Nephroblastoma Treatment and Outcomes in a Low-Income Setting

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PURPOSE Nephroblastoma is a highly curable pediatric cancer that requires multidisciplinary care. Few reports have assessed long-term treatment outcomes in low-resource settings using a task-shifting model of care. We report outcomes of a large cohort and factors associated with survival.

METHODS We performed a retrospective chart review of all patients with nephroblastoma presenting to the Butaro Cancer Center of Excellence in Rwanda between July 2012 and June 2018.

RESULTS In total, 136 patients were identified and treated according to International Society of Pediatric Oncology guidelines for low-income settings. Median age at diagnosis was 39.7 months (interquartile range, 25.3-61.8 months); 56.6% were female. Sixty-one (44.9%) patients presented with stage I-III disease, 35 (25.7%) with stage IV disease, and 6 (4.4%) with stage V disease; the remainder were unstaged (n = 34; 25.0%). Most patients completed surgery (n = 97; 71.3%) and postoperative chemotherapy (n = 82; 60.2%); 17 patients received radiotherapy. With a median follow-up time of 18.1 months, 44.9% of patients were alive, 41.9% had died, 8.8% were lost to follow-up, and 4.4% were referred for palliative care or declined further care at the end of the study. Three-year overall survival was 57.5% (95% CI, 48.1 to 65.8) for the entire cohort, and 80.1% (95% CI, 66.8 to 88.5) and 44.0% (95% CI, 26.8 to 60.0) for stages I-III and IV-V, respectively.

CONCLUSION We demonstrate that patients with nephroblastoma can be successfully treated in a low-resource setting. Survival remains lower than in high-income countries, in part due to early deaths, contributing to approximately 30% of patients not being medically able to receive surgical intervention. Next steps include the development of strategies that focus on earlier diagnosis, supportive care during the early phases of therapy, and efficient and timely transitions between specialties for multimodal care.

INTRODUCTION

Nephroblastoma is the most common pediatric solid tumor, and the third most common pediatric cancer overall, in sub-Saharan Africa (SSA).[1] Overall survival (OS) rates in high-income settings have exceeded 90% with the use of multimodal approaches to therapy, including surgery, chemotherapy, and radiotherapy.[2] However, survival rates are generally < 50% in SSA, ranging from 11% to 66% with short-term follow-up.[3-10] Although data on longer-term survival in SSA are scarce, 5-year survival estimates range from 8% to 42%.[7,8]

Several factors may contribute to poorer outcomes in SSA. Delayed presentation resulting in advanced stages of disease and treatment nonadherence, including treatment abandonment and loss to follow-up (LTFU), are commonly observed.[1,8,11] Optimal treatment requires multimodal therapy. These treatments involve different providers and may occur in different locations resulting in treatment delays. The presence of comorbidities, such as HIV infection and malnutrition, may reduce a patient's tolerance for chemotherapy and increase treatment complications.[12] Additionally, there is suggestive evidence for increased disease aggressiveness and treatment resistance in African patients.[13] Inability to afford therapy, geographic barriers, disparities in health literacy, lack of human resources at health facilities, and frequent drug stockouts may be important social determinants driving treatment nonadherence and treatment failure in these settings.[1]

Nephroblastoma is the most common pediatric cancer treated at the Butaro Cancer Center of Excellence (BCCOE) in Rwanda, a public cancer treatment center based at a rural district hospital. Early reports from BCCOE confirmed both the feasibility of delivering multidisciplinary treatment for nephroblastoma in this setting and reasonable short-term outcomes.[14] In this

CONTEXT

Key Objective

What are the long-term outcomes of nephroblastoma treatment at a rural cancer center in a low-resource setting?

Knowledge Generated

Treatment according to International Society for Pediatric Oncology guidelines in our setting is feasible, with most patients completing treatment and achieving a 3-year overall survival of 57.5%. Although our outcomes and loss to follow-up rates are among the best in the region, major challenges included large tumor sizes on presentation, early mortality, and delays in transitions of care.

Relevance

Nephroblastoma can be treated safely and effectively in a rural public district hospital using a task-shifted model through collaboration with cancer specialists. Nevertheless, our study highlights areas to focus on to improve outcomes for patients in low-resource settings.

study, we report on the longer-term treatment outcomes of 136 patients with nephroblastoma and factors associated with survival in this patient population.

METHODS

Study Setting

The BCCOE opened in 2012 through a partnership between the Rwanda Ministry of Health, Partners In Health, Dana-Farber Cancer Institute, and others. Located 93 km from the capital, the hospital provides basic imaging (x-ray and ultrasound), pathology-based diagnosis, and chemotherapy. Advanced imaging is available in the capital. Patients are referred to one tertiary care hospital for nephrectomy. During the study period, there was no radiotherapy facility in Rwanda; selected patients were referred to Uganda from 2012 to April 2016, and Kenya from June 2016 to 2018, with the cost covered by Partners In Health.

Management and Treatment

Per International Society of Pediatric Oncology (SIOP) recommendations, diagnosis was made on the basis of suggestive clinical and imaging findings, with biopsy obtained only if the imaging was not convincing. Diagnosis and staging were confirmed pathologically at the time of surgery. Patients were excluded if surgical pathology revealed an alternative diagnosis. Treatment was managed by general physicians and pediatricians with routine consultation with international advisors. Treatment is based on SIOP guidelines and adapted to regionally available resources. SIOP studies have shown preoperative chemotherapy can reduce the risk of tumor rupture during surgery and downstage patients, which is especially important for patients in low-resource settings who often present with advanced disease.[15] At BCCOE, patients with localized disease are treated with a 4-week preoperative chemotherapy regimen using vincristine and actinomycin, whereas patients with metastatic disease receive a 6-week regimen with the addition of doxorubicin. Additional cycles of chemotherapy may be given if there is insufficient tumor shrinkage or surgery is delayed. After surgery, postoperative treatment is determined by pathologic staging and histologic risk classification according to SIOP classification. However, given the infrastructural limitations, associated long turnaround time for histologic diagnosis after surgery, and frequent missing or inadequate surgical and pathologic data, all patients at BCCOE are treated with the high-risk postoperative chemotherapy regimen containing vincristine, actinomycin, and doxorubicin. Stage III patients without pathologic classification are assumed to be intermediate or high risk and, thus, candidates for whole flank radiotherapy. Presence of diffuse intraabdominal tumor, tumor rupture, incomplete tumor resection, persistent lung metastases after preoperative chemotherapy, and liver metastases are additional indications for radiotherapy.

From 2012 to 2016, SIOP 2001 guidelines with a 27-week postoperative chemotherapy regimen were followed; since 2016, treatment has followed SIOP 2014 guidelines, with a reduced 15-week postoperative regimen.

Patients who missed an appointment were called to reschedule the visit. In cases where the family could not be reached, where available, a community health worker was recruited to follow-up with the patient in the community.

Data Collection and Analysis

We conducted a retrospective review of all patients evaluated for suspected or confirmed nephroblastoma at BCCOE between July 1, 2012, and June 30, 2018. We reviewed 146 patients for whom the medical record was available; three medical charts were not found. Ten patients were excluded from the study during data collection or analysis, as outlined in Figure 1.

Data were entered into a structured chart abstraction form and analyzed using Stata 15.1 (StataCorp, College Station, TX). Patient and disease characteristics and treatment processes were described using frequencies, medians, and interquartile range (IQR). A chemotherapy regimen was considered delayed if it lasted more than 2 weeks longer than the expected duration, and surgery delay was defined

FIG 1. Patients included in the study. Other diagnoses on pretreatment biopsy included malignant round cell neoplasm of right orbit, neurofibromatosis, and mucinous neoplasm of kidney. BCCOE, Butaro Cancer Center of Excellence; EMR, electronic medical record.
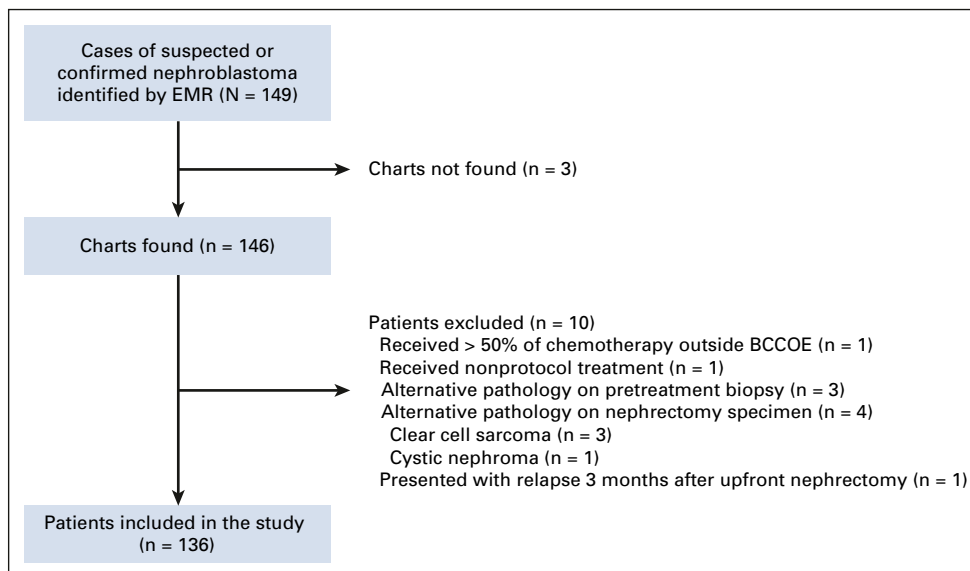
as > 21 days between preoperative and postoperative chemotherapy, according to SIOP recommendation.

OS was estimated using the Kaplan-Meier method and calculated from date of intake at BCCOE to date of death or last known date alive. If a family was unable to estimate the date of death, the earliest possible death date was chosen. Patients were considered LTFU if they did not return to care within 6 months of a missed visit and after two phone call attempts; these patients were censored at their last clinic visit date. One patient became LTFU immediately after the first visit and was excluded from survival analysis. We modeled associations between OS and baseline patient characteristics using Cox proportional hazards. Covariates from the univariate model with $P < .2$ were included in the multivariate model; the final model only included covariates significant at $\alpha = .05$. A subanalysis was performed on patients who received surgery using the same methods. Deaths were considered treatment-related if the patient was receiving chemotherapy within 2 months of death unless there was clear evidence of disease progression. Once therapy was completed, deaths that occurred during follow-up were attributed to disease progression unless recent surveillance imaging confirmed no evidence of recurrence.

Ethics

This study was approved by the Rwanda National Ethics Committee and Inshuti Mu Buzima Research Committee (Kigali, Rwanda).

RESULTS

Patient Demographic and Disease Characteristics

A total of 136 patients were included in the study (Table 1). Median age at diagnosis was 39.7 months (IQR, 25.3-61.8 months). A slight majority of patients were female (n = 77; 56.6%) and most came from Rwanda (n = 126; 92.6%), with the remaining from neighboring Burundi and Democratic Republic of Congo (n = 5; 3.7% each). Reported median time from symptom onset to presentation at BCCOE was 3 months (IQR, 1.5-6 months). The most common presenting complaints were abdominal mass/distension (97.1%), weight loss (42.6%), and fever (24.3%). Where measured (n = 97), median tumor size was 14.2 cm (IQR, 12.0-17.3 cm). Most patients presented with localized, unilateral disease (n = 94; 69.1%), whereas one fourth had metastatic disease (n = 35; 25.7%), six patients (4.4%) had bilateral disease, and one patient (0.7%) had extrarenal nephroblastoma.

Treatment Course

Treatment process and patient events are summarized in Figure 2.

Preoperative chemotherapy. Of the 136 patients, 126 presented to BCCOE before any cancer treatment and one patient was referred after receiving one dose of vincristine at a referral hospital in Kigali. Four patients died and one patient became LTFU before treatment could begin. Of the 122 patients who started preoperative chemotherapy, 100 (82.0%) completed this phase of therapy; 20 patients (16.4%) died, and two patients (1.6%) were LTFU during this phase. About half of the deaths (n = 11) and both LTFU events in this treatment phase occurred after the first cycle of chemotherapy (data not shown). Eleven patients received a median of two additional cycles of chemotherapy due to delays in surgical referrals. Of those who completed preoperative chemotherapy, 12 patients (12.0%) experienced treatment delay of > 2 weeks. There were 43 individual episodes of treatment delay experienced during preoperative chemotherapy, most commonly because of neutropenia (39.5%), infection/illness (25.6%), and missed appointments (14%). Only one instance was due to medication stockout.

TABLE 1. Patient Demographic and Clinical Presentation Characteristics

Characteristic	(n = 136)
Age at diagnosis, months, median (IQR)	39.7 (25.3-61.8)
Symptom duration, months (n = 133), median (IQR)	3.0 (1.5-6.0)
BMI, kg/m^2 (n = 133), median (IQR)	15.4 (14.3-16.8)
Largest tumor dimension, cm (n = 97), median (IQR)	14.2 (12.0-17.3)
Sex, No. (%)	
Female	77 (56.6)
Male	59 (43.4)
Country, No. (%)	
Rwanda	126 (92.6)
Burundi	5 (3.7)
DRC	5 (3.7)
Presenting signs and symptoms,[a] No. (%)	
Abdominal mass/distension	132 (97.1)
Weight loss	58 (42.6)
Fever	33 (24.3)
Hematuria	24 (17.6)
Abdominal pain	4 (2.9)
HIV (laboratory-confirmed), No. (%)	
Negative	95 (69.9)
Unknown	41 (30.1)
Cancer treatment before BCCOE, No. (%)	
No	124 (91.2)
Yes	12 (8.8)
Imaging done,[a] No. (%)	
Chest x-ray	122 (89.7)
Abdominal ultrasound	77 (56.6)
Abdominal CT	127 (93.4)
Disease presentation, No. (%)	
Localization	
Unilateral, localized	94 (69.1)
Unilateral, metastatic	35 (25.7)
Bilateral	6 (4.4)
Extrarenal WT	1 (0.7)
Sites of metastases (n = 36),[a] No. (%)	
Liver	15 (41.7)
Lung	27 (75.0)
Peritoneum	3 (8.3)
Spleen	1 (2.8)

Abbreviations: BCCOE, Butaro Cancer Center of Excellence; BMI, body mass index; CT, computed tomography; DRC, Democratic Republic of Congo; IQR, interquartile range; WT, Wilms tumor.

[a]May not add to 100% as patients multiple presenting signs and symptoms, types of imaging done, or sites of metastases.

Nephrectomy, histology, and staging. After completing preoperative chemotherapy, one patient had poor response, was deemed inoperable, and was referred to palliative care.

Another 10 patients died and one patient became LTFU after referral to Kigali for surgery. Four of these deaths were documented to have occurred while admitted at the tertiary hospital in Kigali; however, it was not clear if they occurred during surgical attempt. Patients who did not survive to surgery had significantly larger tumors than those who did (median tumor size = 16.0 cm v 13.5 cm, P = .001).

Nine patients presented to BCCOE for the first time after nephrectomy, only one of whom had received preoperative chemotherapy according to SIOP protocol. Of those with data available (n = 87), more than half (n = 49; 56.3%) exceeded the recommended 21-day surgical transfer time frame (median transfer time: 23 days; IQR, 18-29 days).

Staging and histology classification are summarized in Table 2. Eighteen patients (18.6%) had documented complications during surgery; injury to the diaphragm and inferior vena cava were the most common complications (data not shown). For those with available data (n = 65), approximately one third (n = 22; 33.8%) were found to have tumor extending beyond the capsule. Of those with data available (n = 48), the majority (n = 40; 83.3%) had surgical margins uninvolved with tumor on pathology.

Postoperative chemotherapy. All but one patient who completed surgery returned to BCCOE for postoperative chemotherapy (n = 96). Most patients completed all postoperative cycles (n = 82; 85.4%); more than half (n = 50; 61.0%) experienced prolonged duration of this final treatment phase. There were 178 individual instances of treatment delay during postoperative chemotherapy, most commonly because of neutropenia (57.9%), missed appointments (15.2%), infection/illness (12.9%), and travel for radiation therapy (7.9%). Only four instances (2.2%) were due to medication stockout.

Radiotherapy. At least 46 patients had indications for radiotherapy according to available data, of whom only 17 (37.0%) completed radiotherapy because of limited availability of funding and logistical challenges. Median time from surgery to start of radiotherapy was 106 days (IQR, 70-154 days). After completing radiotherapy, two patients failed to return to BCCOE in time to complete postoperative chemotherapy; both patients remained disease-free at the time of data collection.

Survival

With median follow-up time of 18.1 months (IQR, 3.0-49.1 months; maximum: 89.4 months), at the time of analysis, 59 patients (43.4%) were alive and disease-free, 57 (41.9%) had died, 12 (8.8%) were LTFU, three (2.2%) had been referred for palliative care at their nearest district hospital, three (2.2%) declined further care, and two (1.5%) were alive but with disease recurrence. One third of deaths (n = 19; 33.3%) were considered treatment-related, and 29 deaths (50.9%) were attributed to disease progression. The remaining nine deaths (15.8%) were unable to be classified because of insufficient data.
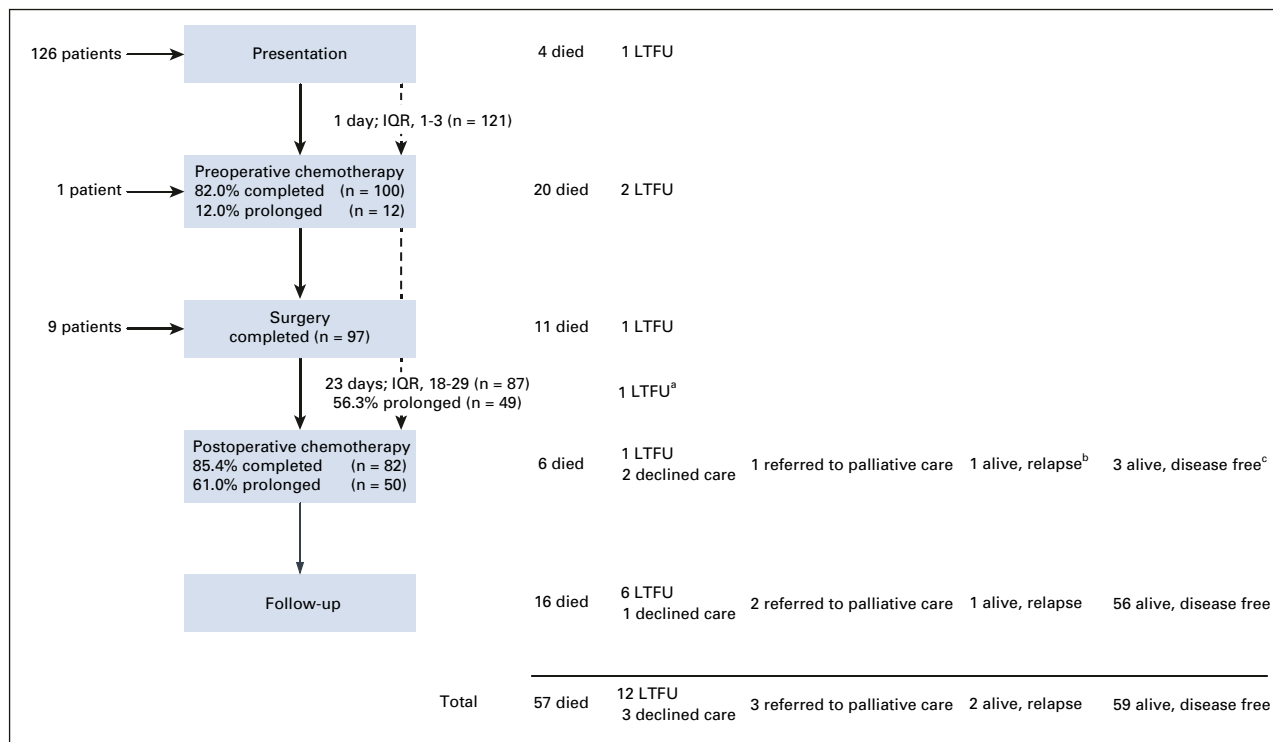
126 patients → **Presentation** — 4 died — 1 LTFU

1 day; IQR, 1-3 (n = 121)

1 patient → **Preoperative chemotherapy** 82.0% completed (n = 100) 12.0% prolonged (n = 12) — 20 died — 2 LTFU

9 patients → **Surgery** completed (n = 97) — 11 died — 1 LTFU

23 days; IQR, 18-29 (n = 87) 56.3% prolonged (n = 49) — 1 LTFU[a]

Postoperative chemotherapy 85.4% completed (n = 82) 61.0% prolonged (n = 50) — 6 died — 1 LTFU, 2 declined care — 1 referred to palliative care — 1 alive, relapse[b] — 3 alive, disease free[c]

Follow-up — 16 died — 6 LTFU, 1 declined care — 2 referred to palliative care — 1 alive, relapse — 56 alive, disease free

Total — 57 died — 12 LTFU, 3 declined care — 3 referred to palliative care — 2 alive, relapse — 59 alive, disease free

FIG 2. Summary of treatment process and patient events. Chemotherapy delay was defined as lasting more than 2 weeks longer than the expected duration. Surgery delay was defined as > 21 days between preoperative and postoperative chemotherapy. [a]Patient completed preoperative chemotherapy then became LTFU after referral for surgery; per family report, patient received surgery but not postoperative chemotherapy. [b]Patient presented at Butaro s/p nephrectomy, received 3 weeks of postoperative DD-4A regimen, was LTFU for 16 months, returned with recurrence; at the time of data collection, finished preoperative chemotherapy and was referred for second surgery. [c]Two patients went for radiation therapy and did not return to Butaro Cancer Center of Excellence in time to complete postoperative chemotherapy; no recurrence at last visit. IQR, interquartile range; LTFU, lost to follow-up.

Survival data are shown in Figure 3. Three-year OS was estimated to be 57.5% (95% CI, 48.1 to 65.8) for the entire cohort, and 80.1% (95% CI, 66.8 to 88.5), 44.0% (95% CI, 26.8 to 60.0), and 28.4% (95% CI, 13.3 to 45.5) for patients with stage I-III, stage IV-V, and unknown stage, respectively. Disease stage ($P < .001$) and tumor size ($P = .001$) were significantly associated with worse survival in univariate analysis. Only disease stage retained significance in multivariable analysis. Compared with stage I-III, hazards ratios were 4.2 (95% CI, 2.1 to 8.4) and 6.5 (95% CI, 3.2 to 13.2) for patients with stages IV-V disease or unknown stage, respectively ($P < .001$ for both). Completion of radiotherapy among those with indications was not associated with improved survival (hazards ratio 0.7; 95% CI, 0.2 to 2.5).

Given the large proportion of early deaths, we also estimated survival on the subpopulation of patients who completed surgery (n = 97). Three-year OS for this smaller cohort was 76.1% (95% CI, 65.2 to 84.0), and 81.1% (95% CI, 67.5 to 89.4), 69.6% (95% CI, 42.7 to 85.8), and 62.3% (95% CI, 27.8 to 84.0) for patients with stage I-III, stage IV-V, and unknown stage, respectively. In univariate analysis, age at diagnosis ($P = .182$) and tumor size ($P = .085$) were significantly associated with survival at $\alpha = .2$. In the

multivariable model, neither age nor tumor size was a significant predictor of survival.

DISCUSSION

Here, we present an update to our previous report of nephroblastoma treatment outcomes with a larger cohort of patients, and longer-term follow-up, demonstrating a 3-year OS of 57.5%.[14] Although this is lower than reports from high-income countries, it appears higher than recently reported outcomes from other centers in SSA. In comparison, 2-year event-free survival at four centers in Kenya was 52.7%, and although this did increase to a reported 94% among children who completed treatment, this study had significant LTFU rates of 50% overall and 40.7% among those who completed therapy.[5] One-year survival rates in Zimbabwe, Uganda, and Kenya were reported to be 61%, 39%, and 66%, respectively, and 3-year survival rates were 38.7%, 15.8%, and 22.9%.[8] One report from a multinational cohort from seven pediatric oncology units in SSA reported a 3-year OS of 72%, although they excluded deaths or abandonment before surgery, patients with unfavorable histology, and stage IV disease that did not respond to chemotherapy.[9] This is comparable with our 3-year OS of 76.1% in patients who completed surgery,

TABLE 2. Staging Distribution and Histology Classification for Patients Who Underwent Nephrectomy

Variable	No. (%)
Postoperative stage	
I	25 (25.8)
II	12 (12.4)
III	22 (22.7)
IV	22 (22.7)
V	4 (4.1)
Unknown	12 (12.4)
SIOP tumor histologic classification (n = 89)	
Low/intermediate	58 (65.2)
High	15 (16.9)
Unknown/missing	16 (18.0)
Excisional margin clear of tumor?	
Yes	40 (41.2)
No	8 (8.2)
Unknown	49 (50.5)
Tumor extended beyond the capsule?	
Yes	22 (22.7)
No	43 (44.3)
Unknown	32 (33.0)
Was the renal vein involved?	
Yes	9 (9.3)
No	52 (53.6)
Unknown	36 (37.1)

NOTE. N = 97, of whom eight had no preoperative chemotherapy.
Abbreviation: SIOP, International Society of Pediatric Oncology.

which improves to 81.1% when limited to patients with stage I-III disease. In a cohort of patients presenting to centers in Malawi, Cameroon, and Ghana, 2-year event-free survival rate was 49.9% with just 12% of patients abandoning treatment.[10] One possible reason for our relatively high survival rate is that treatment abandonment was low with just eight patients (5.9%) LTFU or declining care before completion of treatment, which can be explained by the social support services available at BCCOE including free chemotherapy and transport reimbursement.

Although encouraging when compared with geographically similar reported outcomes, this remains below reported outcomes from high-income countries, where OS rates are frequently > 90%. One contributing factor is larger tumor size on presentation (median, 14.2 cm), which is similar to the median size of 14 cm reported by the Collaborative Wilms Tumour Africa Project, but larger than the median size of 11 cm from a large cohort in the United States.[10,16] It is not clear whether the difference in tumor size is explained largely by the advanced stage at presentation or whether there are other underlying biologic factors. Additionally, early deaths were a significant issue in our cohort, with 30%
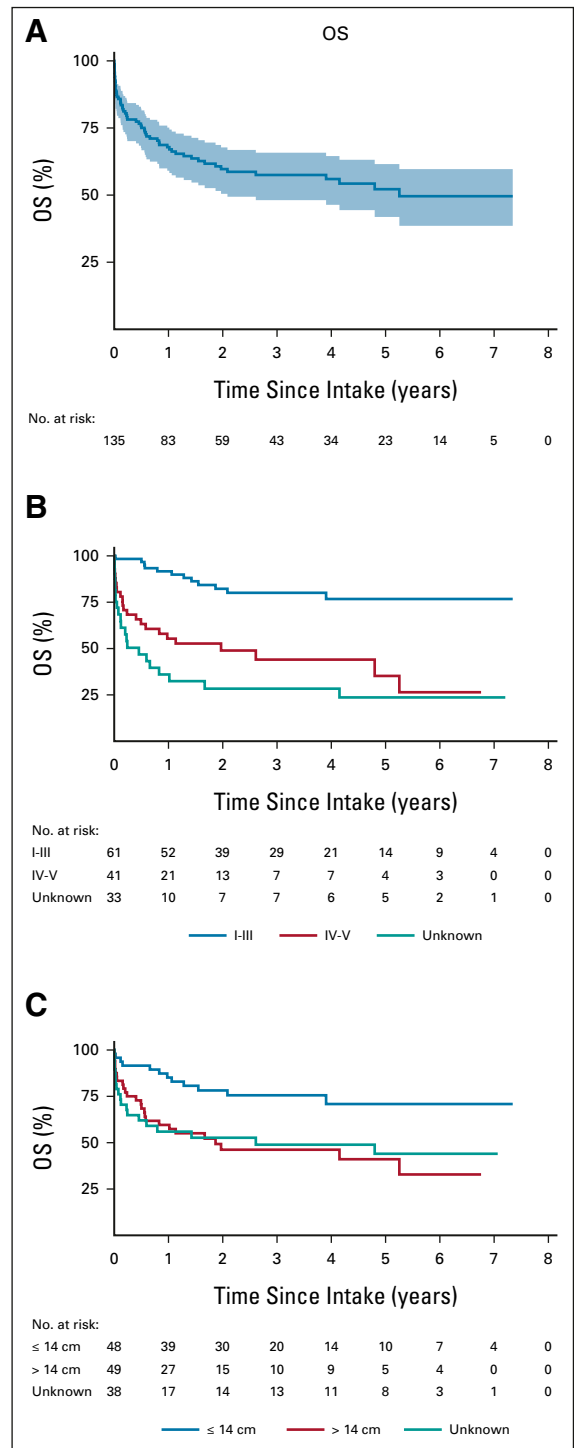
FIG 3. Kaplan-Meier OS estimates (n = 135) by prognostic factors: (A) OS, (B) OS by stage, and (C) OS by size. OS, overall survival.

of patients dying during treatment and more than half of deaths (n = 35/57; 61.4%) occurring before patients recovered from surgery. The cause of early deaths was not clear, and improved information capturing is needed to understand the contributing factors to further improve outcomes. A significant portion of deaths were considered

related to treatment (33.3%), which may be due to comorbidities such as malnutrition, late presentation, severity of illness upon presentation, and limited supportive care. Of note, patients who did not survive to surgery had significantly larger tumors than those who did survive to surgery (median tumor size = 16.0 cm v 13.5 cm, $P = 0.001$). This suggests that in low-income settings, tumor size may be a potential predictor of prognosis that warrants further investigation. If patients can survive to surgery, outcomes are reasonable with 3-year OS of 76.1%, and 69.6% for those with stage IV-V disease, the highest risk group. Treatment abandonment and LTFU are commonly cited causes of lower survival rates in SSA, and although our rates are lower than those reported in other studies in the region, they remain much higher than those in high-income countries.[17] Treatment delays were also frequent, with most patients experiencing delays between preoperative and postoperative chemotherapy (56.3%), as well as during the extended course of postoperative chemotherapy (61.0%). Most delays during chemotherapy treatment were because of neutropenia (54.2%), followed by illness/infection (15.4%) and missed appointments (14.9%). Medication stockouts were a rare cause of treatment delay.

Radiation services were not available in-country during the study period, which limited access to care. This contributed to only 37.0% of eligible patients able to receive radiation therapy. It is worth noting that survival was not statistically different between the patients who received radiation and those having indications for radiation but not able to obtain it, but our sample sizes were small and there may have been unintended consequences of traveling for radiation, including delays in postoperative chemotherapy and routine follow-up.

Limitations of our study include incomplete data because of the retrospective chart review study design, lack of standardized forms, and missing reports. Pediatric surgery is not performed at BCCOE and therefore many patients had missing staging and pathology information or were LTFU during this transition of care. Although a standardized operative form was developed in 2014 to improve communication of surgical findings, it was frequently incomplete. When these reports were received, more than half of patients had unknown margin status and one third of patients did not have information about capsule or renal vein involvement. Because of missing information, patients were conservatively managed with more aggressive treatment, which may have increased treatment-related morbidity. Future efforts should be made to obtain more comprehensive and timelier operative and pathology reports to accurately assess risk and plan postoperative treatment. Also, development of a multidisciplinary team to manage the complex treatment pathway might improve delays, LTFU, and outcomes.

Our data confirm that nephroblastoma can be treated safely and effectively in a rural public district hospital using a task-shifting model through collaboration with cancer specialists. Nevertheless, further efforts are needed to improve outcomes for patients in low-resource settings. Our results suggest that the required chemotherapy can be reliably given but there is a need to better understand and prevent early deaths. Interventions should include improved and standardized documentation of the cause of death, as well as efforts to target suspected contributors, including improvements in early diagnosis, nutrition, and supportive care. Further efforts to minimize treatment delays, abandonment, and LTFU should include enhancing patient navigation, increasing social support, developing more systematic and improved counseling of parents, implementing a tracking system to remind patients of appointments, and improving access to cancer care at additional centers as part of the Rwanda National Cancer Control Plan. Additionally, after this study period, radiation therapy became available in Rwanda; it will be important to study how improved access to this treatment modality affects outcomes as well as treatment-related morbidity among survivors.

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