Effectiveness of a Wilms tumour treatment guideline adapted to local circumstances in sub-Saharan Africa.

A report from Wilms Africa Phase II – CANCaRe Africa.

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Abbreviation's key

WT	Wilms tumour
WHO	World Health Organization
GICC	Global Initiative for Childhood Cancer
EFS	Event free survival
OS	Overall survival
SIOP	International Society of Pediatric Oncology
CANCaRe Africa	Collaborative African Network for Childhood Cancer Care and Research
CRF	Case report form
DM	Data manager
CI	Chief investigator
EOT	End of planned first line treatment
SE	Standard error

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Abstract

Background Wilms tumour (WT) is one of the cancer types targeted by the Global Initiative for Childhood Cancer (GICC). The objective of this study was to describe the outcomes of Wilms Africa Phase II in sub-Saharan Africa.

Methods: Wilms Africa Phase II used a comprehensive WT treatment protocol in a multi-centre, prospective study conducted in eight hospitals in Ethiopia (2), Ghana (2), Malawi, Cameroon, Zimbabwe and Uganda. Eligibility criteria were: age younger than 16 years, unilateral WT, diagnosed between January 1st 2021 and December 31st 2022.

Results: We included 230 WT patients, median age 3 years, 53% male. Median maximum tumour diameter at diagnosis was 13.6 cm and 33% of patients had metastatic disease. Nephrectomy was performed in 71% of patients of whom 21% had a tumour rupture. Two-year event free survival (EFS) was 41.3% ± 3.9% after a median follow up of 17 months (range 1 – 33 months), with treatment abandonment considered an event. Treatment abandonment occurred in 26% and death during treatment in 14%. Disease relapse occurred in 10%. Two-year EFS of the 26 patients who received radiotherapy was 64.5% ± 9.7% with no reported disease relapse.

Conclusion: Patients continue to present late with advanced WT in sub-Saharan Africa and their survival is below the 60% GICC target. Prevention of treatment abandonment and treatment related mortality remain important. Earlier diagnosis and access to radiotherapy are expected to decrease disease related mortality.

Introduction

Wilms tumour (WT), or nephroblastoma, is the most common renal cancer in children and forms 11.1% of all cancers diagnosed under the age of 15yrs in sub-Saharan Africa.[1] It is one of the six common and curable cancer types targeted by the WHO Global Initiative for Childhood Cancer (GICC).[2] WT is a highly curable childhood cancer in well-resourced settings, where overall survival rates exceed 90% using only generic chemotherapy, tumour excision (usually total nephrectomy) and sometimes radiotherapy, according to tumour stage and risk group.[3] The overall aim of the WHO GICC is to increase survival for childhood cancer to at least 60% worldwide and reduce suffering for all by 2030.[2]

Survival rates for children with WT diagnosed in sub-Saharan Africa are substantially lower than in high-income countries. The few published prospective studies on WT survival in sub-Saharan Africa report a 2-year event free survival using an intention to treat approach between 11% and 50%.[4-10] Common barriers to achieving survival from WT in sub-Saharan Africa include a high proportion of children presenting late with advanced disease, limited resources for accurate and timely diagnosis and treatment, limited supportive care and resources for treatment (including access to radiotherapy) and a high proportion of patients not completing treatment due to the impact on family finances and home responsibilities.[11,12]

The Collaborative African Network for Childhood Cancer Care and Research (CANCaRe Africa) was established in 2014 and aims to develop, implement and evaluate treatment guidelines adapted to local circumstances across a regional network of hospitals in sub-Saharan Africa.[13] The network is led by locally active child cancer specialists who design and implement a number of projects that sites can join. The network currently comprises nine hospitals in seven countries.[13] The mission of the network is "to improve survival for children with common and curable childhood cancer types in Sub-Saharan Africa by reducing treatment abandonment and death during treatment and by using locally appropriate treatment guidelines".[14]

Between 2014 – 2017, CANCaRe Africa conducted a four-year prospective clinical study implementing a consensus SIOP (International Society for Pediatric Oncology)-adapted treatment guideline for WT (The Collaborative Wilms Tumour Africa Project or Wilms Africa Phase I).[8,15-17] Two-year event-free survival was 49.9% (SE 3.8%, median follow up 27 months) when treatment abandonment was considered an adverse event.[8]

The Wilms Africa phase II study was designed to build on this encouraging experience. The treatment protocol was comprehensively written up and published online, including recommendations for the use of radiotherapy.[18]

The objective of this study was to describe the outcomes of Wilms Africa Phase II in sub-Saharan Africa.

Methods

Sites

Wilms Africa phase II is a multi-centre prospective clinical observational study undertaken in eight hospitals in six countries (Ghana and Ethiopia two sites, Malawi, Zimbabwe, Cameroon and Uganda one site per country. Ethical approval was obtained from each institutional review board. After explanation the parent or guardian gave written consent for data collection.

Eligibility criteria and enrolment

Eligibility criteria for patient registration include: first diagnosis of a unilateral WT (based on clinical examination and ultrasound) and age less than 16 years. Exclusion criteria were: bilateral WTs, infants below 6 months of age and previous WT treatment. Patients with a histological diagnosis other than WT were excluded. Enrolment took place from 1st January 2021 to 31st December 2022. Not all sites started simultaneously. Ghana, Malawi, Zimbabwe, Cameroon and Zimbabwe started on January 1st, 2021. Other sites opened later; Ethiopia (Jimma and Gondar) on June 1st 2021 and Mbarara, Uganda on April 1st 2022. All sites enrolled until December 31st, 2022.

Data management

Patient data were collected on a study-specific case report form (CRF) by local data managers (DM) for whom funding was provided. The completed CRFs, including pseudo-anonymised patient identifiers, were entered in a study site-specific drop box to which only four people had access – the local DM and PI and the central DM and chief investigator (CI). A site-specific follow-up Excel file was distributed to each centre for updating every 6 months. Data quality and completeness were reviewed every 6 months by the central team. Funding was distributed to all participating centres for dedicated time for local data managers, site leaders and active follow up of patients. Data entry by the local data manager was supervised by the site leader, a paediatric oncologist.

Data collected

Clinical data collected through the CRF on each newly diagnosed WT case comprised: patient demographics, medical history, physical examination findings, type of imaging, imaging results and laboratory test results, tumour stage, preoperative management, surgical management, pathology report and postoperative treatment. Symptom duration and history of weight loss were documented. Tumour size was determined by imaging (ultrasound or computerized tomography scan).

Diagnostic work-up and treatment guideline

All participating centres were able to treat unilateral WT with curative intent. Radiotherapy was available only at the two Ghanaian centres, in Jimma and in Harare. Diagnosis and treatment followed the adapted treatment Wilms Africa Phase II guideline published online and summarised below.[18]

All patients had a plain chest radiography and abdominal ultrasound to document tumour size and presence/absence of metastases. Pre-operative chemotherapy was risk-stratified by the presence of localised or metastatic disease. Children with localised tumours received a two-drug regimen (vincristine and actinomycin-D) for 4 weeks (AV4), with the option of prolongation and addition of doxorubicin for very large tumours. If surgery was delayed, weekly vincristine could be continued. Children with metastases at diagnosis received a 6-week, 3-drug regimen (including doxorubicin) (AVD6). After 6 weeks metastatic disease was re-evaluated with the option of prolonging treatment for 3 more weeks. Patients weighing less than twelve kilograms or with severe

acute malnutrition had a one-third dose reduction of all chemotherapeutic agents. All sites used these preoperative chemotherapy regimens. Post-operative chemotherapy was stratified by pathological stage and histological risk of the tumour according to the SIOP classification, if available, or by SIOP surgical stage where timely pathology services were not available. Choice of postoperative chemotherapy regimen depended on the availability of radiotherapy, supportive care to allow for an intensive 'high risk' regimen and perceived risk of treatment abandonment with longer regimens. The Wilms Africa Phase II guideline described shorter (14 weeks) and longer (26 weeks) regimens that included vincristine, actinomycin and doxorubicin. The guideline also included general recommendations on the use of radiotherapy. Sites in Malawi, Ethiopia and Cameroon elected to use the shorter postoperative regimens. In Ghana and Zimbabwe, postoperative chemotherapy was usually longer and for selected patients included radiotherapy when indicated and available. Indications for radiotherapy included flank or abdominal radiotherapy for patients with a stage III abdominal tumour and whole lung radiotherapy for those with persistent metastases. In Ghana, patients with high-risk disease (stage III or SIOP pathology high risk group) received 'high risk' postoperative chemotherapy, including ifosfamide, carboplatin and etoposide (ICE).

Analyses and statistics

Survival time was calculated in days from diagnosis to date of last contact, either by clinic visit or active follow up (phone or in person). Survival was calculated both with treatment abandonment considered an event and patients with treatment abandonment censored.

Statistical analysis was performed using SPSS 22.0. Survival was calculated using a Kaplan Meier curve. A Pearson Chi-Square test and Mann-Whitney test was used as appropriate. A P value < 0.05 was considered statistically significant.

Results

Enrolment of patients

From January 1st 2021 - December 31st 2022, 230 patients were enrolled. Nine patients with a misdiagnosis were excluded. Enrolments from the different sites were as follows: 52 from Blantyre, 31 from Accra, 25 from Mbingo, 31 from Kumasi, 22 from Gondar, 20 from Jimma, 5 from Mbarara and 44 from Harare. Data collection was >98% complete.

Seventy-one percent of patients had a nephrectomy. Fifty-four percent of patients completed the planned first treatment (EOT) without evidence of disease. See **Figure 1** for further details and the flow diagram of patient identification, enrolment and completion of treatment.

Patient and tumour characteristics at diagnosis

Median maximum tumour diameter on imaging at diagnosis was 13.6 cm and 33.0% of patients had metastatic disease. Maximum tumour diameter on imaging at diagnosis was documented for 222/230 (97% of patients); in 109 patients, CT scan was used to determine the size and in 113 patients ultrasound. See **Table I** for further details of patient and tumour characteristics of the enrolled participants.

Preoperative chemotherapy allocation of regimens

Localised disease was found in 154 patients. One of these patient died before the start of treatment. Of the remaining 153 who started chemotherapy; 120 were started on the 2 drug, 4-week regimen with actinomycin and vincristine (AV4) according to protocol and 33 were started on the 3 drug, 6-week regimen with actinomycin, vincristine and doxorubicin (AVD6)

Seventy-six patients had metastatic disease, one of whom died before commencing treatment. Of the remaining 75; 68 were started on the AVD6 regimen according to protocol, and seven were started on the AV4 regimen.

In total 127 (120 localised disease, seven metastatic disease) patients started regimen AV4. Twenty-six of whom (20%) abandoned treatment. Toxicity of preoperative chemotherapy treatment was evaluated for the remaining 101.
Of the 101 (33 localised disease, 68 metastatic disease) patients who started regimen AVD6; Eleven (11%) abandoned treatment. Toxicity of preoperative chemotherapy treatment was evaluated of the remaining 90 patients.

Toxicity of preoperative chemotherapy regimens.

Death during preoperative chemotherapy was lower in the AV4 than in the AVD6 regimen; 5.0% (5/101) in AV4 versus 14.4% (13/90) in AVD6 (P = 0.02). Overall death during preoperative chemotherapy was 9.4% (18/191), excluding the patients who abandoned treatment.

The proportion of patients with neutropenia (neutrophils < 0.5 x 10^9/ml) was very similar during regimen AV4 and regimen AVD6; respectively 4.9% and 5.6%. Prolonged and profound neutropenia was not found during either regimen. For further details of haematological toxicity during preoperative chemotherapy, see **Table II.**

Efficacy of preoperative chemotherapy regimens.

AV4 preoperative chemotherapy was completed by 96 (101-5 who died) patients and AVD6 was completed by 77 (90-13 who died) patients. Median maximum tumour size at diagnosis was larger in patients who completed AVD6 than in the patients who completed AV4 (15.0 cm versus 12.0 cm, P < 0.001).

The proportion of patients with a tumour rupture was 22.9% in patients who completed AV4, versus 15.6% in patients who completed AVD6 (P = 0.2) and 19.7% (34/173) overall in patients who completed preoperative chemotherapy.
For further details of the efficacy of preoperative chemotherapy in patients receiving AV4 or AVD6 and proportion of patients with surgical stage III disease, see **Table III**

Postoperative chemotherapy
Of the 160 patients who started postoperative chemotherapy, 6.9% received AV 4 weeks, 12.5% AV 14 weeks, 18.8% AVD 14 weeks, 27.5% AV 26 weeks, 25.6% AVD 27 weeks and in 8.8% the regimen was not specified.

Postoperative radiotherapy
A total of 26 patients received radiotherapy; Nine in Accra, 14 in Kumasi, 1 in Jimma and three in Harare. It was not documented whether this was flank or whole abdomen radiotherapy.
Of the 128 patients treated in these four centres, 49 had an indication for radiotherapy according to protocol. Thirteen had persistent chest metastatic disease (one received radiotherapy); five had persistent liver metastases (one received radiotherapy), 31 had a SIOP pathology stage III or a high-risk tumour (16 received radiotherapy). The remaining eight patients had radiotherapy for other and unknown reasons.

Relapse of disease and disease related mortality.
Ten percent of patients (23/230) had a relapse of disease after a median follow up of 17 months. Eight of these were either in the renal bed or abdomen without further specification and for 15 the site was not specified.
In total 14.8% percent (34/230) of patients had a disease related event; two died before treatment, nine had persistent disease at the end of planned first line treatment and 23 relapsed.

Outcome - Event-free survival
Two-year event free survival (EFS) with treatment abandonment considered an event was 41.3% (± 3.9%) and 62.4% (± 4.6%) with treatment abandonment censored (P <0.02). See **Figure 2** for the Kaplan Meier curves.

Outcome of patients with localised and metastatic disease
Two-year EFS was significantly higher for the 154 patients with localised disease than for the 76 with metastatic disease; 47.4% (SE 4.8) versus 23.3% (SE 7.2) (P=0.02) with treatment abandonment considered an event and 70.1% (SE 5.2) versus 42.9% (SE 10.6) (P=0.004) with treatment abandonment censored.
Significantly more patients with localised disease than patients with metastatic disease completed planned first line treatment (EOT) without evidence of disease; 60.4% (93/154) v 42.1% (32/76) (P=0.009). Patients with metastatic disease had significantly more disease related events than patients with localised disease before EOT; 13.2% (10/76) v 2.6% (4/154) (P=0.002). (Table 4). Relapses after the completion of planned first line treatment without evidence of disease occurred in 7.5% (7/93) of patients with localised disease and in 15.6% (5/32) of patients with metastatic disease (P = 0.18).

Outcome of patients treated with radiotherapy
Two-year EFS was of 26 patients who received radiotherapy was 64.5% (SE 9.7) with treatment abandonment considered an event and 78.0 % (SE 8.5) with treatment abandonment censored (P=0.2). No child who received radiotherapy relapsed.

Discussion

This study reports the findings of the second phase of a multi-centre, prospective clinical trial looking at the outcome of patients with WT, using a comprehensive treatment guideline adapted to local circumstances.

As in other studies from sub-Saharan Africa; patients present late and with advanced disease; in our study with a median tumour diameter at diagnosis of 13.6 cm and 33.6% metastatic disease; compared to 14.0 cm and 31% metastatic disease in Wilms Africa Phase I and 14.2 cm and 25.7% in a study in Rwanda.[8,19] These tumours are much larger than for example in the SIOP 9 study in Europe where mean size at diagnosis was 470 ml which would correspond to a tumour size of 9-10 cm and 10% of patients had metastatic disease.[20]

It is key to find the right balance for a certain setting between toxicity and efficacy of chemotherapy. With the preoperative chemotherapy used, the degree of neutropenia was relatively mild with only 4.9% (regimen AV4) and 5.6% (regimen AVD6) experiencing neutropenia, without any prolonged or profound neutropenia. Still, death during preoperative chemothery was 9.4% overall and higher in the AVD6 than in the AV4 regimen (14.4% versus 5.0 % respectively, P=0.02). Unfortunately we don't have the data to know the exact cause of death in these patients, but it can be assumed to be largely treatment related as a previous study on death during the first three months of treatment among patients with common and curable cancers treated with curative intent in sub-Saharan Africa showed that 89% of the deaths were treatment related.[21] In Rwanda, where the same preoperative chemotherapy was used, 16.4% (20/122) of patients died during preoperative chemotherapy.[19] During the pilot in Malawi (2006-2008) when the doxorubicin dosage was not reduced from 50 mg/m^2 to 30 mg/m^2, death during preoperative chemotherapy was 11% (8/72), with 17% (4/24) in the group receiving AVD6 and 8% (4/48) in the group receiving AV4.[22] In the same study, of all patients who completed preoperative chemotherapy, 27% had neutropenia and neutropenia was significantly more common in children who completed AVD6 (50%, 10/20) than those who completed AV4 (50%, 10/20 vs 15%, 6/40), P=0.004).[22] Neutropenia and especially death during preoperative chemotherapy are rare in HICs, even using the standardised dose (50 mg/m^2) of doxorubicin. In the experience of SIOP preoperative chemotherapy haematological toxicity is very mild in European children, though published data on this are, to our knowledge, not available. Graf et al. reported that acute toxicity of SIOP preoperative chemotherapy in European children is restricted to temporary, moderately disturbed liver function in less than 8% of patients and low platelet counts in 4% of patients.[23] We did not document death during preoperative chemotherapy separately in the Wilms Africa Phase I study, but death during treatment overall was 13% (27/201), compared to 14% (32/230) in this Phase II study.[8]

The efficacy of preoperative chemotherapy in our study is difficult to assess and especially to compare with other studies. Tumours are large at diagnosis, some patients' treatment deviated from the protocol, we used different methods to measure tumours before (imaging) and after (ruler) preoperative chemotherapy and usually tumour volumes are reported for which three dimensions are needed. An important outcome measure of efficacy is tumour rupture which was 19.7% overall in our study and not significantly different after receiving AV4 (22.9%) or AVD6 (15.6%) (P=0.2).

Disease related mortality is still a huge challenge. Relapse of disease occurred in ten percent and adding the patients who died before treatment or were inoperable after preoperative chemotherapy; disease related mortality was 14.8%. Earlier presentation of patients would be expected to reduce this number. Encouragingly, the duration of symptoms greater than 2 months before admission in Phase II was less than Phase I; 51% (103/221) v 37% (84/230) (P=0.03). This may reflect the fact that there are several programmes and initiatives in the region to raise awareness of childhood cancer and encourage early diagnosis.

Radiotherapy was rarely available and as far as we could conclude from the data often not given according to the indications in the protocol. The efficacy is difficult to assess as we do not have a good group to rigorously compare outcome with. Two-year EFS of the 26 patients who received radiotherapy was 64.5% ± 9.7% with no reported disease relapse.

Two-year EFS was 41.3% with treatment abandonment as an event and 62.4% with treatment abandonment censored (P<0.02), compared to 49.9% in Phase, treatment abandonment considered an event (P=0.2). Treatment abandonment occurred in 26% and death during treatment in 14%.[24,25] This event-free survival is similar to intention-to-treat event free survivals documented in other prospective studies in sub-Saharan Africa. Two-year EFS was 46% (and five-year EFS 42%) for patients with a unilateral Wilms tumour in Malawi in 2006-2011.[6] Causes of treatment failure in that study were treatment abandonment (7%), death during treatment (15%) and disease-related (persistent disease and relapse, 30%).[6] Two-year EFS was 72.7% for a selected group of patients in a study of the French African Pediatric Oncology Group (GFAOP).[26] Patients who had a nephrectomy were included and those with metastatic disease, persistent disease after surgery, unfavourable histology or treatment abandonment excluded, leading to exclusion of 46% (144/313) of the original cohort of patients.[24] Intention to treat analysis of all patients would report a survival of 46%. Retrospective studies done in Eldoret, Kenya and Lilongwe, Malawi reported a 2-year EFS of 43.5% and 34% respectively.[9,10] We did not analyse overall survival (OS) in our study, since survival after relapse of disease in our setting is extremely rare and follow up after treatment abandonment very difficult. Encouragingly, two-year EFS after nephrectomy (164 patients) in our study was 60.4% ± 4.7%.[27] Overall survival in high income countries (HICs) is currently over 90%.[3] Three-year overall survival was estimated to be 57.5% in Rwanda, with a low proportion of patients (5.9%) abandoning treatment, possibly, as the authors say, explained by social support services, free chemotherapy and transport reimbursement.[19]

A strength of the study is the completeness of data. Facilitators included funding dedicated time for local data managers; persistent, regular and positive encouragement from the central data management team and a more simplified case report form as compared to Phase I.

Limitations of the study are the challenges to compare with other studies.

In conclusion, local evidence is key to improving care and survival and to be able to prioritise interventions with the highest impact on survival. Family support and other interventions to prevent remains treatment abandonment remain key. There is also still much to be done to enable early diagnosis, reduce toxicity and provide radiotherapy services.

FIGURE 1 Flow diagram patient identification, allocation to treatment and receipt of treatment.

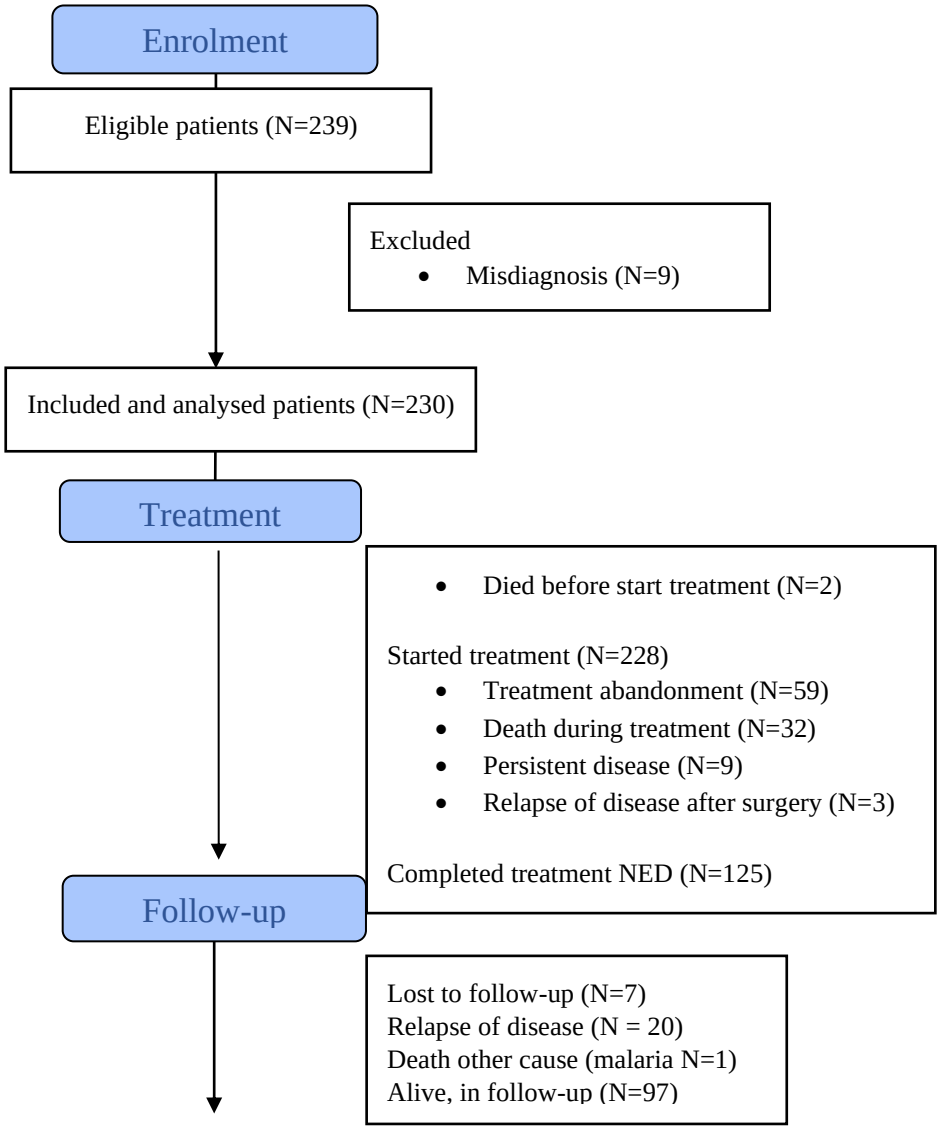

TABLE 1. Patient- and tumour characteristics at diagnosis (N =230)

	2021 – 2022 (Phase II) **N=230**
Patient Characteristics	
Median age in years (range)	3 (0.5 – 14)
Female sex, n (%)	109 (47%)
Duration of symptoms > 2 months, n (%)	84 (37%)
History of weight loss, n (%)	179 (78%)
Tumour Characteristics	
Tumour Side	
Tumour left side	123 (53%)
Tumour right side	107 (47%)
Localized or metastatic disease	
Localized	154 (67%)
Metastatic	76 (33%)
Site Metastases	N=76
Lung only	42
Liver only	15
Lung and liver*	15
Other	4*
Median tumour diameter in cm by imaging (range)	
By imaging	13.6 (2 – 42) (N=222)

*Brain metastasis, peritoneum, not specified

Table 2. Haematological toxicity of patients during regimen AV4 and regimen AVD6

Characteristic	**AV4** N = 101	**AVD6** N=90	**P-value**
Neutropenia	5 (4.9%)	5 (5.6%)	N.S.
Profound neutropenia	0	0	N.S.
Prolonged neutropenia	0	0	N.S.
White Blood Cells < 1.0	1 (1.0%)	0 (0%)	N.S.
Haemoglobin < 7 g/dL	20 (19.8%)	25 (27.8%)	N.S.
Platelets < 150	10 (9.9%)	15 (16.7%)	N.S.

Table 3. Efficacy of preoperative chemotherapy in patients who received regimen 1A (four weeks, AV) or regimen 1B (six weeks, AVD) in terms of tumour response, proportion of patients with a tumour rupture and surgical local stage of disease.

Characteristic	**1A** **4 weeks AV** N = 96	**1B** **6 weeks AVD** N=77	**P-value**
Median tumour size at diagnosis (range)[1]	12.0 cm (1-33.6)	15.0 cm (2-42)	P<0.001
Median tumour size at surgery (range)[2]	10.1 cm (0.9-25)	12.2 cm (2-38)	P=0.1 (N.S.)
Number (%) of patients with tumour rupture	22 (22.9%)	12 (15.6%)	P=0.2 (N.S.)
Surgical local stage III	12 (12.5%)	13 (16.9%)	P=0.4 (N.S.)

[1] – Median maximum tumour diameter on imaging
[2] – Median maximum tumour diameter measured at surgery

TABLE 4. Patients' outcome at the end of planned first line treatment. Comparison between patients with localised or metastatic disease at diagnosis.

End of treatment outcome	**Localised** **N=154**	**Metastatic** **N=76**	**P-value**
Alive, no evidence of disease	93 (60.4%)	32 (42.1%)	P = 0.009
Abandonment of treatment	39 (25.3%)	20 (26.3%)	N.S. (P=0.9)
Death during treatment	18 (11.7%)	14 (18.4%)	N.S. (P=0.2)
Disease related event*	4 (2.6%)	10 (13.2%)	P=0.002
Total	154 (100%)	76 (100%)	

* Death before start of therapy, persistent disease at the end of planned first line treatment, relapse or progressive disease

FIGURE 2 Event free survival of patients with abandonment of treatment considered an event (in red) and abandonment of treatment censored (in blue).

This figure needs to be revised according to the update follow up

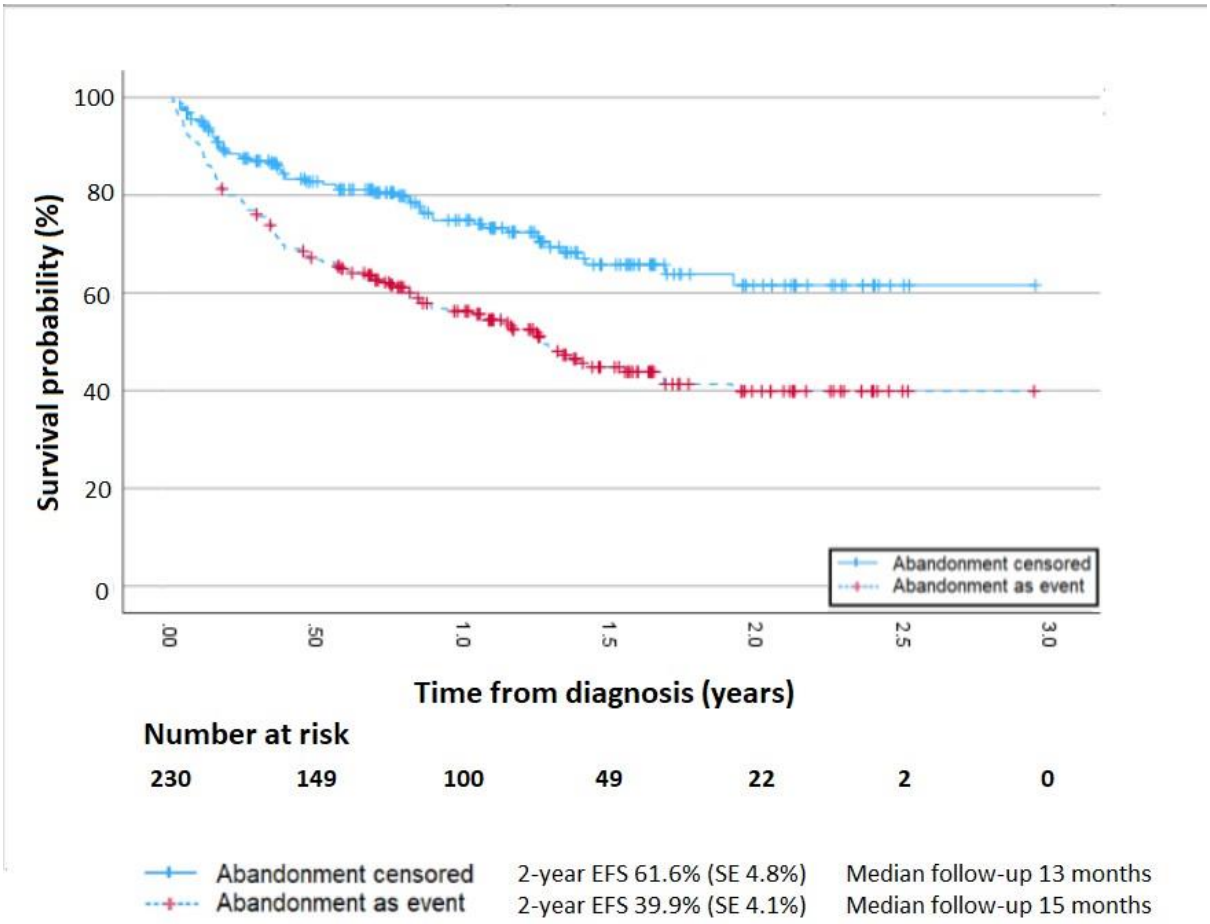

FIGURE 3. Event free survival of patients with treatment abandonment before nephrectomy considered an event and treatment post-nephrectomy considered either an event (in blue) or censored (in red). (*This figure still needs to be produced).*

References

1. Nakata K, Colombet M, Stiller CA, Pritchard-Jones K, Steliarova-Foucher E, Contributors I-. Incidence of childhood renal tumours: An international population-based study. Int J Cancer. 2020;147(12):3313-27.
2. World Health Organization . CureAll framework: WHO Global Initiative for Childhood Cancer. Increasing access, advancing quality, saving lives. [press release]. Geneva: WHO2021.
3. Dome JS, Graf N, Geller JI, Fernandez CV, Mullen EA, Spreafico F, et al. Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration. J Clin Oncol. 2015;33(27):2999-3007.
4. Abuidris DO, Elimam ME, Nugud FM, Elgaili EM, Ahmed ME, Arora RS. Wilms tumour in Sudan. Pediatr Blood Cancer. 2008;50(6):1135-7.
5. Moreira C, Nachef MN, Ziamati S, Ladjaj Y, Barsaoui S, Mallon B, et al. Treatment of nephroblastoma in Africa: results of the first French African pediatric oncology group (GFAOP) study. Pediatr Blood Cancer. 2012;58(1):37-42.
6. Israels T, Pidini D, Borgstein E, Bailey S, Tump C, Chagaluka G, et al. Survival of children with a Wilms tumor in Blantyre, Malawi. Pediatr Hematol Oncol. 2018;35(3):196-202.
7. van Heerden J, Balagadde-Kambugu J, Angom R, Lusobya RC, Chantada G, Desjardins L, et al. Evaluating the baseline survival outcomes of the "six Global Initiative for Childhood Cancer index cancers" in Africa. Pediatr Hematol Oncol. 2022:1-21.
8. Chagaluka G, Paintsil V, Renner L, Weijers J, Chitsike I, Borgstein E, et al. Improvement of overall survival in the Collaborative Wilms Tumour Africa Project. Pediatr Blood Cancer. 2020;67(9):e28383.
9. Holmes DM, Matatiyo A, Mpasa A, Huibers MHW, Manda G, Tomoka T, et al. Outcomes of Wilms tumor therapy in Lilongwe, Malawi, 2016-2021: Successes and ongoing research priorities. Pediatr Blood Cancer. 2023;70(5):e30242.
10. Uittenboogaard A, Njuguna F, Mostert S, Langat S, van de Velde ME, Olbara G, et al. Outcomes of Wilms tumor treatment in western Kenya. Pediatr Blood Cancer. 2022;69(4):e29503.
11. Ekenze SO, Nwangwu EI, Ezomike UO, Orji EI, Okafor OO. Continuing barriers to care of Wilms tumor in a low-income country. Pediatr Blood Cancer. 2019;66(1):e27416.
12. Ekenze SO, Okafor OC, Obasi AA, Okafor DC, Nnabugwu, II. Wilms tumor in Africa: A systematic review of management challenges and outcome in two decades (2000-2019). Pediatr Blood Cancer. 2020;67(11):e28695.
13. International Society of Pediatric O. Wilms Africa webpage 2023 [Available from: https://siop-online.org/collaborative-wilms-tumour-africa-project/.
14. International Society of Pediatric O. CANCaRe Africa - The Collaborative African Network for Childhood Cancer Care and Research 2023 [Available from: https://siop-online.org/cancareafrica/.
15. Paintsil V, David H, Kambugu J, Renner L, Kouya F, Eden T, et al. The Collaborative Wilms Tumour Africa Project; baseline evaluation of Wilms tumour treatment and outcome in eight institutes in sub-Saharan Africa. Eur J Cancer. 2015;51(1):84-91.
16. Israels T, Paintsil V, Nyirenda D, Kouya F, Mbah Afungchwi G, Hesseling P, et al. Improved outcome at end of treatment in the collaborative Wilms tumour Africa project. Pediatr Blood Cancer. 2018;65(5):e26945.
17. Israels T, Moreira C, Scanlan T, Molyneux L, Kampondeni S, Hesseling P, et al. SIOP PODC: clinical guidelines for the management of children with Wilms tumour in a low income setting. Pediatr Blood Cancer. 2013;60(1):5-11.
18. Wilms Africa Phase II treatment guideline 2023 [Available from: https://siop-online.org/wp-content/uploads/2020/04/Treatment-Guidelines-Collaborative-Wilms-Tumour-Africa-Project-Phase-II-doc-v1.8-FINAL.pdf.

19. Shyirambere C, Villaverde C, Nguyen C et al. Nephroblastoma Treatment and Outcomes in a Low-Income Setting. J Glob Oncol 2022: Jul:8:e2200036
20. Tournade MF, Com-Nougue C, de Kraker J, et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: results of the Ninth International Society of Pediatric Oncology Wilms' Tumor Trial and Study. J Clin Oncol 2001;19:488–500.
21. Israels T, Afungchwi GM, Chagaluka G, Hesseling P, Kouya F, Paintsil V, et al. Early death and treatment-related mortality: A report from SUCCOUR - Supportive Care for Children with Cancer in Africa. Pediatr Blood Cancer. 2021;68(9):e29230.
22. Israels T, Chagaluka G, Pidini D et al. The efficacy and toxicity of SIOP preoperative chemotherapy in Malawian children with a Wilms tumour. Pediatr Blood and Cancer 2012 Oct;59(4):636-41.
23. Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000;27:443–454.
24. Israels T, Arora RS, Sung L. The value of reporting on end-of-treatment outcome of patients in low-income settings. Pediatr Blood Cancer. 2023;70(12):e30686.
25. Barnabas Atwiine, Cecilia Mdoka, Mushabe Branchard et al. Prevention of treatment abandonment remains an important challenge to increase survival of Wilms tumour in sub-Saharan Africa. A report from Wilms Africa - CANCaRe Africa. Submitted to Pediatr Blood Cancer.
26. Atteby J, Moreira C, Traoré F et al. Treatment of Wilms Tumor in Sub-Saharan Africa: Results of the Second French African Pediatric Oncology Group Study. J Glob Oncol 2019; 1-8
27. William Appeadu-Mensah, Cecilia Mdoka, Seifu Alemu et al. Surgical aspects and outcomes after nephrectomy for Wilms tumour in sub-Saharan Africa. A report from Wilms Africa Phase II - CANCaRe Africa. Submitted to Pediatr Blood Cancer.