East African Medical Journal Vol. 97 No. 8 August 2020
EARLY SURGICAL MANAGEMENT OUTCOMES OF CHILDREN WITH WILMS' TUMOUR AT MOI TEACHING AND REFERRAL HOSPITAL IN ELDORET-KENYA
Nancy Kerubo Nyakundi (MBChB, Registrar - General Surgery) Department of Surgery and Anesthesiology, Moi University School of Medicine, Eldoret-Kenya, P.O Box 4606-30100, Eldoret-Kenya, Pius Musau (MBChB, MMed-Surg, MSc-Urol), Department of Surgery and Anesthesiology, Moi University School of Medicine, Eldoret-Kenya, Peter Saula (MBChB, MMed-Surg, MMed-Pediatric Surgery), Department of Surgery and Anesthesiology, Moi University School of Medicine, Eldoret-Kenya.

Corresponding author: Dr. Nancy Kerubo Nyakundi, Department of Surgery and Anesthesiology, Moi University School of Medicine, Eldoret-Kenya. P.O Box 4606-30100, Eldoret-Kenya. Email: `obeginyakundi@yahoo.com

EARLY SURGICAL MANAGEMENT OUTCOMES OF CHILDREN WITH WILMS' TUMOUR AT MOI TEACHING AND REFERRAL HOSPITAL IN ELDORET-KENYA

N. K. Nyakundi, P. Musau and P. Saula

ABSTRACT

Background: **Paediatric cancers such as Wilms' tumour are a major cause of morbidity and mortality while also interfering with the quality of life among affected children. This creates a need for early detection and intervention to improve management outcome.**

Purpose: **To evaluate the early surgical outcomes of children with Wilms' Tumour at a resource constrained teaching hospital in Western Kenya.**

Materials and Methods: **A prospective study among children with Wilms' tumour who underwent radical nephroureterectomy at Moi Teaching and Referral Hospital. They were reviewed prior to surgery while diagnostic and neoadjuvant chemotherapy sessions data were obtained through chart reviews. Clinical staging was determined using diagnostic radiology while sociodemographic data was collected using a questionnaire. Statistical associations between patient characteristics and surgical outcomes were determined.**

Results: **Of the 30 children studied; 19 (63.3%) were females with an overall mean age of 3.8 (SD± 1.5) years. All the children presented with abdominal mass with 66% of the masses being on the left side. Majority (53.3%) of them received 6 cycles of neoadjuvant chemotherapy. The early postoperative complications were intestinal obstruction (6.7%), surgical site infection (3.3%) and tumour rupture (3.3%). Averagely, the children stayed in the post-operative surgical ward for 6.5 (SD±1.6) days. There was a statistically significant association between duration of symptoms and duration of surgical ward stay (p=.044). No perioperative deaths were observed over the 12-day follow-up duration in the surgical ward.**

Conclusions: **This study reports favourable early surgical outcomes among children with Wilms' tumour who underwent radical nephrouretectomy.**

INTRODUCTION

Wilms' tumour (nephroblastoma) is the most common childhood kidney tumour as it accounts for approximately 91% of all kidney tumours[1]. It represents the most common abdominal tumour in infants and children below seven years in sub-Saharan Africa[2], thereby affecting their quality of life. Furthermore, most children with Wilms' tumour present late for treatment leading to poor prognosis. The treatment of nephroblastoma has been considered one of the greatest success stories in modern medicine. Its management in many low and middle-income countries (LMICs) consists of neo-adjuvant chemotherapy followed by radical nephroureterectomy, adjuvant chemotherapy and in some cases radiotherapy. Despite advances in neo-adjuvant therapy[3], surgery is still the mainstay oncologic treatment and is also critical for proper staging of the disease which aids in directing adjuvant therapy[4]. However, surgical complications are a recognized morbidity of the treatment of patients with Wilms' tumour[5]. This creates the need to focus on early surgical outcomes as part of paediatric oncologic treatment and overall patients' wellbeing[3]. This is further necessitated by advances in medical and surgical care of paediatric solid tumours[6]. This study evaluated the early surgical outcomes in patients who had undergone radical nephroureterectomy for Wilms' Tumour at MTRH and the factors associated with the surgical outcomes. The findings on the study will not only add to the pool of existing knowledge on Wilms' tumour, but also shed more light on the surgical outcomes to everyone rendering services to patients with Wilms' tumour. In addition, the study will highlight the patient outcome as well as factors associated with the outcomes.

MATERIALS AND METHODS

This was a prospective cohort study among children with Wilms' tumour conducted at the Moi Teaching and Referral Hospital (MTRH) paediatric oncology and paediatric surgical wards.

The children presenting with Wilms' tumour were identified by taking their history, conducting physical examination, laboratory, and medical imaging investigations. The most commonly presenting feature of interest was a painless abdominal mass. However, the patient could present with pain, fever, haematuria and hypertension. They were also examined for stigmata of other conditions that may be associated with Wilms tumour. Laboratory and imaging investigations were conducted to confirm diagnosis, delineate the extent of the tumor, determine whether the contralateral kidney was affected, discover any metastasis, and ensure the child was fit for surgery. Complete blood count was assessed for anaemia or thrombocytosis, urinalysis assayed for urinary catecholamine, while serum urea, electrolytes and creatinine were ordered to determine whether they were normal or deranged. Ultrasound was performed to localize the mass to the kidney and distinguish from other causes of renal masses. Doppler examination was further performed to examine the renal vein and inferior vena cava for the presence of tumor

thrombus. Computerized tomography (CT) scan of the abdomen was used to assess heterogeneous soft-tissue density masses, areas of calcification (up to 15%) and fat-density regions. Because the enhancement was patchy, CT scan allowed for better delineation of the relationship between the mass and kidney.

Eligibility to participate in the study depended on clinical, laboratory and imaging diagnosis of Wilms' Tumour and being scheduled for radical nephroureterectomy. Those who had metastasis, comorbidities and lacked parental consent were excluded.

The participants underwent radical nephrouretectomy at MTRH during the study period between July 2017 and June 2018. The study received prior ethical approval from the MU/MTRH Institutional Research and Ethics Committee (Approval Number:0001665) and parental informed consent was obtained for all the children enrolled. The parents were explained to the reason why their children met the eligibility criteria to participate in the study, their autonomy to participate or withdraw from the study without any implication to their children's clinical care and how their privacy and confidentiality will be maintained.

The investigators reviewed each patient's file a day prior to the scheduled surgery to gather clinical characteristics such preoperative chemotherapy cycles, laboratory investigations and medical images. Neo-adjuvant chemotherapy was given by the medical oncology team (physicians, oncology pharmacists and nurses) prior to surgery. Operative and post-operative techniques were standardized using SIOP (Society of Paediatric Oncology) guidelines that were adopted in the Paediatric Oncology Manual (version 5) of MTRH.

Intraoperative findings were collected during surgery while post-operative complications were noted over the duration of stay in the surgical ward. Excised tumors were sent to an anatomical pathologist for pathological staging and histological subtypes. These histopathology results were then noted in the data collection form. The patients were then transferred back to the medical oncology wards to continue with their chemotherapy regimens. Early surgical outcomes of interest were intraoperative findings and postoperative outcomes during the patients' stay in the surgical ward. The independent study variables of interest were the participants sociodemographic characteristics (age and gender), duration of symptoms, preoperative chemotherapy cycles, histopathological staging and subtypes; while the dependent variables included tumor rupture, intestinal obstruction, surgical site infections, duration of hospital stay and mortality if any. The test of associations between the patient variables and the early surgical outcomes were done using Pearson chi-square and Spearman's correlation tests.

RESULTS

A total of 30 children with Wilms' tumour were recruited into this study, of which nearly two thirds (63.3%; n=19) were female while the rest were male. Participants' age ranged between 2 to 7 years with a mean age of 3.8 years (±1.5). All the presented with abdominal mass, 14 (46.7%) had fever while 2 (6.7%) presented with macroscopic hematuria. The median duration of symptoms was 8 weeks (IQR 4, 12). Over half (53.3%) of the participants received 6 courses of cytotoxic neoadjuvant chemotherapy with the rest receiving seven (30%) and eight (16.7%)

courses depending on the disease stage. Among those who received six courses of cytotoxic as neoadjuvant chemotherapy, intravenous vincristine (2mg/m^2) was administered weekly for six weeks; while actinomycin D (1.4mg/m^2) was infused on the first, third and fifth weeks. In addition, Adriamycin (a maximum dose of 50mg/m^2) infusion over four hours was administered on the first and fifth weeks. On the seventh week, the patients were evaluated for a surgical plan.

Two thirds of the tumours were on the left side while more than half (53%) of all tumours were classified as intermediate risk tumours based on the predominant histological component. Majority (66.7%; n=20) of the children had clinical stage II of Wilms' tumour with the least proportion (6.6%; n=2) being those at stage IV. There were no clinical stages I and V of the disease. Early postoperative complications observed in the first 12 days in the surgical ward were intestinal obstruction (6.7%), surgical site infection (3.3%) and tumour rupture (3.3%) The median duration of participants' follow-up in the surgical ward was 6 (IQR: 5,12) days, while the mean duration of stay in the surgical ward was 6.5 (SD±1.6) days (Table 1). Cumulatively, the participants were followed up for a total of ten weeks; of which, some spent nearly two weeks in the surgical ward and no mortality was observed during the entire study period.

Table 1

Clinical characteristics of study participants

Variable (N=30)	Mean (SD) or n (%)
Duration of symptoms	
≤8 weeks	17 (56.7)
8.1-16 weeks	10 (33.3)
>16 weeks	3 (10)
Pre-operative chemotherapy courses	
6	16 (53.33)
7	9 (30)
8	5 (16.67)
Clinical Staging	
I	0
II	20 (66.7)
III	8 (26.7)
IV	2 (6.6)
V	0
Histological sub classification	
Blastemal	1 (3.33)
Anaplastic	1 (3.33)
Epithelial	3 (10)
Mixed	6 (20)
Stromal	6 (20)
Not outlined	13 (43.4)
Complications	
Intestinal obstruction	2 (6.7)
Surgical site infection	1 (3.3)
Tumour rupture	1 (3.3)

Table 2

Effect of sociodemographic and clinical characteristics on Duration of stay in the surgical ward

Variable	Duration of stay		
	N	ϱ	p-value
Age	30	-0.090	0.634
Chemotherapy sessions	30	0.014	0.941
Duration of symptoms	30	0.396	0.044
N-Population; ρ-Spearman Correlation			

There was a statistically significant association (p=0.044) between duration of symptoms and stay in the surgical ward (Table 2).

There was no statistically significant associations between sociodemographic characteristics, clinical staging, and post-operative complications. Mortality rate was 0%.

Postoperatively, the patients received vincristine (2mg/m^2) weekly on the eight to eleventh week; while actinomycin D (1.4mg/m^2) was infused on the ninth and eleventh week.

DISCUSSION

Wilms' tumour represents one of the greatest success stories in modern medicine. The availability of the chemotherapy agents and antibiotic therapy have been major factors in the management of this tumour. However, surgical intervention is the mainstay of Wilms' tumour management. This study's demographic findings compare well with those of previous studies done in Kenya[6,7], Malawi[9] and China[10]. This is because Kenya and Malawi are both developing economies with similar socioeconomic and demographic characteristics.

However, the findings contrast those of a Nigerian study[11] where the mean presentation age was 6 years. The difference in mean presentation age between the current and Nigerian studies could be attributed to differences in study design and methodology. Although the current study was a prospective cohort study among children with Wilms' tumor scheduled for nephrouretectomy, the Nigerian study[11] adopted chart reviews of oncology notes and histology slide reports for 30 proven cases of nephroblastoma over a five-year period (2009-2013). Retrospective studies are always fraught with incomplete data further lowering the number of eligible study participants and interfering with study findings. Furthermore, a previous study[12] has attributed late presentation of children with Wilms' Tumor to low awareness of the condition in some Sub-Saharan African countries, limited availability of chemotherapy agents and lack of proper Wilms' tumour management mechanisms.

This study further reports that all the children enrolled presented with a palpable abdominal mass, while nearly half of them had fever while less than one-tenth presented with macroscopic hematuria. This finding is comparable with that reported in Malawi[9] where all patients presented with abdominal mass; and half of them had additional complaints including abdominal pain, haematuria, dyspnea, edema and or weight loss. This hallmark of Wilms' tumour differential diagnosis were also reported in a Pakistani study[13] where a large proportion (75%) of children with the disease presented

with abdominal mass alongside reports of fever, hematuria, weight loss among other symptoms. This was also corroborated in a retrospective study conducted in Nigeria [12] where abdominal mass was the main presentation in all the children enrolled.

The average duration of symptoms before admission was 8 weeks (IQR 4, 12) that was comparable to a Kenyan study[8] where the majority of the patients presented within the first three months of symptoms onset. However, this study's finding contrasts two Nigerian studies[11,12] where the duration of pre-clinical presentation was 4-14 months, and 4.7 months respectively. This late presentation of children with Wilms' tumor in Nigeria was attributed to ignorance, poverty and caretakers seeking other modes of treatment before finally seeking medical attention.

We further report that more than half (53.3%; n=16) of the participants received six cycles of neo-adjuvant chemotherapy before surgery, while 30% had seven cycles and 16.7% got eight cycles depending on the disease staging. This decision was informed that more than two-thirds of all the enrolled study participants presented with an early clinical staging. Studies conducted by the Society of Paediatric Oncology (SIOP) have reported a more than half mean reduction after a single cycle of chemotherapy and a further 50% reduction after the second cycle[14–16]. Furthermore, studies done in South Africa[17] showed a mean reduction by 24% in tumour size following similar chemotherapy regimens. Neo-adjuvant chemotherapy plays an important role in complete surgical removal of a shrunken tumour, avoiding mutilation caused by surgical procedures and early treatment of micro-metastasis that were not visible at diagnosis[1,5,15].

The early clinical outcomes of children with Wilms' Tumour have significantly improved with combined therapeutic approaches integrating chemotherapy, surgery and radiotherapy[16]. The SIOP guidelines recommend that all Wilms' Tumour patients should undergo pre-operative chemotherapy before surgery. This SIOP protocol has led to lower incidence of tumour rupture by reducing the vascularity of the tumour, risk of tumour spillage, a more favorable stage distribution and reduced treatment burden [14,15]. This study's setting adopted the SIOP protocol to manage Wilms tumour' in 2009. The use of SIOP protocols and the establishment of a multidisciplinary care team has led to improved management and better outcomes[8]. None of the children we enrolled died during the study period, however 13.3% of them had early complications.

Although early post-operative outcomes vary, local incidence of surgical outcomes following radical nephroureterectomy in Kenya has not been documented. Despite this, collaborative efforts among paediatric surgeons, pathologists, paediatric medical oncologists, and radio-oncologists have been regarded as a major factor in improving nephrouretectomy outcomes[12]. The incidence of surgical complications reported in this study (13.3%) matched those of other trials, in the National Wilms' Tumor Study - 4 where complication rates of 12.6% were reported[18].

Intestinal obstruction was the most common post-operative complications following radical nephroureterectomy among children with nephroblastoma. This study confirms previous reports that small bowel obstruction occurs between 5% to 12% among children with Wilms' tumour[19]. In Germany, 8.82% of the children enrolled had to be reoperated because of small bowel obstruction[20]. In this study, the etiology of intestinal obstruction

was small bowel intussusception, with the participants presenting with vomiting, abdominal pain, and passage of red currant jelly stool three days after initiation of feeding.

Surgical site infection is one of the post-operative complications that is associated with longer hospital stay, higher treatment costs and significant related morbidity and mortality. It includes superficial incisional, deep incisional, organ or space surgical site infections occurring in any area of the body other than skin, muscle and surrounding tissues that were involved in the surgery. In this study, 3.33% had surgical site infections that were treated through daily wound cleaning and dressing, and antibiotics administration. The proportion of wound infection reported in this study is similar to that in Canada where 2.6% of wound infections were reported[3].

The goal of radical nephroureterectomy is complete resection of the tumour with tumour free margins and avoidance of intra-operative tumour rupture or spillage. This intra-operative spillage could increase risk of peritoneal seeding, upstaging of the tumour and a further recurrence. In this study, 3.3% rate of tumour rupture was reported intraoperatively due to surgical manipulation. In China, 4.5% of the patients had tumor rupture that could be attributed to fact that most patients presented in stage III[10]. However, much higher (21%) tumor spillage proportions were reported in South Africa[17] that was attributed to the fact that the patients presented with large tumors.

The mean duration of stay in the surgical ward was 6.5 days which compared to a Pakistani study that reported 6.89 days[13]. Both studies were conducted in LMICs that may be experiencing similar health challenges. The duration of stay in the surgical ward was significantly associated with the duration of patient's symptoms.

CONCLUSIONS AND RECOMMENDATIONS

This study reports favourable early surgical outcomes among children with Wilms' tumour who underwent nephrouretectomy. There is need for further studies conducted to determine reasons for late presentation among children with Wilms' tumour. Furthermore, there is need to create and intensify awareness on Wilms Tumour to enable prompt medical attention for children with an abdominal mass.

ACKNOWLEDGEMENTS

We would like to thank the Lecturers at Moi University School of Medicine and Consultant Surgeons at Moi Teaching and Referral Hospital who care and manage Wilms tumor patients. Furthermore, we would like to thank the hospital's management for allowing us to conduct the study, the study participants and their parents for agreeing to take part in this study.

REFERENCES

1. Axt J, Abdallah F, Axt M, *et al.* Wilms Tumor Survival in Kenya. *J Pediatr Surg* 2013; **48**: 1254–62.
2. Abdur-Rahman LO, Hitchcock R. Paediatric surgery; A comprehensive text for Africa. *Ist Ed Glob Help Benin City* 2002; : 581–9.
3. Hall G, Grant R, Weitzman S, Maze R, Greenberg M, Gerstle JT. Predictors of surgical outcome in Wilms' tumor: a single-institution comparative experience. *J Pediatr Surg* 2006; **41**: 966–71.
4. Kieran K, Ehrlich PF. Current surgical standards of care in Wilms tumor. *Urol Oncol* 2016; **34**: 13–23.

5. Ritchey ML, Shamberger RC, Haase G, Horwitz J, Bergemann T, Breslow NE. Surgical complications after primary nephrectomy for Wilms' tumor: report from the National Wilms' Tumor Study Group. *J Am Coll Surg* 2001; **192**: 63–8; quiz 146.
6. Israels T, Borgstein E, Pidini D, *et al.* Management of children with a Wilms tumor in Malawi, sub-Saharan Africa. *J Pediatr Hematol Oncol* 2012; **34**: 606–10.
7. Tenge CN, Were PA, Aluoch LH, Wekesa JW, Patel K, Kuremu RT. Management and Outcome of Patients with Wilms' Tumour (Nephroblastoma) at the Moi Teaching and Referral Hospital, Eldoret, Kenya. *East Afr Med J* 2012; **89**: 121–7.
8. Njuguna F, Martijn HA, Kuremu RT, *et al.* Wilms tumor treatment outcomes: perspectives from a low-income setting. *J Glob Oncol* 2017; **3**: 555–62.
9. Wilde JC, Lameris W, van Hasselt EH, Molyneux EM, Heij HA, Borgstein EG. Challenges and outcome of Wilms' tumour management in a resource-constrained setting. *Afr J Paediatr Surg* 2010; **7**: 159–62.
10. Yao W, Li K, Xiao X, *et al.* Outcomes of Wilms' tumor in eastern China: 10 years of experience at a single center. *J Invest Surg* 2012; **25**: 181–5.
11. Anyanwu L-JC, Atanda AT, Atanda JO. Wilms' tumour in African children: Can an institutional approach improve outcome? *African J Paediatr Surg AJPS* 2015; **12**: 7.
12. Ekenze SO, Agugua-Obianyo NE, Odetunde OA. The challenge of nephroblastoma in a developing country. *Ann Oncol* 2006; **17**: 1598–600.
13. Sarin YK. Short term surgical outcomes of Wilms tumour from a single institute. *JPMA* 2019.
14. Paya K, Horcher E, Lawrenz K, Rebhandl W, Zoubek A. Bilateral Wilms' tumor--surgical aspects. *Eur J Pediatr Surg* 2001; **11**: 99–104.
15. Safdar CA, Aslam M, Awan SH, Ahmed I, Badshah S. Wilms' tumour: a comparison of surgical aspects in patients with or without pre-operative chemotherapy. *J Coll Physicians Surg Pak* 2006; **16**: 521–4.
16. Sarin YK, Bhatnagar SN. Wilms' tumor-roadmaps of management. *Indian J Pediatr* 2012; **79**: 776–86.
17. Hadley GP, Shaik AS. The morbidity and outcome of surgery in children with large pre-treated Wilms' tumour: size matters. *Pediatr Surg Int* 2006; **22**: 409–12.
18. Fuchs J, Kienecker K, Furtwangler R, *et al.* Surgical aspects in the treatment of patients with unilateral wilms tumor: a report from the SIOP 93-01/German Society of Pediatric Oncology and Hematology. *Ann Surg* 2009; **249**: 666–71.
19. Ritchey ML, Kelalis PP, Etzioni R, Breslow N, Shochat S, Haase GM. Small bowel obstruction after nephrectomy for Wilms' tumor. A report of the National Wilms' Tumor Study-3. *Ann Surg* 1993; **218**: 654–9.
20. Seseke F, Zoller G, Ringert RH. Wilms' tumor--single-center experience with renal surgery. *Scand J Urol Nephrol* 2004; **38**: 373–7.