximize efficacy and safety.

Bugando Medical Center (BMC) is the tertiary referral hospital for the Lake Zone of Tanzania and the only cancer treatment center in this region, serving a population of 15 million people. Approximately 120 pediatric patients are treated at BMC annually [8]. Common diagnoses include Burkitt lymphoma, non-Hodgkin lymphoma, Wilms' tumor, acute leukemia, and retinoblastoma. Radiation therapy is an essential treatment modality for many of these cancers, but Tanzania currently has only one radiation therapy center (Ocean Road Cancer Institute, Dar es Salaam). Radiation therapy installation at BMC is underway, but its potential benefit for pediatric cancer patients is uncertain. The purpose of this study was to estimate the clinical benefit of radiation therapy for pediatric cancer patients in the Lake Zone region of Tanzania.

Material and Methods

In this IRB-approved retrospective study, all recorded hospital admissions, and clinic visits to the Pediatric Oncology service at BMC between January 2010-December 2014 were reviewed. There were 240 patients identified, and 221 charts were available for review. Recorded data included date of consultation, patient diagnosis, age, cancer group/stage, anatomic site when applicable, and the treatment received (chemotherapy, surgery, or both). Radiation therapy was not used for any patients due to a lack of access. The indication for radiation therapy and whether it would be for either curative or palliative intent was judged using contemporary International Society of Pediatric Oncology (SIOP) and Children's Oncology Group (COG) protocols (Appendix). Two radiation oncologists (A.O., N.L.) independently evaluated the need for radiation therapy based on the clinical data provided by the treating oncologist (K.S.). Initial scoring for the use of radiation therapy was "Yes", "No", or "Additional information needed". Clinical information was further abstracted from the patient chart by K.S. If the recommendations were discordant after re-review, a joint review was performed to reach a consensus recommendation.

Statistical Analysis

Descriptive statistical analysis was performed to determine the distribution of diagnosis, treatment, and demographic information on the full study sample. Statistical analyses were performed with Excel 2017 (Microsoft, Redmond, WA) and STATA v15.1 (StataCorp, College Station, TX).

Results

A total of 221 patient records were available for review, and one patient record was found to be a duplicate and was excluded, leaving a total of 220 patient records for analysis. Patient and treatment characteristics are listed in Table 1. Treatment received at BMC included chemotherapy alone for 163 patients (74%), surgery alone for five patients (2%), and a combination of chemotherapy and surgery for 30 patients (14%). A total of 22 patients (10%) did not receive any treatment due to death (n = 8), abandonment (n = 12), or unknown reasons (n = 2).

Seventy-seven (35%) records had insufficient clinical information to determine the potential benefit of radiation therapy and were excluded from analysis. Of the remaining 144 cases, radiation therapy would have been indicated for 49 patients (34%, 95% CI 26-42%). Of these, 41 patients (84%, 95% CI 74-94%) would have been treated with curative intent, and 8 patients (16%, 95% CI 6-26%) could have benefited from palliative radiation therapy (Figure 1). The diagnoses with associated radiation intent are shown in Table 2.

Table 1. Patient and Treatment Characteristics

Patient & Treatment Characteristics (n = 220)	
Age in years, median (range)	6 (0.25-18)
Diagnosis, n (%)	
Burkitt Lymphoma	36 (16.3%)
Non-Hodgkin's Lymphoma	33 (15.0%)
Wilms Tumor	32 (14.5%)
Acute Leukemia	28 (12.7%)
Retinoblastoma	23 (10.5%)
Sarcoma	18 (8.2%)
Kaposi Sarcoma	9 (4.1%)
Hepatoma	7 (3.2%)
Hodgkin Lymphoma	7 (3.2%)
Germ Cell Tumor	6 (2.7%)
Other	22 (10.0%)
Treatment received, n (%)	
Chemotherapy only	163 (74.1%)
Surgery only	5 (2.3%)
Combination of chemotherapy and surgery	30 (13.6%)
No treatment	22 (10.0%)

Table 2. Radiation Intent by Diagnosis

		Radiation Intent		
Pediatric Oncology Diagnoses at BMC	**Total Number in study (%)**	**Indicated for Radiation**	**Curative**	**Palliative**
Burkitt Lymphoma	36 (16)	0		
Non-Hodgkin's Lymphoma	33 (15)	0		
Wilms Tumor	32 (14)	11	10	1
Acute Leukemia	28 (13)	14	14	0
Retinoblastoma	23 (10)	9	4	5
Sarcoma	18 (8)	0		
Kaposi Sarcoma	9 (4)	0		
Hepatoma	7 (3)	0		
Hodgkin Lymphoma	7 (3)	0		
Germ Cell Tumor	6 (3)	0		
Other	22 (10)	15	13	2
Total	221	49	41	8

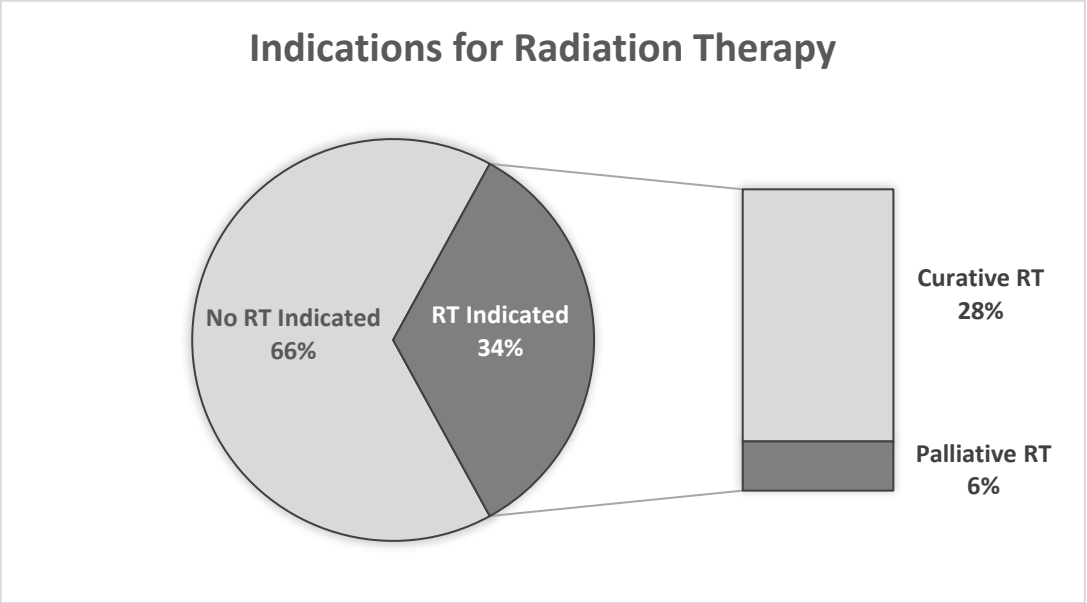

Figure 1. Radiotherapy Indication Percentage by Curative or Palliative Intent.

Discussion

In the analysis of the potential clinical impact of radiation therapy access in the Lake Zone of Tanzania, it found that approximately one-third of pediatric cancer patients would have benefited from radiotherapy if it were available.

Insufficient access to radiation therapy is a problem that will continue to worsen as the global cancer burden shifts to LMICs [9]. Datta *et al,* 1976 [6] estimated access to radiation therapy in 84 of these countries by analyzing their infrastructure and staffing requirements, and found that 6.4% of patients in Tanzania have access to radiation therapy. They proposed three approaches to address the gap in access to radiation therapy: the gathering of actual data at the country level, the collaboration with manufacturers of radiation therapy equipment, and coordination with international agencies. This study analysis addresses the first, which is to estimate the future radiation therapy needs at a specific site in Tanzania. It has been shown that approximately one-third of pediatric cancer patients in the Lake Zone of Tanzania would have benefited from radiotherapy if it were available, compared to the estimated 6.4% of patients in the whole country that have access.

It is especially important to quantify the potential for improvement in cancer care for the pediatric population specifically. This population has much higher cure rates as well as greater longevity of a cancer-free life. In LMICs, the economic impact is likely substantial, as these patients age and enter the workforce. Further research on the economic impact of pediatric disease is urgently needed. Recently published models by Atun *et al.*, 2015, [10] estimate the economic cost and benefit of scaling up worldwide access to radiotherapy. They calculate an estimated cost of $96.8-184 billion dollars with an accompanying increase of 26.9 million life-years in LMICs. Their models predict a $278.1-365.4 billion dollar net economic benefit to this investment.

In addition to the potential of lessening economic burden, increasing radiation access could lessen tumor burden as well. Upon review of the contributions and advancements of radiation oncology, it was ultimately found that cure rates have improved, and mortality has decreased since the beginning of radiotherapy use in pediatric cancers in 2000. The addition of posterior fossa radiotherapy to chemotherapy improved survival in children < 3 years old with medulloblastoma, compared with chemotherapy alone. It was also found that regimen M chemotherapy with whole-lung radiotherapy resulted in excellent survival for patients with stage IV favorable-histology Wilms tumors with a slow incomplete response to DD4A chemotherapy. In addition to the expanded protocol for use of radiotherapy, the previously associated risks are decreasing. It was found that the more modern radiotherapy techniques are lessening the previous risks to surrounding normal tissues in Hodgkin lymphoma. For retinoblastoma, exchanging the use of external beam radiotherapy and incorporating brachytherapy when suitable led to greater event-free survivals [11]. These studies show that when expanding implementation of radiotherapy in LMICs, it is best to use more advanced technologies that have shown better outcomes to decrease avoidable risks to this patient population.

Many partnerships between HICs and LMICs have successfully expanded pediatric cancer care, and the

establishment of a comprehensive pediatric cancer in an LMIC requires multiple considerations. It was suggested based on evidence that any new similar undertakings for pediatric cancer care in LMICs should provide care regardless of patients' ability to pay, and long-term sustainability should be aimed for by engaging local members, both public and private, who collaborate with community and governmental leadership. It is also most beneficial to have trained nurses specific to pediatric oncology, development of an organization that advocates and fundraises for pediatric oncology, and a designated project mentor in the HIC for support and collaboration [12]. These previously practiced methods would increase efficacy and survivorship of a newly established comprehensive cancer center in a LMIC.

To further establish the need for radiotherapy access, it is notable to witness the change in outcomes that arise when previous access disappears. Delays in radiation treatment were reported in 46% of LMIC centers in a study investigating the effect of the COVID-19 pandemic on Middle Eastern, North African, and West Asian pediatric cancer care. Clinical care delivery was reported as negatively affected in 27% of centers, and there is a fear that these high rates of delay will lead to tumor relapse and treatment failure [13].

There are many barriers to the tangible implementation of a comprehensive cancer center, particularly for the delivery of radiation therapy. Upfront equipment costs are often prohibitive in LMICs, and the adequate training of personnel is both resource- and time-consuming. As previously seen in Uganda where technological problems led to the loss of their only Cobalt-60 machine, the maintenance of these facilities can be challenging and costly [14]. The presence of only one machine for a large region also leads to severely long wait times, as seen in Ethiopia where the wait time for treatment by their single Cobalt machine was a median of 5 months [15]. Kandelhardt *et al.* 2013 [16] showed that the proportion of patients with advanced-stage cervical cancer increased from 44% to 69% during the wait time. In addition to the infrastructure and technology necessary for treatment, a team with quality assurance and operational maintenance training is required. A retrospective cross-sectional study examining a Chinese GWGp90 Cobalt-60 unit in Kampala found the machine had 47 faults, with 2 of this requiring downtime of over one week and were due to failure of the "force back system" of the radioactive source [17]. Without the support of a maintenance team, the work invested into creating the facility can prove to be of little worth.

Importantly, access alone will not solve the problem. A recent quality assessment study analyzed the use of radiation therapy in the Dominican Republic [18]. It was estimated that only one-third of pediatric cases warranting radiation received it. Perhaps even more alarming, 95% of those cases that did receive radiation experienced a deviation from the standard of care in delivery. While some of these problems were due to multifactorial issues like timing and continuity, others were attributed to oncologist-controlled variables such as dose and field arrangement. This challenge might be manageable, as Hatcher *et al.*, 2020, [19] found that a short-term, low-cost live video training program for cancer centers in LMICs significantly improved confidence in radiation treatment delivery for clinicians. However, cultural barriers to care are also present. In Botswana, the stigma of a cancer diagnosis and the reliance on alternative care interfere with the ability of residents to take full advantage of a new radiation oncology center [20]. These same barriers to care are present in Tanzania as well. Overcoming these challenges requires collaboration, planning, education, and resources.

Additional notable findings from the analysis in this region include a high number of cases of cancers not frequently seen in high income countries, such as Wilms' tumor. There is a reported global incidence of 4-10 million in the literature, and recent research found the incidence in Northwestern Nigeria towards the high end of this range at 9 million [21-22]. Recently reported survival rates in developing LMICs include a two-year event-free survival rate of up to 53%, and a five-year survival rate of 40% [23-25]. This is in comparison to a greater than 90% five-year survival in developed countries [26]. The prospective database shows that children with Wilms' tumor comprised 32/220, or 14%, of the cases of pediatric cancer in the Lake Zone of Tanzania. This is significantly higher than previously published numbers [5, 21, 27].

The study has several limitations. Nearly one-third of the patients in the original database had incomplete staging information and thus were not able to be included in this analysis. Additionally, the indication for treatment was based on protocols that were developed in high-income settings due to the limited availability of protocols for radiation treatment in Africa. Given differences in equipment, technology, and infrastructure, these protocols may not always translate perfectly into a LMIC setting. Resource-stratified protocols to optimize outcomes for pediatric cancer are urgently needed.

Conclusions

In conclusion, one-third of pediatric cancer patients in the Lake Zone of Tanzania would have potentially benefited from radiation therapy. Many of these patients would have been treated with curative intent, leading to potentially highly meaningful clinical and economic improvements. Due to the lack of a reliable chemotherapy supply, limited surgical capacity, and a more advanced stage of cancer at presentation in LMICs, in addition to the economic benefit, expanding radiation therapy access is urgently required to improve pediatric cancer care and outcomes in Tanzania.

Abbreviations

BMC: bugando medical centre; SIOP: international society of pediatric oncology; COG: children's oncology group; HIC: high income country; LMIC: low- and middle-income countries.

Author Contributions

All authors contributed to this study. All authors gave their final approval.

Competing Interests

We declare no competing interests.

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