

# Improved outcome after Wilms tumor treatment in Sudan: a 10-year single-center experience

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## Abstract

**Abstract Background:** the survival of Wilms tumor is very low when evaluated in 2008. The impact of establishing pediatric oncology service on survival is studied, and the obstacles of treating Wilms tumor patients were identified. **Procedure:** All Wilms tumor patients from 2005 to 2014 were analyzed retrospectively. Patients received treatment based on the NWTS IV protocol. Patients were analyzed for overall survival, and event-free survival, and these outcomes were correlated with age, sex, stage at presentation, and histology. **Results:** We analyzed 143 files of Wilms tumor. The male to female ratio is 1.75. The mean age of patients at diagnosis is 3.5. The follow-up period is five years. Most patients (83%) had advanced disease stage 3, and 4. There is a very high abandonment rate (37%). The event-free survival among patients who completed treatment is 75.6%, and the overall survival is 43.4% **Conclusions:** There is a remarkable improvement in Wilms tumor survival from 11% to 43 % and 75.6%. Much needs to be done to reduce abandonment rates and establish a surgical pediatric oncology service.

## Introduction

There is a shortage of data about the epidemiology, pathology, treatment, and prognosis of Wilms tumor from Sudan. Dafalla O. Abuidris et al. <sup>1</sup> published one study in 2008. They noted a high proportion of locally advanced and metastatic disease (Stage III (67.6%) and Stage IV (10.8%).) and poor results. This group reported a survival rate of 11%.

Sudan Population is 43 746 000 <sup>2</sup>. In 2019, The urban population for Sudan accounted for 34.9 %. In 2018, the population aged 0-14 years for Sudan was 40.5 % <sup>3</sup>. Forty-seven percent of the population lives below the poverty line. Twenty-six percent of people living in Khartoum state is below the poverty line. Poverty increase to 70% in the North Darfur western Sudan<sup>4</sup>.

This study is conducted in the Khartoum oncology hospital (KOH). It is a government hospital and the larger of two oncology centers in Sudan. The hospital is state-funded. Necessary investigations, chemotherapy, and radiotherapy are provided free. The oncology unit treats children from all over Sudan. It is situated in Khartoum, which has a population of 9.0 million. Many patients come from rural areas.

The department of Pediatric hematology-oncology was established in April 2004. Three full-time consultants staff the oncology unit. The unit accepts an average of 350 new patients for treatment per year. KOH lacks Intensive care facilities, and there is no department of pediatric surgery. The pediatric oncology unit accepts Wilms tumor patients after surgery or biopsy from all over Sudan. General pediatric surgeons from other hospitals perform surgery then refer the patients. A qualified radiation oncologist administers radiotherapy. Due to technical problems, lung and whole abdomen radiotherapy are not possible to treat. Three-D radiotherapy is not available. The radiology department lacks CT and MRI machines.

This study is conducted to identify the obstacles in managing Wilms tumor. It also assesses the impact of the establishment of the pediatric oncology department on the outcome of Wilms tumor.

## METHODS

The study is a retrospective analysis of all patients diagnosed with Wilms tumor in KOH between April 2005 and December 2014. A total of 177 patients are registered as Wilms tumor. Thirty-four patients are excluded from the study because the information is incomplete.

Details of presentation, histology, and management were extracted from patient records. All patients were staged radiographically with chest and abdomen CT and during surgery. The national Wilms tumor study group (NWTSG) is used for staging (5). Patients are divided into two main groups. The first group is patients who completed treatment (chemotherapy surgery and radiotherapy), and the rest did not start or did not complete treatment. Standard practice throughout this period was that patients were assessed at diagnosis by the pediatric surgeon outside the center. Primary surgery was undertaken where possible. For tumors considered inoperable, pre-operative chemotherapy was given after Tru cut biopsy. These tumors were regarded as stage III. The histopathology was reviewed at different labs and by a different pathologist. Chemotherapy and radiotherapy are started as soon as possible. Since surgery and the pathology review were done outside the center, there was a considerable delay in starting treatment promptly. Chemotherapy was delivered according to NWTSG IV (5) Relapses were treated with surgery if local only, followed by chemotherapy. Surgical removal of the liver and pulmonary metastasectomy is not available and were treated with chemotherapy only. Radiotherapy for lung and liver metastases is technically not possible. Radiation is given to local relapses if not given initially. The relapse chemotherapy regimens used include vincristine, actinomycin, doxorubicin, cyclophosphamide, ifosfamide, etoposide, and carboplatin.

Outcome at the end of treatment was categorized as (a) alive without evidence of disease, (b) treatment abandonment, (c) death from disease persistent disease (unresectable disease, relapse of disease, or persistent disease after the completion of the full treatment), or (e) death from treatment side effect. Relapse patients who achieved a complete response after second-line treatment are considered as group (a). Survival time was calculated from diagnosis to the last moment of contact, either by clinic visit or active follow up.

The event was defined as no treatment initiated, incomplete treatment, and death. OS and event-free survival are estimated using the Kaplan-Meier and Log-rank test by SPSS 24.

## Results

Between 2005 and 2014, 2497, children with cancer were registered. 143 (5.7%) patients were confirmed cases of Wilms tumor eligible for evaluation. The male to female ratio is 1.75 (91 male, 52 female). The age range is between 8 months and 12 years, with a mean of 3.5 years. The follow-up period was up to 61 months. A hundred patients (70%) are between 1 and 5 years.

Other characteristics are shown in Table 1

## Surgery

No surgery was performed on 31 patients because they either refused treatment, were lost for follow up, died from chemotherapy side effect, had poor performance status, or had bilateral disease. The type of surgery did not have any significant impact on survival or completion of treatment  $p < 0.05$ .

## Chemotherapy

A total of 82 (57.3%) patients completed therapy (surgery chemotherapy and radiotherapy), while 53 (37%) did not. The event-free survival among patients who completed treatment is 75.6%, and the overall survival is 43.4%. See figure 1 and figure 2. Survival among patients who completed chemotherapy, surgery, and radiotherapy is significantly better than who did not  $p < .01$  No chemotherapy was given to 8(6%) patients because they were lost for follow-up or refused treatment. One patient was given chemotherapy for palliation.

The actuarial survival is 100 % for stage I, 73.3% for stage II (censored), and 57 % for stage III (censored) 55% for stage IV and 16.7% for stage V.

### **Abandonment**

A total of 64/143 (44.8%) patients abandoned treatment, 38 (26.6 %) did so in the first six months. Eight patients refused treatment upfront, and one was given treatment as palliation. Sixty-one patients (42.7%) did not start or did not complete treatment.

### **Relapses**

A total of 25 patients relapsed, constituting 17.4%. The relapse rate is higher among stage III (17) patients and stage IV (6) patients. One patient had progressive disease while on chemotherapy, and three patients had partial/no response. Five patients were salvaged with second-line treatment and are alive and well when last seen. Five died, and 15 patients were lost for follow up. Most relapses occurred in the patients who completed treatment (18). The most common site of relapse is primary site 17(68%), lung and local 7(28%).

### **Deaths**

A total of 17 (11.9%) died during the study. Fourteen were disease-related, and three were treatment-related.

### **Discussion**

This study reflects the situation in the largest oncology hospital in Sudan. Compared to previous studies, the subject number is reasonably large, and the duration of follow up is longer. It is the largest data from Sudan about the outcome of Wilms' tumor using the NWTS 4 protocol. It identifies many problems that face Wilms tumor management. The incidence of Wilms tumor in our study is (5.7%). The incidence, age, and sex distribution are comparable to most international studies and other Low-income countries (LIC) countries<sup>5, 6,7, 8,9</sup>. However, these figures are drawn from hospital-based records and might not reflect the population incidence.

Most of our patients presented with advanced disease stage. Stage 3 and 4 constituted (83 %) of all cases. This is in contrast to other more extensive studies that have the bulk of their patients presenting with early-stage disease<sup>10</sup>. It is also higher than other low income and middle-income countries<sup>5,8,11,12,13,14</sup> Favorable histology is the most common (86%). It is consistent with a study by Hoda M Awadalla. In their study, 82.2 % of Wilms tumor in Sudanese children was the favorable triphasic type<sup>15</sup>

Primary nephrectomy is the most frequent type of surgery. All surgeries are performed outside the hospital. There is a significant delay in doing the surgery due to the long waiting lists. There is also a delay in obtaining the histopathology report. Much information is collected through personal communication and imaging. It takes at least one month after surgery to start chemotherapy and radiotherapy.

Pre-operative chemotherapy, followed by nephrectomy appears to be a reasonable approach. The fact that there are no surgical facilities at the hospital makes it difficult to adapt the SIOP pre-operative chemotherapy. Many patients who received neoadjuvant chemotherapy had significant delays when referred for surgery. In some cases, the tumor increased in size significantly. This approach is also challenging to adapt too. Pre-operative chemotherapy seems the right strategy, but it is not possible to use it now. A project to establish a surgical unit has inside the hospital has started.

Although chemotherapy is free, some families refused to start treatment or discounted therapy early during the disease 61 (43%). This reluctance is due to many financial restrains and social beliefs. Although a large number of patients refused treatment, there a significant improvement when compared to the previous study<sup>1</sup>. As expected, the survival rate in these two groups is reduced. Our results are comparable to some low-income countries<sup>16,17,18</sup>.

Because surgery is done outside the hospital, radiotherapy is delayed for more than 1-month in all cases. This delay might contribute to the poor results.

Age, sex, and stage of presentation did not have a statistically significant impact on survival. Treatment completion is the most significant prognostic factor in our study  $p < 0.0001$ . It is known that Histopathology type is the most significant prognostic factor<sup>8,19,20</sup>. Guruprasad et al. found that only the nodal status to be independently associated with survival.

The event-free 43.3 % is comparable to many African and third world countries. Although considered as inferior, this is a significant improvement from the previous study in Sudan<sup>1</sup>. The survival among the patients who completed therapy is good (75%) and comparable to many middle-income countries<sup>17</sup>. Because most patients (83%) presents with advanced disease, the recurrence rate is high (17.4%)<sup>20</sup>

There is a high rate of local recurrence, either isolated 17(68%) or with distant metastasis 6(24%). Most studies report a higher incidence due to lung relapse<sup>21</sup>. The delay in starting radiotherapy might explain such findings.

We had one of the highest abandonment rates in Africa<sup>20,21</sup>. The cost of treatment is not the reason; because chemotherapy and radiotherapy are free. Three guesthouses provide free accommodation. The high rate of abandonment is multifactorial. The long-distance from the facility, poverty, long waiting times, anxiety about what to expect, are some reasons. Illiteracy, many social and religious believes about cancer are other reasons. Close Follow-up, including home visits when needed, might reduce this problem<sup>21</sup>. Chagaluka et al.<sup>22</sup> found that funds used to cover treatment, travel, and other associated costs for patients, significantly reduced the abandonment rate. In our setting, a different approach to minimize abandonment might be more useful. A project aiming at giving part of the treatment at the local hospital will be started soon. Unlike Israels T et al.<sup>21</sup>, the death rate is lower and contributes to 11.9 % of treatment failure. The department has begun measures to improve communication with patients with poor compliance.

This study has shown the benefit of settling a specialized or semi specialized unit of pediatric oncology in low-income countries. The survival rate improved from 11% to overall survival of 43% and 75% for patients who complete therapy. There is a high abandonment rate that needs further attention. Institutionalized measures such as those adopted by L F Chukwuemeka Anyanwu,<sup>23</sup> might improve results The study also highlights some problems that face LIC. It emphasizes the importance of having an in-house surgical unit to reduce radiotherapy delays.

**CONFLICT OF INTEREST**The authors declare that there is no conflict of interest

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