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Outcomes of Wilms tumor treatment in western Kenya

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Abstract

Background/objectives: Wilms tumor (WT) is a curable type of cancer with 5-year survival rates of over 90% in high-income countries, whereas this is less than 50% in low- and middle-income countries. We assessed treatment outcomes of children with WT treated at a large Kenyan teaching and referral hospital.

Design/methods: We conducted a retrospective record review of children diagnosed with WT between 2013 and 2016. Treatment protocol consisted of 6 weeks of preoperative chemotherapy and surgery, and 4–18 weeks of postoperative chemotherapy depending on disease stage. Probability of event-free survival (pEFS) and overall survival (pOS) was assessed using Kaplan–Meier method with Cox regression analysis. Competing events were analyzed with cumulative incidences and Fine–Gray regression analysis.

Results: Of the 92 diagnosed patients, 69% presented with high-stage disease. Two-year observed EFS and OS were, respectively, 43.5% and 67%. Twenty-seven percent of children died, 19% abandoned treatment, and 11% suffered from progressive or relapsed disease. Patients who were diagnosed in 2015–2016 compared to 2013–2014 showed higher pEFS. They less often had progressive or relapsed disease ($p = .015$) and borderline significant less often abandonment of treatment ($p = .09$). Twenty-nine children received radiotherapy, and 2-year pEFS in this group was 86%.

Conclusion: Outcome of children with WT improved over the years despite advanced stage at presentation. Survival probabilities of patients receiving comprehensive therapy including radiation are approaching those of patients in high-income countries. Additional improvement could be achieved by ensuring that patients receive all required treatment and working on earlier diagnosis strategies.

KEYWORDS
chemotherapy, outcomes research, pediatric oncology, sub-Saharan Africa, surgery, Wilms tumor

Abbreviations: CI, confidence interval; CT, computed tomography; EFS, event-free survival; HR, hazard ratio; IQR, interquartile range; MTRH, Moi Teaching and Referral Hospital; NHIF, National Health Insurance Fund; OS, overall survival; pEFS, probability of event-free survival; pOS, probability of overall survival; SIOP, International Society of Pediatric Oncology; WHO, World Health Organization; WT, Wilms tumor.

1 | INTRODUCTION

Nephroblastoma or Wilms tumor (WT) is a childhood tumor of the kidney.[1] It is thought to arise from nephrogenic rests, which are remnants of embryonal development that become malignant.[1] The incidence of WT is characterized by racial and geographical disparities.[2] According to World Health Organization (WHO) global cancer registries, age-adjusted rate of WT in low-income countries is 9.8 cases per million compared to 8.6 cases per million in high-income countries.[2] It is the second most common type of childhood tumor in sub-Saharan African countries, whereas it ranks fifth in North America.[3] Moreover, survival rates of 25%–53% in low-income countries have been reported as opposed to 70%–97% in high-income countries.[2] In 2018, the WHO set a global survival target of 60% for children with cancer by 2030.[4,5] This can be achieved by improving access to high-quality care and focusing on curable types of cancer such as WT.[5,6] Improving treatment outcomes of children with WT in resource-limited settings can thus contribute to a significant increase in global childhood cancer survival.

Successful treatment for WT requires a multidisciplinary approach with involvement of pediatric surgeons, pediatric oncologists, radiologists, radiation oncologists, pathologists, and nurses.[1] A treatment guideline for resource-limited countries was developed by the Pediatric Oncology in Developing Countries Committee of the International Society of Pediatric Oncology (SIOP).[7] The SIOP treatment approach establishes the minimal requirements for treatment of WT with curative intent in resource-limited settings and focuses on diagnostic ultrasonography, preoperative chemotherapy with reduced intensity for malnourished children, surgery, and postoperative chemotherapy based on surgical staging.[7] This treatment approach has been implemented in six sub-Saharan African countries by the Collaborative Wilms Tumor Africa Project.[8] In a recent multicenter prospective trial from this consortium, survival without evidence of disease at end of treatment increased from 52% to 69% in 4 years.[9] While this shows the potential for cure when children with WT are treated in a locally appropriate standardized manner, it does leave scope for improvement. Further insight in improvement of survival can be achieved by analyzing data from other treatment centers in sub-Saharan African countries. Furthermore, long-term follow-up data are necessary to draw solid conclusions about the efficacy of the SIOP approach.

In this retrospective record-review study, we report long-term treatment outcomes of nearly 100 children with WT treated according to a protocol closely modeled on the SIOP approach at a large teaching and referral hospital situated in western Kenya. Furthermore, to gain insight into how improvements could be realized, we assessed which factors affect treatment outcomes in this population.

2 | METHODS

2.1 | Setting

Kenya is a lower middle-income country located in eastern Africa with over 54 million inhabitants, of which nearly 40% are younger than 15 years.[10] This study was conducted at Moi Teaching and Referral Hospital (MTRH), a large teaching and referral center located in Eldoret, a town 300 km northwest of capital city Nairobi. It is estimated to serve a catchment population of 18–20 million people. Over 150 children with cancer were treated annually in its pediatric oncology unit during the study period. The unit was overseen by one pediatrician, highly experienced in pediatric oncology, and two pediatric surgeons were available. The center did not offer radiotherapy services and all patients requiring radiotherapy were referred to Nairobi.

Patients pay for health care costs either out-of-pocket or via private or government-owned health insurance. National Health Insurance Fund (NHIF) is a state corporation that offers health insurance for approximately 5 USD per month per family for casual workers or a fee dependent on income for those formally employed.[11] NHIF enrollment enables a family to access inpatient health services in government-owned health facilities.

2.2 | Treatment protocol

Patients with WT were treated according to a protocol closely modeled on the SIOP approach (File S1). Clinical and computed tomography (CT) findings were used to establish the diagnosis, while chest X-ray was used to document lung metastases. Treatment consisted of preoperative chemotherapy, surgery, postoperative chemotherapy and if required, radiotherapy. All patients irrespective of stage received 6 weeks of preoperative chemotherapy consisting of vincristine, actinomycin-D, and doxorubicin. Staging was performed according to the SIOP staging system.[12] The presence or absence of lung metastases and nephrectomy with subsequent histology determined whether patients were considered to have low-, standard-, or high-risk disease. Patients with low-risk disease (stage I with favorable histology) received 4 weeks of postoperative chemotherapy consisting of vincristine and actinomycin-D. Patients with standard-risk disease (stages II and III with favorable histology) received 6 months of treatment with vincristine and actinomycin-D, whereas patients with high-risk disease (stage IV or pathology with anaplasia or extensive residual elements) received additional doxorubicin. Those with stages III and IV disease were referred for radiotherapy in Nairobi. The MTRH protocol advised 10 Gy to tumor bed, but patients received a dosage according to the specific hospital protocol. A detailed description of dosage and

weekly chemotherapy schedules can be found in File S1. The main difference between this treatment protocol and the SIOP protocol was that all patients irrespective of stage received 6 weeks of preoperative chemotherapy and that they all received postoperative chemotherapy. The vincristine dosage was 2.0 mg/m^2 as opposed to conventional 1.5 mg/m^2, because of the low incidence of vincristine-induced peripheral neuropathy in this population.[13–15] All patients treated at MTRH followed the same treatment protocol.

2.3 | Study design

This was a retrospective record-review study. All patients diagnosed with WT between 2013 and 2016 were included in this study. Ethical approval was received from the institutional review board. The following data were extracted using a data collection form: sociodemographic characteristics (sex, age at diagnosis, height at diagnosis, weight at diagnosis, distance to hospital, NHIF at diagnosis, NHIF at end of treatment) and clinical characteristics (year of diagnosis, duration of symptoms before diagnosis, previous treatment, disease stage, surgical delay, time to event, treatment outcome). Treatment outcomes were event-free survival (EFS), overall survival (OS), death, progressive or relapsed disease, and abandonment of treatment. EFS was defined as alive without evidence of disease until first treatment failure event (abandonment of treatment, death, and progressive or relapsed disease). Abandonment of treatment was defined as not starting or not continuing treatment for 4 or more consecutive weeks.[16] OS was defined as alive at last follow-up, regardless of whether a patient abandoned treatment or was diagnosed with progressive or relapsed disease. Duration of follow-up after diagnosis for those at risk was at least 2 years.

2.4 | Statistical analysis

Sociodemographic and clinical characteristics were described using frequency distributions, means with standard deviations (SD), and medians with interquartile ranges (IQR). The observed (unadjusted) percentages of treatment outcomes were described. The following contributing factors were assessed for effect on treatment outcome: year of diagnosis (2013–2014 and 2015–2016), disease stage (stages I–II or III–V), duration of symptoms before diagnosis (<3 or ≥3 months), distance to hospital (<50, 50–100, or >100 km), BMI at diagnosis, surgical delay (no delay: ≤7 weeks, minor delay: 7–9 weeks, or major delay: >9 weeks between start of preoperative chemotherapy and surgery), NHIF at diagnosis (yes/no), and NHIF at end of treatment (yes/no).

Kaplan–Meier method was applied to estimate the probability of EFS (pEFS) or OS (pOS). pEFS was measured from date of diagnosis to treatment failure or last follow-up and pOS was measured from date of diagnosis to death or last follow-up. Subsequent log-rank testing was performed to determine statistical significance of contributing factors. If differences were found, hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Both observable unadjusted pEFS and Kaplan–Meier-estimated pEFS were reported. We decided to do this because the Kaplan–Meier method assumes that all patients who have not yet had an event of treatment failure will do so in the future, implying a higher percentage of treatment failure than actually occurred.[17]

The competing risk method was used to estimate the cumulative incidence of competing events, which were death, progressive or relapsed disease, and abandonment of treatment. With Gray testing, the statistical significance of contributing factors on competing events was assessed and subsequent Fine–Gray regression analysis was done to calculate subdistribution hazards with 95% CI. We decided to apply the competing risk method rather than calculating Cox proportional hazards, because the latter inappropriately treats competing risks as censoring, while patients are no longer eligible for the failure from one competing event (e.g., death) if another competing event (e.g., abandonment of treatment) has occurred. Fisher's exact test was used to test for differences among contributing factors. Associations were considered to be significant if p-value was below .05. All tests were two-sided. Statistical analysis was conducted using R, version 4.0.3 (Rstudio Inc.), using the "cmprsk" package for competing risk analysis and "crr-addson" formula for Fine–Gray regression analysis.[18,19]

3 | RESULTS

3.1 | Sociodemographic and clinical characteristics

Ninety-two patients with WT were diagnosed between 2013 and 2016, of which 54.2% were female. Sociodemographic and clinical characteristics are listed in Table 1.

Most children (58.7%) lived more than 100 km from MTRH (Table 1). Children had experienced median 3 months of symptoms (IQR 1.00; 4.75 months) prior to admission at MTRH. Sixty-nine percent of patients presented with high-stage disease (stages III–V). At diagnosis, 34.8% of children were enrolled with NHIF, which increased to 73.6% at end of treatment (Table 1). Eighty (87.0%) children were referred from other health care facilities and six had received previous cancer treatment. This was mostly surgery; one center followed the upfront surgery-first approach, and in other centers surgeons may have operated on patients with kidney masses and referred them to MTRH after histology was obtained. Some patients were diagnosed in other centers, given initial chemotherapy, and then referred to our hospital mainly because of distance from their residence.

3.2 | Received treatment

Figure 1 shows treatment received by the 92 patients with WT. Two patients died before start of treatment at MTRH and two patients received surgery at MTRH as a first-line treatment. Eighty-six patients received preoperative chemotherapy, of which 23.3% died during this treatment phase. Sixty-one out of 64 eligible patients underwent surgery at MTRH and two patients likely had received surgery at a previous treatment center. Of the patients who received surgery at

TABLE 1 Sociodemographic and clinical characteristics of patients with Wilms tumor diagnosed at Moi Teaching and Referral Hospital between 2013 and 2016 ($n = 92$)

	2013–2016 ($n = 92$)	2013–2014 ($n = 47$)	2015–2016 ($n = 45$)
Age at diagnosis, years (mean ± SD)	4.04 ± 2.06	4.17 ± 1.99	3.89 ± 2.14
BMI at diagnosis (mean ± SD)	15.06 ± 1.88	15.04 ± 1.59	15.08 ± 2.16
Sex, *n* (%)			
Male	42 (46)	22 (47)	20 (44)
Female	50 (54)	25 (53)	25 (56)
Distance to MTRH, *n* (%)			
<50 km	14 (15)	5 (11)	9 (20)
50–100 km	24 (26)	15 (32)	9 (20)
>100 km	54 (59)	27 (57)	27 (60)
Duration of symptoms before first admission to MTRH, *n* (%)			
0–3 months	43 (47)	16 (34)	27 (60)
≥3 months	49 (53)	31 (66)	18 (40)
Stage of disease at diagnosis, *n* (%)			
Stage I	3 (3.3)	2 (4.3)	1 (2.2)
Stage II	21 (23)	10 (21)	11 (24)
Stage III	32 (35)	17 (36)	15 (33)
Stage IV	20 (22)	12 (26)	8 (18)
Stage V	2 (2.2)	1 (2.1)	1 (2.2)
Unknown	14 (15)	5 (11)	9 (20)
Health insurance status at diagnosis, *n* (%)			
NHIF	32 (35)	13 (28)	19 (42)
No NHIF	60 (65)	34 (72)	26 (58)
Health insurance status at end of treatment, *n* (%)			
NHIF	67 (73)	33 (70)	34 (76)
No NHIF	24 (26)	13 (28)	11 (24)
Unknown	1 (1.1)	1 (2.1)	0 (0)
Surgical delay: weeks between start of preoperative chemotherapy and surgery, *n* (%)			
≤7	22 (37)	9 (31)	13 (43)
8–9	20 (34)	7 (24)	13 (43)
>9	17 (29)	13 (45)	4 (13)
Proportion of eligible patients who received radiotherapy (%)	44	17	55

Abbreviations: NHIF, National Hospital Insurance Fund; SD, standard deviation.

MTRH, 72.2% received surgery within 9 weeks of starting preoperative chemotherapy (Table 1). In total, 66 patients started postoperative chemotherapy. Postoperative chemotherapy was not completed by 26 patients: 11.5% died, 65.4% abandoned care, and 23.1% suffered from progressive or relapsed disease.

3.3 | Treatment outcomes

Observed EFS was 43.5%. Twenty-seven percent of children died, 18.5% abandoned treatment, and 10.9% suffered from progressive or relapsed disease. Two-year pEFS was 39.9% (95% CI: 30.3%–52.6%) (Figure 2). Observed OS based on status at last follow-up was 67.4%. Two-year pOS was 67.7% (95% CI: 58.7%–78.2%). Five out of 10 children with progressive or relapsed disease died, resulting in a total of 30 registered deaths. All but one death occurred within the first 3 months; one child relapsed after 27 months and died shortly thereafter. Six and three deaths were related to the malignancy and to treatment, respectively; one death was due to surgical complications and two occurred during postoperative chemotherapy. The 21 other deaths did not have a known cause, although 95.2% occurred during postoperative

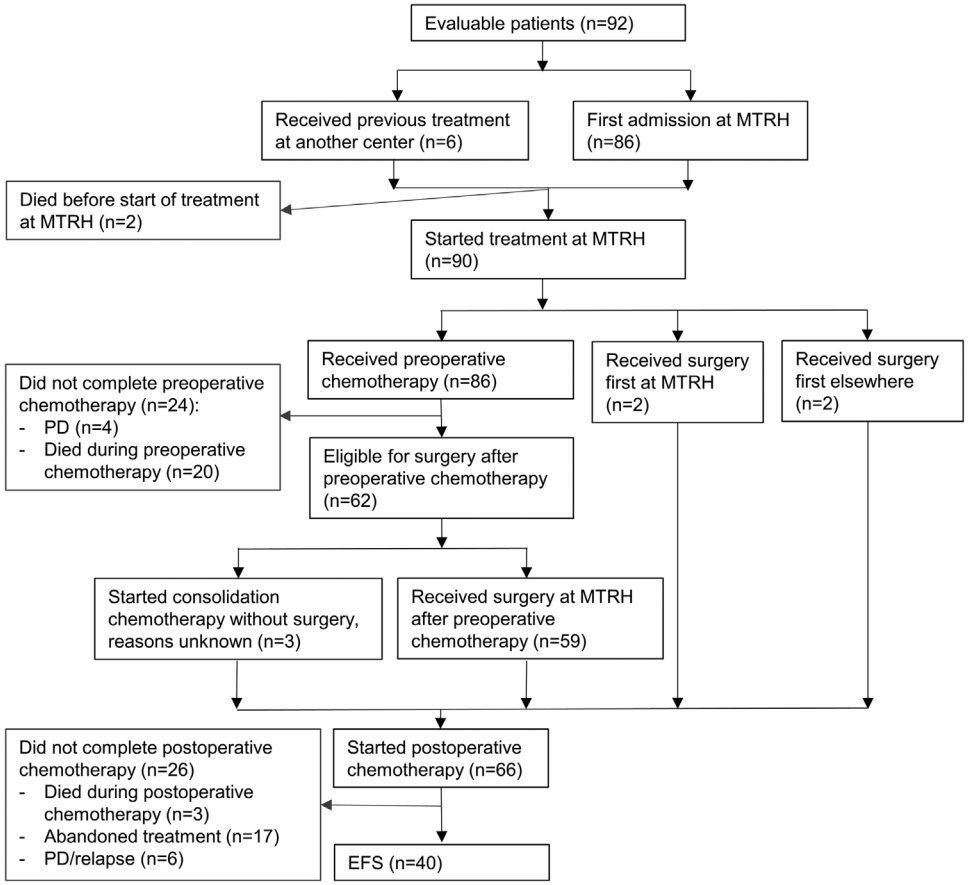

FIGURE 1 Treatment received by patients with Wilms tumor between 2013 and 2016

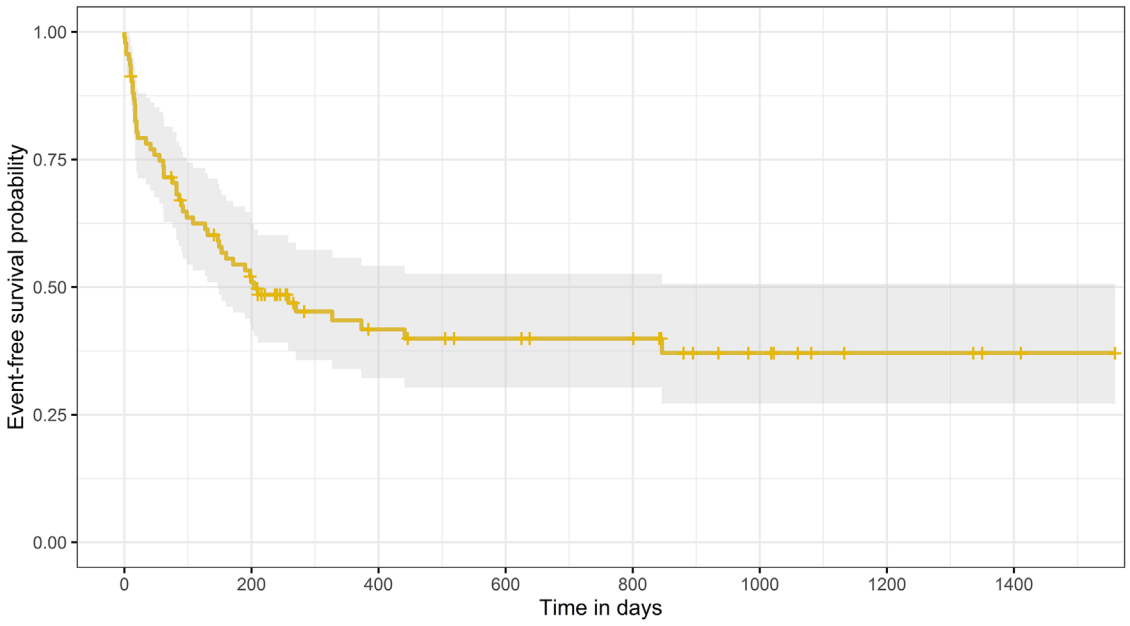

FIGURE 2 Event-free survival probability with 95% confidence intervals of patients with Wilms tumor diagnosed between 2013 and 2016

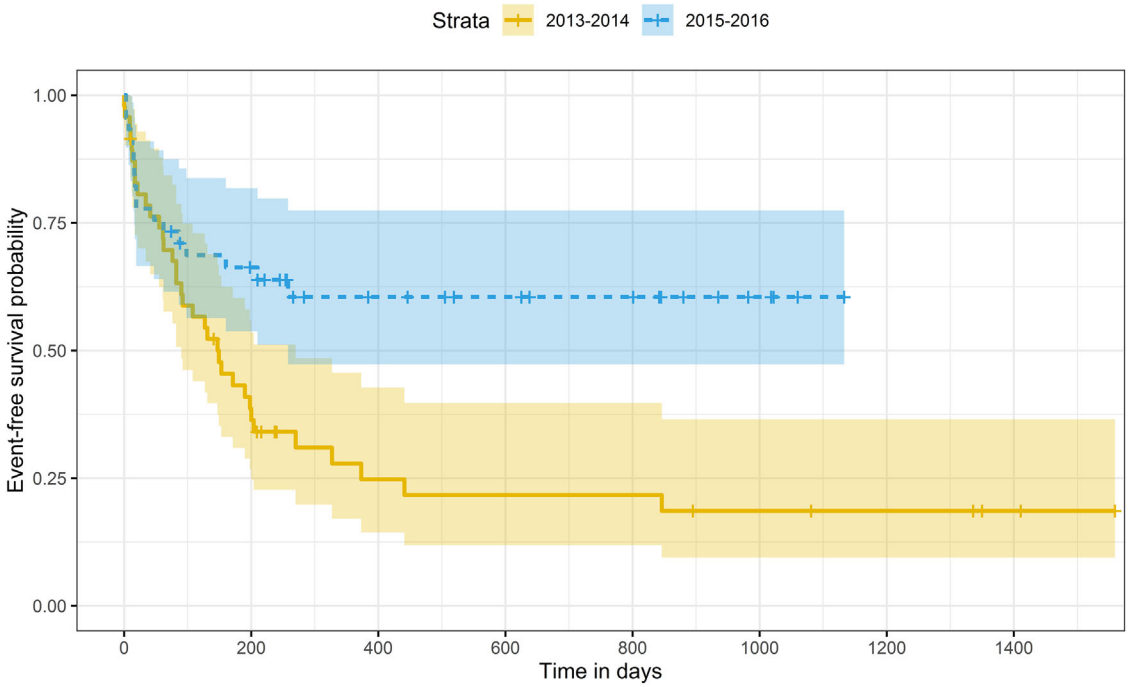

FIGURE 3 Event-free survival probability with 95% confidence intervals (CI) of patients with Wilms tumor per year (yellow: 2013–2014, and blue: 2015–2016). Patients who were diagnosed in 2015–2016 compared to 2013–2014 showed higher probability of event-free survival (respectively, 60.5%, 95% CI: 47.3–77.4, and 18.6%, 95% CI: 9.5–36.5, $p < .001$)

chemotherapy. All patients who abandoned treatment did so after surgery (median 149 days after diagnosis, IQR 103–194 days).

Patients who were diagnosed in 2015–2016 compared to 2013–2014 showed higher 2-year pEFS (respectively, 60.5%, 95% CI: 47.3%–77.4%, and 18.6%, 95% CI: 9.5%–36.5%, $p < .001$) (Figure 3). HR of treatment failure in 2015–2016 compared to 2013–2014 was 0.42 (95% CI: 0.24–0.76). Patients less often suffered from progressive or relapsed disease in 2015–2016 compared to 2013–2014 (respectively, 2.5%, 95% CI: 0.2%–11.3%, and 17.1%, 95% CI: 7.2%–30.7%, $p = .015$), and borderline significant less often abandoned treatment (respectively, 12.6%, 95% CI: 4.4%–25.3%, and 27.7%, 95% CI: 15.1%–41.9%, $p = .09$) (Figure 4). The subdistribution hazards of progressive or relapsed disease and abandonment were, respectively, 0.11 (95% CI: 0.02–0.86) and 0.42 (95% CI: 0.15–1.18) when comparing 2015–2016 to 2013–2014. Patients who were diagnosed in 2015–2016 compared to 2013–2014 received radiotherapy significantly more often ($p = .003$), had less surgical delay between preoperative chemotherapy and surgery ($p = .026$), and experienced a shorter duration of symptoms before diagnosis ($p = .021$) (Table 1). Disease stage or NHIF at diagnosis were not significantly different between the two groups ($p = .932$ and .190, respectively) (Table 1).

In patients who received surgery, pEFS was significantly higher in patients without or with a minor surgical delay in comparison with patients with a major surgical delay (HR treatment failure 0.26, 95% CI: 0.09–0.73, $p = .011$, and HR treatment failure 0.36, 95% CI: 0.14–0.91, $p = .03$, respectively) (Figure S1). Surgical delay did not significantly affect the cumulative probabilities of death, abandonment of treatment, or progressive or relapsed disease ($p = .85, .11, .23$, respectively). The cumulative probabilities of treatment outcomes were not significantly dependent on disease stage, NHIF status, distance to hospital, BMI at diagnosis, or duration of symptoms.

3.4 | Radiotherapy

Fifty-two patients were eligible for radiotherapy, of which 23 patients received radiotherapy (Table 1). Twenty-two of these children completed preoperative chemotherapy, surgery, and postoperative chemotherapy. Of the children that received radiotherapy, respectively, 69.6% and 30.4% were diagnosed with stages III and IV disease. No events were observed for 20 patients (87.0%), one patient abandoned treatment (4.3%), and two patients had progressive or relapsed disease (8.7%). pEFS was significantly higher in the children receiving radiotherapy in comparison to those who were eligible but did not receive it (HR 0.09, 95% CI: 0.03–0.3, $p = .000$) (Figure 5).

4 | DISCUSSION

In this retrospective record-review study, we assessed treatment outcomes of children with WT treated according to an adapted SIOP protocol at a large Kenyan teaching and referral hospital between 2013 and 2016. Two-year observed EFS was 43.5%. The most common cause of treatment failure was death, followed by abandonment of treatment and progressive or relapsed disease.

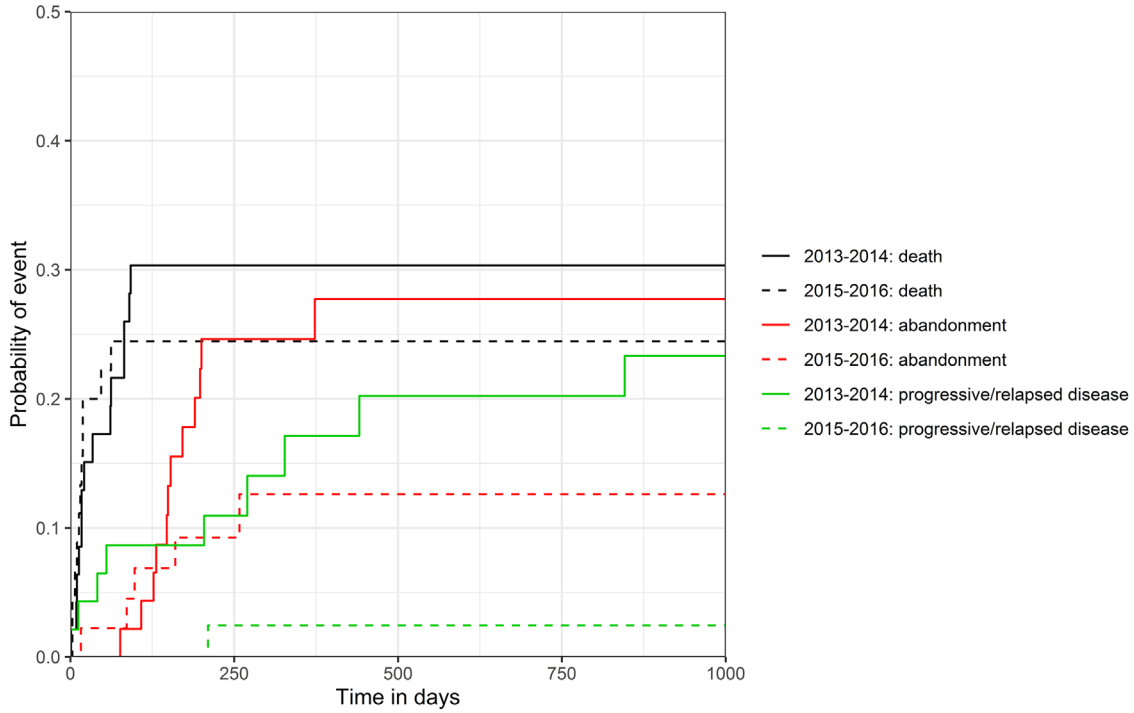

FIGURE 4 Cumulative incidence functions of competing risks. Patients who were diagnosed in 2015–2016 compared to 2013–2014 showed less progressive or relapsed disease (respectively, 2.5%, 95% confidence interval [CI]: 0.2–11.3, and 17.1%, 95% CI: 7.2–30.7, $p = .015$), and borderline significant less abandonment of treatment (respectively, 12.6%, 95% CI: 4.4–25.3, and 27.7%, 95% CI: 15.1–41.9, $p = .09$)

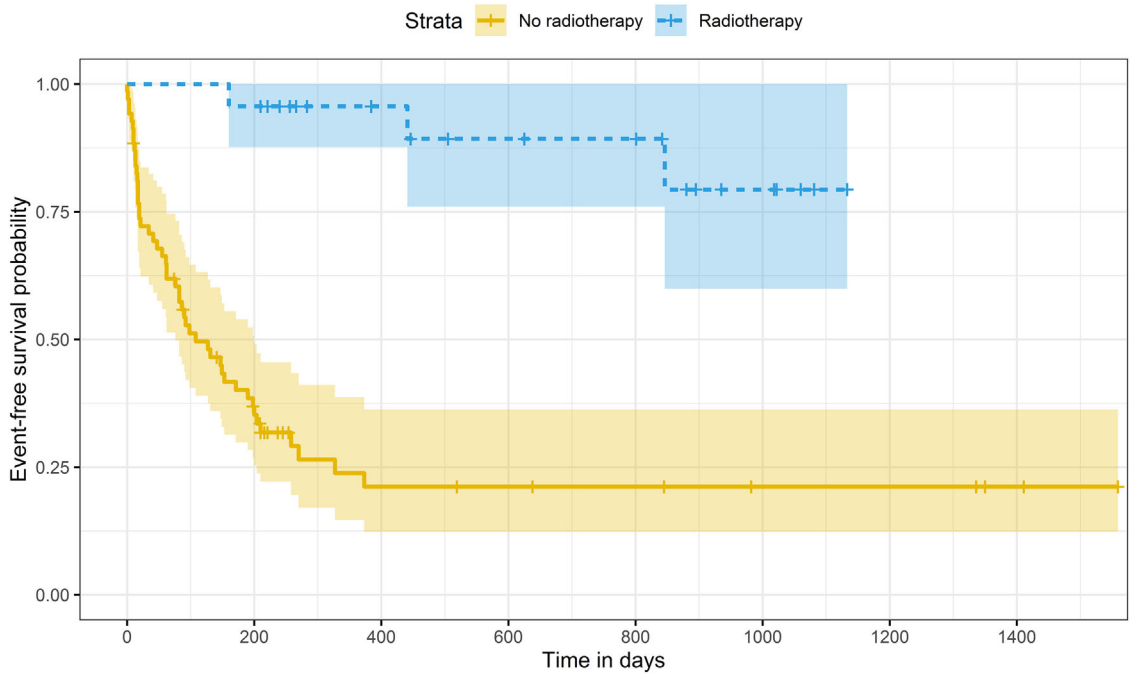

FIGURE 5 Probability of event-free survival (pEFS) in children eligible for radiotherapy. Children who received radiotherapy had a higher pEFS than those who did not (hazard ratio 0.09, 95% confidence interval: 0.03–0.3, $p = .000$)

This study is in continuity of two previously published reports from the same treatment center (Table S1).[20,21] Assessment of treatment outcomes showed that after an initial increase in EFS from 28.9% in 2000–2007 to 41.0% in 2010–2012, a decrease occurred (25.5% in 2013–2014), followed by an increase to 52.2% in 2015–2016.[20,21] The treatment abandonment rates, on the other hand, showed a steady decline from 42.2% in 2000–2007 to 30.8% in 2010–2012, 25.5% in 2013–2014 and finally 11.1% in 2015–2016.[20,21] Death rates remained similar, ranging 23.1%–29.8%, with its highest rate in 2013–2014.[20,21] The highest number of patients with relapsed or progressive disease was seen in 2013–2014 (19.1%).[20,21]

The overall increase in EFS over time can be partially explained by the gradual evolvement of the treatment protocol. In Table S1, an overview is provided of treatment practices, health care service capacity, and treatment outcomes between 2000 and 2016. In 2000–2007, both the upfront surgery and preoperative chemotherapy approach were followed. Until 2010, urosurgeons performed the surgeries in the absence of pediatric surgeons. There were no dedicated pediatric oncology nurses. Ultrasound was the only diagnostic imaging tool available until 2010, after which CT-abdomen and chest X-ray were used. Furthermore, preoperative chemotherapy became the standard from 2010 onward and patients initially received 4 weeks of preoperative chemotherapy for nonmetastatic disease and 6 weeks of preoperative chemotherapy for metastatic disease. A uniform protocol with 6 weeks of preoperative chemotherapy was adopted in 2013 after realizing that most of the tumors were very large and many patients did not have adequate response by week 4. The annual number of treated patients with WT showed a substantial increase from an annual average of six between 2000 and 2007,[21] to 13 between 2010 and 2012,[20] 24 between 2013 and 2014, and finally 23 between 2015 and 2016 (Table S1). This may be due to ongoing efforts in educating health care providers in the hospitals that are part of the catchment area for MTRH. An annual workshop is given to health care providers on identification and referral of children with suspected cancers. There have also been increased public campaigns on cancer, although they largely focus on adult malignancies.

Interestingly, EFS was lower in 2013–2014 than in 2010–2012. This could be explained by the substantial increase of treated patients, which resulted in an increased demand for the surgeons. Disease staging was similar in the two time periods, although duration of symptoms before first admission was longer. Furthermore, a change in the procurement process for chemotherapy in 2013 resulted in stock outs during this year, although this could not be quantified. Finally, less patients were enrolled with NHIF at diagnosis, which has been shown in previous studies to affect treatment outcome.[24]

The results from this study show that patients receiving radiotherapy have survival rates similar to those of high-income countries.[2] This increase was established by giving information to families about the importance of radiotherapy treatment to increase survival chances. Furthermore, MTRH worked on creating linkages with institutions that offer radiotherapy and guiding patients on how they can access the facilities. Parents who had managed to receive radiotherapy services were also helpful in guiding and assisting others. We received philanthropic funds that helped patients with the costs of transport, accommodation, and the hospital bills. The center has started the process of radiotherapy on site, which will be functional by the second half of 2021.

We found that patients that experienced no or minor surgical delay had higher pEFS in comparison to patients with a major surgical delay. This difference appeared to be caused by an increase in abandonment rates of patients with major surgical delay, although this difference was not statistically significant. Furthermore, during the waiting period, patients may have missed out on chemotherapy and the tumor may have started growing again.

A recent systematic review on treatment outcomes in eastern African patients with WT showed that OS adjusted for abandonment in 2010–2019 was 46.1% (range 25%–63.2%), which corresponds to survival rates seen in our study.[30] In the Collaborative Wilms Tumor Project, however, EFS was higher than in our study (respectively, 69% compared to 43.5%), but they excluded patients with bilateral tumors.[9] In Egypt, a lower middle-income country with resources comparable to Kenya, 3-year EFS in children with metastatic WT between 2008 and 2015 was 48.2%.[31] In contrast, high-income countries report survival rates of 95%–100% for patients with favorable histology, even those with high-stage disease.[32]

In this study, we noted a reduction in abandonment rates, which was established after we first identified the main reasons for abandonment of treatment: namely, financial difficulties, inadequate access to health insurance, and misunderstanding of treatment plans, including health beliefs that cancer cannot be cured and use of alternative medicine.[22–24] To address this, parental/patient education was given and increased NHIF uptake was ensured. Notably, all patients who abandoned care did so after preoperative chemotherapy and surgery. Once the children are diagnosed, they remain in the wards until after surgery, after which they are discharged and come back for continued care (e.g., postoperative chemotherapy). A further decline in abandonment rates could thus possibly be established by organizing shared care facilities for postoperative chemotherapy at regional, close-by hospitals.

As opposed to treatment outcomes of earlier years (2000–2007 and 2010–2012), the main cause of treatment failure was death, with almost all deaths occurring within 3 months after diagnosis. Patients often present with very large and necrotic tumors that start hemorrhaging after initiation of preoperative chemotherapy, resulting in early deaths. The use of abdominal CT rather than ultrasound for diagnosis may have contributed to this finding, as even those children with very large abdominal necrotic masses could be included in our analysis, whereas they might be misdiagnosed or not diagnosed in other centers using ultrasounds. Of note, due to financial restrictions, chest X-ray as opposed to chest CT was used for detection of pulmonary metastases. The latter has been shown to be superior and has been associated with improved treatment outcomes due to adequate risk stratification and subsequent treatment.[25–28] Therefore, pulmonary metastases may have been missed in a proportion of patients. To address high early mortality rates, earlier diagnosis and earlier referral are keys. We are implementing telehealth to reach out to health

care workers by organizing regular online sessions between MTRH and the hospitals within its catchment area.[29] Furthermore, the improvement of supportive care is essential to limit therapy-related mortality, although it was not possible to distinguish therapy- and disease-related mortality for the majority of patients in this study.

The main limitation of this study was missing data due to retrospective data collection. Furthermore, not all patients were treated uniformly, as a small proportion was previously treated in other centers according to a different protocol. The strength of this study was the use of competing risk analysis in addition to survival analysis to analyze treatment outcomes.

In conclusion, treatment outcomes improved significantly over the years despite advanced stage at presentation and highlight the importance of radiotherapy for high-risk patients. When patients are given comprehensive and timely therapy in this resource-limited setting, survival rates approach those of patients in high-income countries. Although this significantly contributes to achieving the WHO global survival target for childhood cancer, a great challenge remains to detect, diagnose, and treat the many children with WT who are currently not identified as such.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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