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Assessing Concordance to an Intensified Upendo Ward Wilms Tumor Treatment Protocol in Tanzania: An Institutional Review

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Abstract

Background
In Tanzania Wilms tumor (WT) ranks second among the most frequently diagnosed childhood cancer. Due to late presentation an intensified treatment protocol was established aiming for tumor reduction before surgery for achieving better surgical outcomes. We used two indicators for measuring the protocol concordance. First indicator was assessing the number of patients that received radiotherapy and second was number of patients treated with the high-risk regimen as per the protocol indications.

Methodology
This was a cross sectional study. Data was collected using a retrospective chart review of all children with WT at Muhimbili National Hospital Pediatric Oncology Unit for a period between April 2016 to May 2017 who were treated using the intensified treatment protocol (combination of two WT protocols with neoadjuvant as per SIOP-PODC and adjuvant as per modified SIOP International). Analysis was conducted using excel sheet and SPSS v20.

Results
A total of 74 children were eligible. The median age was 3 years ranging from 6 months to 17 years with small female predisposition of 57% (n=42). On clinical presentation all patients presented with history of abdominal swelling. In terms of clinical stage; 45% (n= 33) and 43% (n= 32) presented with stage 4 and 3 disease, respectively. Radiotherapy treatment was administered to 30% (n=22). As per protocol stage III and IV disease require radiotherapy thus only 34% of eligible candidates received radiotherapy. On histology report; 34% (n = 25) reports were never found and 66% (n=49) were available. High-risk cases were 27% (n = 20). We noted high-risk regimen was given to 12% (n=9) of study participants; thus only 45% of eligible candidates received high-risk regimen. All patient had intention to treat on admission with noted 19% (n = 14) default rate.

Conclusion
Measuring concordance with guidelines allows for identification of best practices, which in turn inform on quality improvements. This snapshot identified opportunities for improvement in protocol uptake in our unit.

Key words: Wilms Tumor, low income country, pediatric malignancy.

Background

Wilms' tumor (WT) also known as nephroblastoma, is an embryonal type of renal cancer and accounts for about 90% of all pediatric tumors of the kidney[1] in the general population. The usual treatment approach in most patients is a combination of surgery and chemotherapy, with the addition of radiotherapy in selected patients. Although WT is the most common childhood kidney cancer worldwide, its incidence, behavior, and treatment outcome vary according to income status, ethnicity and geographic location[2].

In Tanzania WT ranked second among the most frequently diagnosed childhood cancers at the Muhimbili national referral pathology laboratory[3]. This frequency differs from North American childhood cancer incidences, which place WT fifth behind leukemia, lymphoma, Central Nervous System (CNS) tumors, and neuroblastoma.

Challenges faced by WT patients in our setting are not unique to challenges reported in other African Low and Middle Income Countries (LMIC) countries[4], with late presentation with gross disease being the most significant. Our center through government ministry and supportive organizations have devised a standard treatment guideline to insure quality of care provided and also "free out of pocket cost" for treatment for cancer patients. Thus, upon getting the diagnosis all treatment modalities and accompanying investigations are covered for by the scheme.

The protocol employed at the Muhimbili National Hospital (MNH) pediatric oncology unit include an extended pre-operative chemotherapy as proposed by the Collaborative Wilm's Tumor African Project. The Preoperative chemotherapy for patients with localized disease is planned for 4 - 6 weeks and consist of Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly and Actinomycin D 45 µg/kg (maximum dose 2 mg) two weekly. Chemotherapy for metastatic disease planned for 9 – 12 weeks total and include Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly; Actinomycin D 45 µg/kg (maximum dose 2 mg) two weekly and Doxorubicin 30 mg/m2 every four weeks. For post-operative; Patient's treatment decisions are based on: disease stage; response to treatment for metastatic children at week 6 pre-operative and pathological results. All intermediate and high risk to receive Radiotherapy, given from week 2 of post-operative chemotherapy. For stage I – Low risk only follow up 3 monthly for 1 year then 6 monthly for next 2 years. For stage I – Intermediate risk receive post-operative chemotherapy for 4 weeks which include; Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly and Actinomycin D 45 µg/kg (maximum dose 2 mg) two weekly. Stage II, III and completely resected stage IV – low risk to receive post-operative chemotherapy for up to 27 weeks which include; Vincristine 1.5 mg/m2 (maximum dose 2 mg) weekly and Actinomycin D 45 µg/kg (maximum dose 2 mg) two weekly. For high risk stage II, III and completely resected stage IV, receive Cyclophosphamide 450 mg/m^2 for 3 consecutive days with Doxorubicin 50 mg/m^2 on day one of this course (making total of 6 courses) on weeks 1, 7, 13, 19, 25 and 31 (with week 34 for stage IV). Doxorubicin total cumulative dose of doxorubicin must not exceed 300mg/m^2. Etoposide (VP16) 150 mg/m^2 for three consecutive days together with Carboplatin 200 mg/m^2 also for three consecutive days (a total of 6 courses) given every 6 weeks from week 4 onwards hence on weeks 4, 10, 16, 22 and 28 (with week 34 for stage IV).

We aimed to assess protocol concordance among health care providers to the tailored intensified guideline used in the unit. Concordance was assessed by analysis the number of patients that received radiotherapy and number of patients treated with the high-risk regimen as per the protocol indications.

Materials and Methods

Study area

The pediatric Oncology unit consists of two wards namely Upendo where very sick children are admitted and Tumaini ward which admit stable patients who still need care. The unit was officially opened at MNH in August 2013. The Upendo/Tumaini children's cancer ward complex is the only specialized children's cancer ward in Tanzania, providing cancer care and treatment at no out of pocket cost from patients and their families. Through donor partners, MNH and from government funding the unit is able to provide diagnostic and treatment services to patients aged from infancy to 18 years' age without out of pocket family cost regardless of the malignancy type, disease stage or treatment modality needed. Chemotherapy and surgery are provided within the MNH compound and radiotherapy is provided at Ocean Road Cancer Institute.

The unit also offers food and shelter during the long treatment stay for patients from upcountry at Ujasiri home. Primary education and play therapy to patients is also available. Upon completion of treatment patients and their guardians/parents are provided bus tickets to return back home. All these services are put in place to reduce the burden of childhood cancer on individual families in the country.

Study design and Participants

This was a retrospective chart review of patients treated from April 2016 to May 2017. The study included patients who presented to MNH Pediatric Oncology Unit with suspected or confirmed diagnosis of WT and had not received any oncology related treatment. Ethical approval was obtained prior to the study.

Inclusion Criteria

Confirmed or suspected WT diagnosis

Chemotherapy or surgery naive patient with WT diagnosis

All patients who had completed treatment fully, partially or absconded from treatment in the 12 months' study period.

Exclusion criteria

Any children who had up-front nephrectomy without neo-adjuvant chemotherapy, because neoadjuvant chemotherapy is a major component of the treatment protocol.

Data Collection and Analysis

Data was collected from patients' files using a structured data abstraction form to include demographic data, disease stage at admission, pre and post-operative treatment given,

histology and post – operative classification. Data cleaning and analysis was done using SPPS version 20.0 by the research team.

Ethics Statement

Ethical approval was obtained from the Muhimbili University of Health and Allied Science Institutional Review Board. Waiver of consent was granted, because the research involved no added risk to subjects and used secondary data analysis of patients that had already consented to treatment thus did not adversely affect the rights and welfare of the subjects whose identities were not revealed to ensure confidentiality.

Results

Socio-demographic and clinical characteristics

As summarized in Table 1, a total of 118 patients with presumptive diagnosis of WT were admitted from April 2016 to May 2017. From these, 74 (63%) patients eligible for final analysis. The remaining 44 (37%) were excluded during the analysis because 19 (43%) were still on treatment and 25 (57%) had missing records. The male to female ratio distribution of the study population was 1:1.3. The median age of the study population was 3 years, ranging from 6 months to 17 years with an Interquartile range IQR (2 – 5).

Table 1: Socio-demographic characteristics of participants (n=74)

Variable	Frequency	Percent (%)	
Sex			
Male	32	43	Ratio 1:1.3
Female	42	57	
Age (years)			
<1	3	4	
1-3	36	48	
4-6	26	35	Median = 3 yrs
7-9	5	7	
≥10	4	6	IQR (2 – 5)

All 74 patients were HIV negative. Majority of the patients were noted to be referrals, of which 28(38%) were from coastal zone followed by the southern zone 13(17%) as shown in Figure 1.

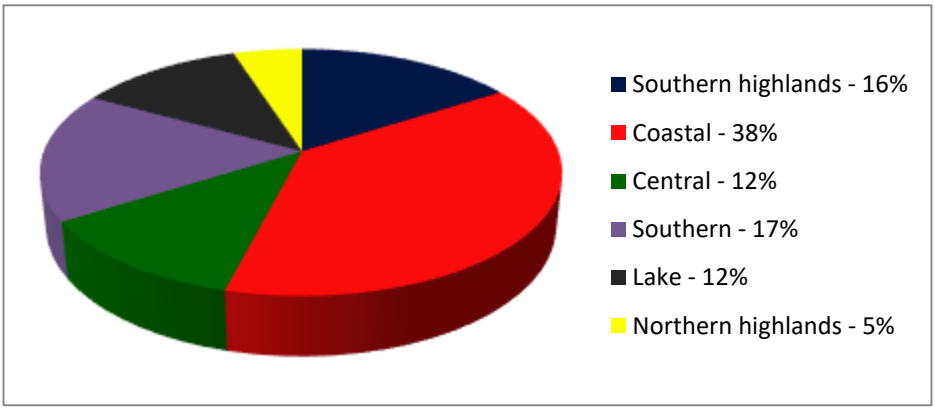

Figure 1: Distribution of WT patients by zones of the country

Southern Highlands - Mbeya, Iringa, Rukwa, Ruvuma, Njombe
Coastal - Dar es salaam, Pwani, Zanzibar, Morogoro, Tanga, Pemba
Central - Dodoma, Singida
Southern - Lindi, Mtwara, Ruvuma
Lake - Tabora, Kigoma, Shinyanga, Kagera, Mwanza, Mara, Simiyu, Geita, Katavi
Northern highlands - Arusha, Kilimanjaro, Manyara

Disease profile and treatment given

Majority of the patients presented with clinical stage III disease (46%) and IV (42%) as shown in Figure 2. The noted commonest site for metastatic disease was the Lungs (83%).

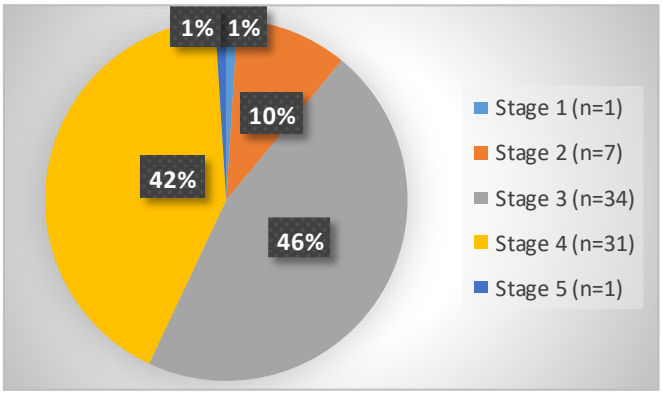

Figure 2: Disease stage

The main presenting complaint was abdominal swelling in all 74 patients participating in the study. Also noted (77%) presented at lag period less than 6 months and (52%) of patients were correctly diagnosed at the initial health facility prior to referral to MNH. All children in the study were HIV negative.

We had 63% of patients completing treatment (Figure 4) with remaining unable to complete due to defaulting treatment (19%), disease progression (19%) leading to switching intent from curative to palliative treatment and death (4%). The number of reported histopathology samples post operatively were 66% (n=49) out of which high risk 27% (n=20), Intermediate

risk 31% (n=23) and low risk 8% (n=6) (Figure 3). High risk regimen was administered to 12% (n=9) out of eligible 20 high risk patients. Histology report were missing for 34% (n=25) of all operated specimen.

Patients eligible for Radiotherapy were 65 (88%) and those who received radiotherapy were 22 (30%) out of eligible candidates.

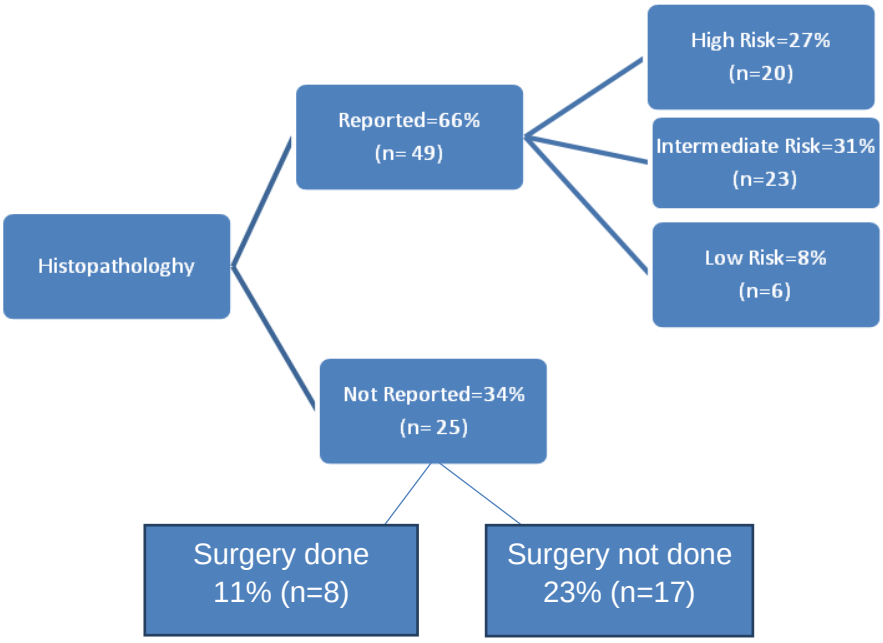

Figure 3: Histopathology report

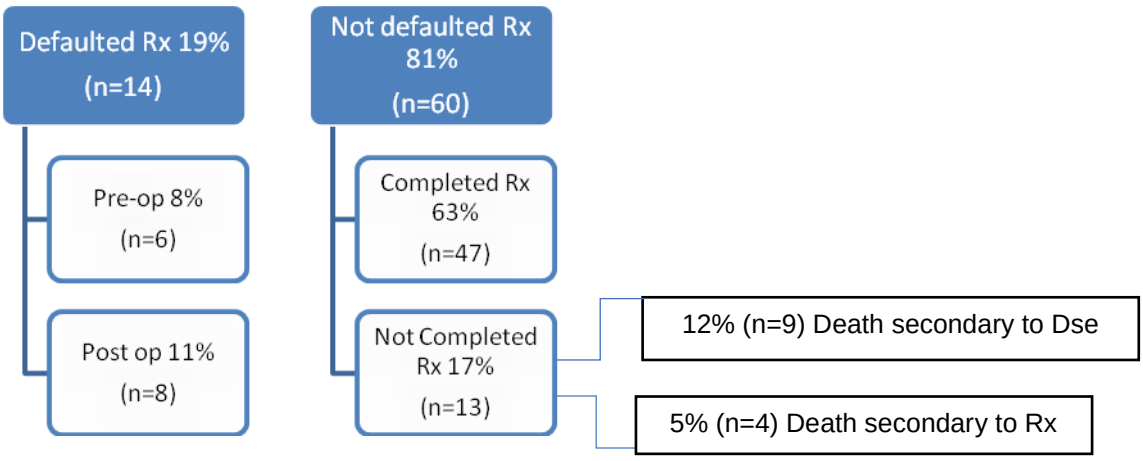

Figure 4: Treatment Completion (N=74)

Discussion

Our results showed a high burden of disease at a single specialized pediatric oncology unit, with around 118 new cases per annum treated. The whole unit is estimated to cater for around 350[5] new cancer patients per annum thus WT accounts for 34% of total pediatric oncology cases. This incidence is in range to other sub-Saharan countries with around 114 to 130 cases per annum[6] as reported in the collaborative Wilms Tumor Africa project report. The patients were all HIV negative, this is similar to other studies done in sub-Saharan Africa[7,8] thus supporting that WT is not a HIV related malignancy[9]. Most of the patients had locally advanced disease stage III (49%) and stage IV which is the metastatic disease (42%). The rate of metastatic disease is higher than reported in neighboring countries Malawi (29%)[7], Uganda (36%) and Kenya (16.8%)[10]

All patients had curative intent to treat on admission and we noted most children tolerated well the tailored treatment protocol which included chemotherapy/surgery/radiotherapy with deaths presumed as treatment related (neutropenia) around (5%), this is low compared to (15%)[7] in Malawi using the intensified pretreatment protocol used in collaborative Wilms Tumor Africa project; thus the protocol was relatively safe to use in the ward.

The formulation of a tailored and specific guideline alone was not sufficient to result in widespread adoption into routine practice in the ward depicted clearly in the use of the high-risk regimen; this was given to only 45% of eligible candidates that needed it as per protocol. In terms of local radiotherapy treatment, the protocol called for all stage III and IV disease to receive radiotherapy, but our results showed radiotherapy treatment was administered to 30% (n=22). Comparing all stage III (n=34) and stage IV (n=31) we noted overall only 34% of eligible candidates received radiotherapy. Our study also showcased guideline concordance is not just affected by lack of protocol ownership by the treatment team, inability of families to cover cost of chemotherapy agents and lack of radiotherapy machines as reported in surveys showcasing barriers faced by oncology providers in LMICs to successful implementation treatment guidelines[11,12]. Hence other factors have to be considered for the low concordance to the protocol in our setting like patients which were noted by 19% (n = 14) default rate and even physician related causes[13,14]. A survey done at Ocean Road Cancer Center pointed that some of the barriers faced by oncologists in implementing treatment guideline included not being accustomed to guideline-based practice and provider perception that more effort is required to reference guidelines than seek (or make) an experience-based decision[15]. We also acknowledge that 34% of histology reports were not found even post tracing in pathology department data base. This is a noted problem in LMIC were histology reports can be lacking during treatment.

Conclusion

Improving treatment outcomes in LMICs calls for measuring concordance to guidelines in place as this allows for identification of best practices and inform on possible quality improvements practices. This snapshot identified opportunities for improvement in protocol uptake in our unit and also highlighted the need to conduct more research to explore existing barriers caused by either patients or health care providers in implementing evidence-based treatment practices.

Recommendation

To combat provider behavior related causes, the unit can consider utilizing automated prescriptions software's and also employing sustained behavior change implementation models that will aim to change unproductive practices and improve cost of care[16]. This can be achieved through employing trainings[17] to keep staff updated in treatment guideline and selection of guideline agents that can act as champions[18] for others in promoting guideline-based practices in the unit.

Study limitations

Limitation noted included incomplete pathology report, hence missing the pathological subtype and only denoting WT as diagnosis; also, radiotherapy notes were not available in the patient's files.

Competing Interests

Authors declare no competing interests

Author contribution

Study design was done by SN, PS and ND; SN did field work and acquired data; Data analysis and interpretation was done by SN and PS. SN formulated the Initial manuscript draft; ND, PS, EM and GF revised the manuscript. All authors contributed to the draft and approved the final manuscript.

Acknowledgement

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List of Abbreviations

CNS:	Central Nervous System
DSM:	Dar es Salaam
HIV:	Human Immunodeficiency Virus
LMIC:	Low and Middle Income Countries
MNH:	Muhimbili National Hospital
MUHAS:	Muhimbili University of Health and Allied Sciences
ORCI:	Ocean Road Cancer Institute
PODC:	Pediatric Oncology in the Developing Countries
SIOP:	Société International D'Oncologie Pédiatrique International Pediatric Oncology Society
SPSS:	Statistical Package for Social Science
WT:	Wilm's' Tumour

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