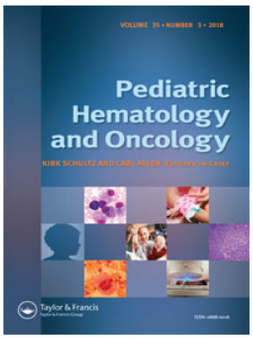

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Survival of children with a Wilms tumor in Blantyre, Malawi

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ABSTRACT

Wilms tumor (WT) has a survival rate above 90% in high income countries. Reported survival rates in sub-Saharan Africa are much lower and long-term outcome is not well known as follow-up is challenging. In Blantyre, Malawi, an adapted WT treatment guideline with preoperative chemotherapy, supportive care, and strategies to enable children and parents to complete treatment was introduced in 2006. Between 2006 and 2011, 73 children with a unilateral WT were treated. Follow-up, including home visits when needed, was done. Median follow-up time is 5 years (range 14–95 months). Two and five-year event free survivals are 46 and 42%. Causes of treatment failure are: 7% (5/73) abandonment of treatment, 15% (11/73) death during treatment and 30% (22/73) disease-related deaths (persistent disease and relapse). Long-term follow-up is challenging but necessary to be able to assess outcome and the true impact of interventions.

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Wilms tumor; low income countries; survival; abandonment; adapted treatment guidelines

Introduction

Wilms tumor (WT) is a childhood renal cancer.[1] In high income countries, survival has increased significantly over the last decades. A multidisciplinary approach combining chemotherapy, radiotherapy, and surgery has resulted in long-term survival rates above 90% in Europe and North-America.[2] Survival rates in low- and middle-income countries are much lower, especially in sub-Saharan Africa, where reported survival rates range from 11 to 46%.[3–6]

A study from Sudan by Abuidris et al. reported 11% survival of children with WT at the end of treatment (no further follow-up). More than half of the children did not have a nephrectomy and only 11% completed treatment. Causes of treatment failure were a combination of death during treatment and abandonment of treatment.[6]

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A 5-year event-free survival (EFS) of 56–77% (+/– abandonment documented as an adverse event) was reported for patients with localized WT in Casablanca, Morocco after a median follow-up of 70 months.[7]

Moreira et al. reported in 2012 on survival in children with WT in the French-Africa Paediatric Oncology Group (GFAOP). They selected the group of operated patients with a low or intermediate risk tumor, without residual metastatic disease or progression postoperatively. Two-year event free survival in this group of children was 73–87% for children in North Africa and 47% for children in sub-Saharan Africa. The intention to treat survival analysis that would include all children is not reported.[3,4]

Longer term follow-up is needed to record late relapses and establish the true survival rate. Follow-up is very challenging in low income countries and especially in sub-Saharan Africa. Parents have other priorities than returning to the hospital with a healthy child; funds are often lacking for follow up and when they are available, bad roads and lack of home addresses hamper active follow up. Mobile phones are not always available and working. Therefore survival data from low income countries with longer term follow-up are rare.

In the Queen Elizabeth Central Hospital in Blantyre, Malawi, an adapted WT treatment guideline was introduced in 2006 aiming to improve care and survival. The guideline includes preoperative chemotherapy, supportive care, nutritional support and strategies to enable parents to complete treatment of their child.

Malawi is one of the poorest countries in the world according to the world bank classification with a gross national income per capita of 320 US dollar.[8] Childhood mortality has decreased in the last decade, but still, 55 of 1000 live born children die before their fifth birthday.[9] The Queen Elizabeth Central Hospital is in the city of Blantyre that has a population of one million. It is a government hospital and medical treatment is free. It serves as the district hospital of Blantyre, the referral center for the southern half of Malawi and the main clinical teaching unit of the College of Medicine of the University of Malawi. About 250–300 children with newly diagnosed malignancies are admitted every year.

Overall and event-free survival was 46% after a median follow-up of 16 months (range 1–52 months).[5] At the end of treatment, 67% (49/73) of children with a unilateral tumor were alive without evidence of disease, seven percent (5/73) had abandoned treatment, 15% (11/73) died during treatment and 11% (8/73) had persistent disease.[5]

Here, we report the outcome of the same group of children with WT after a much longer (median 5 years) follow-up period.

Materials and methods

All children who presented to the Queen Elizabeth Central Hospital in Blantyre, Malawi, between 2006 and 2011 with a unilateral WT were included and managed as described previously.[5] Histological examination of the surgical specimens was done by the institutional pathologist according to the guidelines of the International Society of Pediatric Oncology (SIOP).

The first 20 patients were taken home after their first post-operative chemotherapy course and Global Positioning System (GPS) coordinates documented to be able to trace them. For later patients, contact phone numbers and the names of the home village and nearby hospital, school or church were recorded to enable active follow up if patients did not return. After one post-treatment year, all patients were invited for annual

checkup visits and were actively followed up by phone if they did not come. About twice a year a team would go out by car into the country to try to find and visit the children who did not come for planned visits and could not be contacted by phone. All follow-up data were recorded in an excel database.

Events considered for event-free survival (EFS) were relapse, death or abandonment of treatment. Living patients were censored at the time of last follow-up. Patients were considered lost to follow-up when they had not come for their annual visit and could not be reached by active follow-up for over a year. Statistical analyses including the Kaplan–Meier survival curves were performed with SPSS (SPSS for Windows, version 16·0, SPSS, Chicago, Illinois).

Results

Patient and tumor characteristics at diagnosis

Seventy-three patients are included of whom 33 (45%) were female and 40 (55%) were male with a median age of 37 years (range 9 months to 12 years) (Table 1). Tumor characteristics at diagnosis; site and size of the primary tumor, and presence and site of metastases, are also in Table 1 as previously described.[5]

Survival analysis

Two-year and 5-year event-free survival (EFS) and overall survival (OS) are 46% (SE 0.06) and 42% (SE 0.06). Figure 1 shows the Kaplan–Meier survival curve. Median follow-up is 58 months (range 9–95 months).

Two-year and 5-year EFS and OS of all patients with localized disease is 46 and 43% (SE 0.07), respectively. For children with metastatic disease 2-year EFS and OS is 48% (SE 0.11) and 5-year EFS and OS 40% (SE 0.12).

Two-year and 5-year EFS and OS of patients who had surgery, without high risk disease and without residual disease postoperatively is 76 and 68%, respectively.

All children with a relapse of disease died, event-free survival and overall survival are identical.

Death from other causes

Three patients (4%) died presumably of another cause. One child who had been treated for a low risk Stage 1 WT died with a typical picture of malaria (high fever, vomiting,

Table 1. Patient and tumor characteristics at diagnosis ($N = 73$).

Patients	
Sex	33 (45 %) female, 40 (55 %) male
Age	median 3.7 years (range 9–144 months)
HIV	All negative
Tumors	
Site	30 (41%) left side, 43 (59%) right side
Size*	23 (32%) $<$ 15 cm, 29 (40%) 15–25 cm, 20 (27%) $>$ 25 cm, 1 (1%) N.A.
Localization	52 (71%) localized, 21 (29%) metastatic
Site metastases	$N = 5$ liver, $N = 13$ lung, $N = 3$ lung and liver

*Size was estimated by measuring the maximum diameter of the tumor with a tape measure. N.A. is not available.

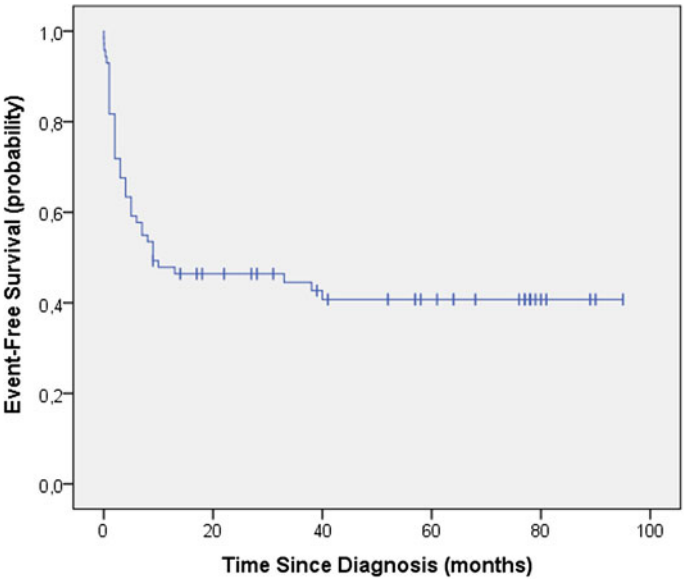

Figure 1. Kaplan–Meier curve showing a 2-year EFS of 46% and 5-year EFS of 42%.

short illness). Two others died long after the end of treatment without any signs of recurrent abdominal or chest disease (no fatigue, weight loss, abdominal swelling or shortness of breath) and with signs of an infectious disease (relatively short illness, fever, diarrhea).

Follow up

Median follow-up is 58 months (range 9–95 months). All children were followed for at least a year, only four children were lost to follow up within 2 years. Ten children were eventually lost to follow-up. Median follow-up time in this group of ten children was 25 months (range 14–52 months).

Causes of treatment failure

Treatment failed in 38 patients. Figure 2 shows the causes of treatment failures (deaths) as a percentage of all the patients ($n = 73$) with unilateral WTs. Five of 73 (7%) failed to complete treatment. Eleven of 73 patients (15%) died during treatment of a presumed treatment-related cause of whom eight (11%) died during pre-operative chemotherapy and three (4%) peri-operatively.

Twenty-two of 73 patients (30%) died of the disease; eight (11%) had unresectable disease after preoperative chemotherapy; two because of a huge primary tumor and six because of metastatic disease. A further 14 (19%) had recurrent disease. Relapses occurred a median period of 7 months after diagnosis (range 3–40). Thirteen were abdominal relapses, one was a pulmonary relapse. Of all 14 children with a relapse, three patients (21%) had metastatic disease at diagnosis ($2 \times$ chest, $1 \times$ liver) and 11 (79%) had local disease.

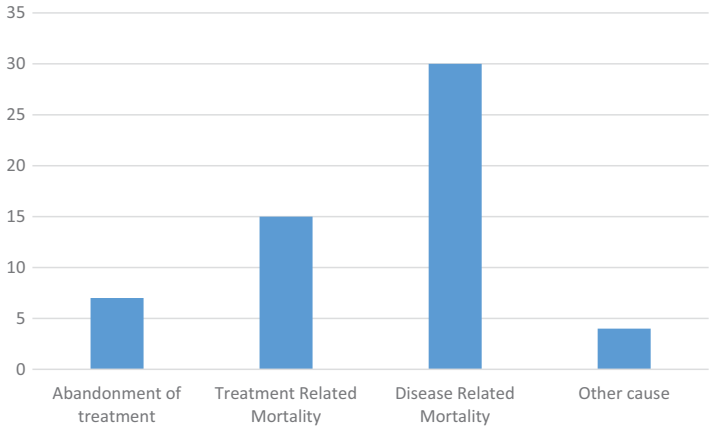

Figure 2. The different causes of treatment failure in percentages.

Table 2. Pathology stage and risk group of resected tumors ($N = 48$) and number of relapses in brackets.

	Stage 1	Stage 2	Stage 3	Total
Low risk	5 (0)	0 (0)	0 (0)	5 (0)
Intermediate risk	5 (0)	13 (3)	15 (4)	33 (7)
High risk	2 (0)	4 (1)	4 (4)	10 (5)
Total	12 (0)	17 (4)	19 (8)	$N = 48$

Pathology stage and risk group and relapse of disease

Forty-eight of these 73 patients had a pathology report after nephrectomy. Stage and risk group are in Table 2 with the number of relapses in brackets. Of the 19 patients with stage III tumors, all had an incomplete excision, additionally 11 patients of this group also had a tumor rupture (2 minor, 7 major). Of the 15 patients with a stage III, intermediate risk tumor, the histological subtypes were epithelial type (2), stromal type (3), mixed type (4), regressive type (4), stromal with focal anaplasia (1) and unknown (1).

Two patients with a relapse had no pathology report. Of the 48 patients with a pathology report, 12 had a relapse. No low risk or stage 1 tumors relapsed. All stage III, high risk tumors relapsed. Relapses of patients with stage III tumors were all abdominal. Of the four patients with a stage III, intermediate risk tumor who had a relapse of disease, the histological subtypes were stromal subtype,[1] stromal with focal anaplasia,[1] mixed subtype[1] and unknown.[1] Of the children with a stage III tumor who had a relapse, five had a tumor rupture (3 major, 2 minor).

Discussion

This is one of the very few reports of long-term survival from childhood cancer in sub-Saharan Africa.[10] Two-year and 5-year event-free survival (and overall survival) in this group of children with a unilateral WT is 46 and 42% after a median follow-up of almost 6 years.

There are few data available with which to compare this survival. Survival in high income countries is above 90%.[2] End of treatment survival in Sudan was only 11%.[6]

A retrospective file study in Kenya showed a three year event-free survival of 41%, very similar to our results.[11] The 47% 2-year event free survival in centers in sub-Saharan Africa in the GFAOP study is for a selected population (after surgery, no high risk disease, no residual disease or postoperative disease progression) and would be much lower when calculated for the whole group.[3,4] In our study group 2-year survival of this selected group of patients is 76%.

We chose to do an intention to treat analysis (ITT), including all children diagnosed with unilateral WT tumors. This makes it possible to assess and address some of the reasons for failure such as incomplete treatment, treatment-related or disease-related causes, and plan appropriate interventions to improve outcomes for all children with WT.

Median follow-up time is almost 6 years. All children were followed for at least a year, only four children were lost to follow up and all within 2 years. This satisfying rate of follow up under very challenging circumstances has been possible thanks to the commitment of local staff and a simple, effective system of follow-up appointments with active follow-up (first phone calls, then home visits) if needed. Careful note of all possible mobile phone contacts and detailed maps of directions to the patients' homes are essential. When planning therapeutic protocols in low income countries, the need to pay for follow up visits and any necessary, active follow-up should be acknowledged.

Patients present late with advanced disease. More than a quarter of patients (30%) died of directly disease-related causes (unresectable disease 11% and relapse 19%). As expected, relapses occurred mostly in higher stage and risk group tumors. Earlier presentation is essential to improve prognosis and outcome. Radiotherapy is not available in Malawi. We may now need to consider intensification of chemotherapeutic treatment to compensate for this, but need to avoid increasing the treatment-related mortality. The aim is, as always, to find the optimal balance of treatment intensity for the population in the local setting to avoid both treatment and disease-related deaths.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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