Original Article

A 5-Year Multidisciplinary Care Outcomes in Children with Wilms' Tumour Managed at a Tertiary Centre: A Retrospective Observational Study

Felix M. Alakaloko[1], Adeseye M Akinsete[2], Justina O. Seyi-Olajide[1], Adedayo O Joseph[3], Olumide O. Elebute[1,4], Oluwaseun A. Ladipo-Ajayi[1], M. Olatokunboh Odubanjo[5], Omodele A. Olowoyeye[6], Adesoji O. Ademuyiwa[1,4], Edamisan O. Temiye[2], Adebola A Akinsulie[2], Christopher O. Bode[1,4]

[1]Pediatric Surgery Unit, Department of Surgery, Lagos University Teaching Hospital, [2]Paediatric Hematology & Oncology Unit, Department of Pediatrics, College of Medicine, University of Lagos/Lagos University Teaching Hospital, [3]Lagos University Teaching Hospital (LUTH) Cancer Center and Nigerian Sovereign Investment Authority (NSIA), Lagos University Teaching Hospital, [4]Paediatric Surgery Unit, Department of Surgery, College of Medicine, University of Lagos & Pediatric Surgery Unit, Department of Surgery, Lagos University Teaching Hospital, [5]Department of Anatomic and Molecular Pathology, College of Medicine, University of Lagos/ Lagos University Teaching Hospital, [6]Department of Radiology, College of Medicine, University of Lagos, Lagos

Abstract

Background: Over the last two decades, there has been significant improvement in the outcomes of children with Wilms' tumour (WT) in high income countries (HICs) with approximately 85% survival rate globally. This is partly attributable to a multi-disciplinary team approach to care and the evolution of more robust treatment measures. A previous review in our centre prior to multi-disciplinary team shows a survival rate of 31.48%, However, the survival rates from low- and middle-income countries are still low when compared to HICs due to delays in access to care at all levels, poor to non-existent health insurance coverage, limited workforce resources, weak health-care systems and infrastructure. The aim of this study is to determine the impact of a multi-disciplinary team approach on the treatment outcomes of children with WT. **Methodology:** This is a 5-year retrospective review of all patients managed with WT at the Lagos University Teaching Hospital, Lagos, Nigeria. Information was extracted from the patients' case notes, operation notes and ward admission records. The data were analysed with SPSS 25, and $P < 0.05$ was considered to be statistically significant. **Results:** Forty patients were included in the study; male to female ratio was 1.6:1. The disease occurred in the right kidney in 23 patients (57.5%) and on the left in 17 patients (42.5%). The average duration of symptoms before presentation was 3.6 months (range 1–7 months), majority of patients presented with abdominal masses and were assessed as per unit protocol with abdominal Computerized tomography scan, chest X-ray and abdominal ultrasound scan to assign the patient International Society of Paediatric oncology regimen. The predominant stage at surgery was Stage III 26 (65%), while Stage IV was 9 (22.5%). Morbidity after chemotherapy was 10 (25%). Twenty-five patients (63%) completed chemotherapy while 15 patients (37%) started chemotherapy but defaulted midway. The 5-year survival rate was 75%. Increasing age and male sex were associated with reduced odds of mortality; however, this was not statistically significant. Increased duration of treatment, being treated with chemotherapy alone, as well as advanced tumour stage and histology were associated with increased odds of mortality, however, this was not statistically significant. **Conclusion:** The development of an institutional WT treatment pathway involving a multidisciplinary team has resulted in improved outcomes. There is need for increased community awareness to improve the time to presentation.

Keywords: Barriers to early presentation, multidisciplinary team, survival, Wilms' tumour

Introduction

Wilms' tumour (WT, Nephroblastoma) is a malignant embryonal neoplasm derived from nephrogenic blastemal cells that both replicates the histology of developing kidneys and often shows divergent patterns of differentiation.

Address for correspondence: Dr. Felix M. Alakaloko, Department of Surgery, Pediatric Surgery Unit, Lagos University Teaching Hospital, Lagos, Nigeria.
E-mail: felixalakaloko@gmail.com

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Classical WT is triphasic and comprises three histological components - blastemal, epithelial and stromal components. It is the most common paediatric renal malignancy and has a racial predilection worldwide; it is more common in African-Americans than whites and least common among the orientals.[1] The incidence in Nigeria is unknown because of non-availability of complete data but the reported incidence worldwide is about 4–10/million.[2]

The treatment of WT in low- and middle-income countries is limited by challenges of delayed presentation, low health insurance coverage, poverty, inadequate workforce and support infrastructure.[3,4] On the contrary, in high-income countries (HICs), treatment of children with WT has evolved with use of genetic markers for risk stratification in addition to the employment of targeted therapy to reduce adverse effects in low risk disease and improve overall outcome in high risk disease. This has resulted in increased survival rate approaching 90% for exclusively abdominal tumour and 70% for metastatic disease.[5]

The multi-disciplinary approach to the treatment of WT is poorly developed in most tertiary centres in Nigeria. A previous review over the last decade in our centre prior to the introduction of multi-disciplinary team approach shows a WT survival rate of 31.48%.[6]

The aim of this study is to determine the impact of a multi-disciplinary team approach on outcome of treatment of children with WT.

Methodology

This was a retrospective review of patients that presented to the Lagos University Teaching Hospital with histologic diagnosis of WT between January 2014 and December 2018. Our hospital is the major referral centre in Lagos, a city with a population estimate of 20 million people, 45% of whom are children. Ethical clearance was obtained from the hospital's Health Research Ethics Committee. Data were extracted from patients' case notes, operation notes and ward admission records. Information retrieved included age, gender, duration of symptoms before presentation, source of referral, side of the lesion, duration of follow-up, the insurance status of patients, treatment modality and outcome. The treatment groups were chemotherapy and surgery (CAS), chemotherapy, surgery and radiotherapy.

Outcome measures are mortality, disease recurrence, survival, complete response with no residual tumour and patients lost to follow-up.

Measures of outcome during follow-up are disease-specific survival, progression-free survival and overall survival. The analysis was with Statistical Package for Social Sciences Statistics IBM Version 25 (Armonk- New York USA). and *P* value was set at <0.05.

The multi-disciplinary team included the paediatric surgeon, paediatric oncologist, radiation oncologist, radiologist, renal pathologist, nutritionist, nurse and pharmacist. The team meets twice every month to review the new patients and debrief on ongoing cases as well as discharge summaries. The institutional algorithm utilises the International Society of Paediatric oncology (SIOP) treatment protocol. Patients are risk-stratified into low risk and high-risk disease. Low risk diseases are Stages 1 and 2 while high risk diseases for our setting are Stages 3–5. All the patients had screening abdominal ultrasound scans, chest radiographs and abdominal Computerized tomography or magnetic resonance scan as well as pre-treatment baseline blood investigations. All the patients were reviewed by the surgical team within 48 h of presentation and 1 week by the radiation oncologists. The risk stratification for each patient was assigned by the team. The treatment plan was then agreed for each patient. The institutional protocol is that all patients with Stages 2 and above received pre-operative chemotherapy for 6 weeks utilising the SIOP protocol. Those with moderate size Stage 1 disease received upfront resection and adjuvant chemotherapy. The patients with anaplastic type have doxorubicin added to their drugs while those with favourable histology utilise vincristine and Actinomycin D. The histopathology of tumour is reported according to Vujanic and Sandstedt.[7]

- Stage I tumour. (A) Viable tumour at the same level as peri-renal fat, suggesting the tumour was extra-renal, but now covered by a pseudocapsule, hence, still Stage I. (B) Non-viable tumour thrombus in the renal sinus vessel. (C) Chemotherapy-induced changes in the renal sinus (note a large nerve, confirming it is the sinus). (D) Chemotherapy-induced changes in the peri-real fat are not regarded as a criterion for Stage II. Viable tumour is always taken into account for staging. (A) Stage II: Viable tumour thrombus in a renal sinus vessel. (B) Stage II: Viable stromal thrombus showing similar features as the main tumour
- Stage III tumour. (A) Chemotherapy-induced changes at the inked resection margin. (B) Non-viable tumour thrombus at the resection margin of the renal vein. (C) A part of a lymph node is replaced with non-viable tumour. (D) Non-viable blastema at the inked resection margin
- Stage III: Viable tumour presents at the inked resection margins. (E) Stage III: Viable lymph node metastasis.

The overall treatment period spans between 6 months and 1 year depending on risk stratification. Surgery follows on between weeks 7 and 8 for most of the patients. We use the en bloc tumour delivery before vascular pedicle ligation otherwise called the 'tumour delivery technique'[8] as often as possible when there is little or no adhesions. The patient is positioned supine after general anaesthesia is administered and a small sandbag is placed under the ipsilateral flank for slight elevation of the renal bed. Access is through a wide transverse muscle cutting incision from the tip of the ipsilateral 12th rib which extends towards the midline, midway between xiphoid process and the umbilicus. The incision could be extended to the contralateral side for adequate exposure in large tumours.

We then make a gentle reflection of the small bowel towards the contralateral side while the colon is medially mobilised after incision of the white line of Toldt. Subsequently, peritoneal attachments of the spleen or liver are divided depending on the side. The ureter is identified and traced to the renal pelvis. A surgical plane is formed between the posterior aspect of the kidney/renal mass and the musculature of the posterior abdominal wall by blunt careful dissection. Pushing from behind with the whole palm of the hand, the entire renal mass is then delivered through the abdominal wall incision, outside the abdominal cavity, while it is only attached to the major blood vessels by the renal pedicle. Subsequently, the renal hilum is ligated and transected separately with a Satinsky clamp to enable *en bloc* tumour removal, while the ureter is divided and transfixed close to the vesicoureteric junction.

Following surgery, all patients with Stage 3 high risk and above disease had external beam radiation therapy with doses of 25.2 Gy to the flank with boost of 10.8 Gy to the involved lymph nodes for high risk Stage 3 diseases and 14.4 Gy to flank with boost of 10.8 Gy to involved lymph nodes for intermediate risk Stage 3 disease. Whole lung irradiation to 15 Gy is employed for low to intermediate risk Stage IV disease with lung metastases not resolved after initial chemotherapy; or for high risk Stage IV disease. Radiation treatments are delivered through intensity-modulated radiotherapy/ volumetric-modulated arc therapy using a linear accelerator.

Most children are successfully simulated and treated without any sedation as we utilise the play and behavioural therapy to help children cope with the processes of immobilisation for simulations and treatments. Young children (below 2 years old) may require sedation by anaesthesiologist according to unit protocols in addition to continued play therapy.

Results

In the 5-year study period, data were completely retrieved for 40 patients with WT who presented with clinical and radiological features of WT and were treated and followed up in the clinic. Fifteen (37.5%) of the patients were lost to follow-up following their initial treatment.

There were 25 males and 15 females (ratio 1.6:1) with a mean age of 3.9 ± 2.9 years (range 6 months to 12 years). Twenty-three (57.5%) had right-sided tumour and 17 (42.5%) had left-sided. There was no case of bilateral disease during this review.

The average duration of symptoms was 3.6 (range 1–7) months. All patients had an abdominal ultrasound scan, computerised tomography scan and chest radiographs prior to the commencement of therapy. The most common presentation was an abdominal mass [Figure 1]. The pre-dominant stage at presentation was Stage 3. There were no record of Stages 1 and Stage 5 during the study period.

The comparison of features and outcomes of WT in different local studies from Nigeria is shown in Table 1. There is an

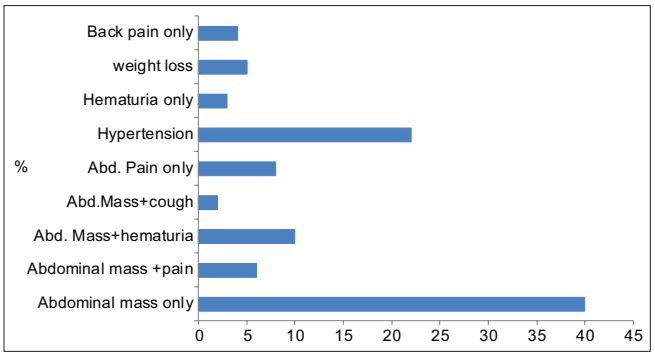

Figure 1: Clinical presentation spectrum

improvement with about 63% of patients completing their chemotherapy courses and this correlates well with an actuarial overall 5-year survival of about 75%.

The mean survival time was about 7 times higher for patients who were treated with both CS ($P < 0.001$) [Table 2]. Age of 4 years or less, treatment duration of 5 months or less and being treated with chemotherapy alone, as well as advanced tumour stage and histology were associated with increased odds of mortality, however, this was not statistically significant. Male sex were associated with reduced odds of mortality, however, this was not statistically significant as well [Table 3].

Table 4 shows that there was a statistically significant correlation between the stage of the disease and the outcome ($P = 0.001$) as outcome is better with low risk stage. The duration of symptoms prior to presentation and outcome had a positive correlation with the outcome ($P = 0.001$).

There was no significant correlation between the age at presentation and the outcome ($P = 0.577$). Only 4 (10%) of our patients were enrolled on health insurance policy. This did not have statistical significance on the outcomes. One patient had a relapse following CAS. The histologic grade shows SIOP I, II and III were 4 (10%), 8 (20%) and 23 (57.5%), respectively, while Anaplastic type was 5 (12.5%).

Discussion

The management of WT in Nigeria has evolved over the last two decades. There is a steady increase in the incidence in WT in our centre; from two cases per year reported by Elesha and Abdukareem[9] in 1999, 35 cases in 5 years reported by Akinsulie *et al*.[10] in 2005. The relatively small number seen in these series may also be due to incomplete data set for some of the patients as well as varying periods of industrial actions engaged by different hospital workforce leading to truncation of services in the hospital. They also had a survival rate of <50% in this review. The mean age of presentation of 37 months is similar to reported mean age of 43 months in girls and 37 months in boys.[11] However, less than that was observed in a study from Northern-Nigeria.[12] Out of the 40 cases in our study 21 (52.5%) were at least 3 years old. A study from the United Kingdom Children's Cancer, WT study group

Table 1: Comparison of outcomes in Wilms from regional studies in Nigeria[9]

Characteristics	LUTH review	Osuoji *et al*.	Uba *et al*.	Ekenze *et al*.	Abubakar *et al*.
n	40	35	32	42	44
Age (mean) years	3.9	3.4	4.0	4.1	3.0
Male: female	1.6:1	1.5:1	1.9:1	1.1:1	1:1.4
Mean duration of symptoms (months)	3.6	3.5	Late	4.7	Late
Pre-dominant stage	III	III	IV	III	IV
Percentage of patients that completed chemotherapy	62.8	14.3	37.5	42.9	3.7
Percentage outcome (alive) after 5 years	75	14.3	18.8	23.5	Nil

Table 2: KaplanMeier survival analysis on patient treatment group

Treatment	Died, *n* (%)	Survived, *n* (%)	Survival time (months), mean±SE	95% CI		*P*
				Lower bound	Upper bound	
Chemotherapy only	7 (70.0)	3 (30.0)	7.8±1.53	4.8	10.8	<0.001
Chemotherapy and surgery	2 (6.7)	28 (93.3)	56.5±2.4	51.8	61.2	

CI: Confidence interval, SE: Standard error

Table 3: Binary logistic regression for predictors of 5 years mortality (R^2=0.79)

Variable	*β*	OR	95% CI		*P*
			Lower bound	Upper bound	
Age (years)					
≤4	0.5	1.7	0.074	37.25	0.751
>4 (reference)	-	-			
Duration of treatment (months)					
≤5	21.4	1.9×10^9	0.0		0.999
>5 (reference)	-	-			
Sex					
Female (reference)	-	-			
Male	−0.50	0.61	0.019	19.54	0.780
Treatment					
Chemotherapy and surgery (reference)	-	-			
Chemotherapy alone	1.41	4.07	0.042	393.21	0.547
Stage					
Stage 2 (reference)	-	-			
Stage 3	17.9	5.8×10^7	0.0	-	0.999
Stage 4	19.7	3.5×10^8	0.0	-	0.999
Histology					
SIOP I (reference)	-	-			
SIOP II	−0.1	1.0	0.0	-	1.000
SIOP III	18.0	6.4×10^7	0.0		0.999
Anaplastic	18.4	9.4×10^7	0.0	-	0.999

CI: Confidence interval, SIOP: International Society of Pediatric Oncology

demonstrated that advanced age is associated with poorer prognosis.[13] In this study, there was no association between age of presentation and the outcome ($P = 0.577$). Our finding was corroborated by a report from Durban South Africa that age is not a prognostic factor in WT beyond Stage 1 in Africa.[14]

Our study shows a slight male preponderance which is similar to other studies around Africa; however, there was no statistically significant association between gender and outcome in our study.[15-17]

In concordance with other studies in Nigeria, delayed presentation was prevalent among our patients.[16,17] Delayed presentations in our study population, suggests barriers to presentation due to ignorance and poverty. There is primary and secondary delay. Parents with low socioeconomic class have a poor health seeking behaviour as well as financial incapability. In addition, the symptoms of WT are often initially subtle and not incapacitating thus delaying presentation at an adequate care facility. The practice of unorthodox medicine by traditionalist who prescribes herbal concoctions further

Table 4: Treatment outcomes in children with Wilms tumor and influence of duration of symptoms before presentation, health insurance status and disease stage at presentation

Outcome factors	Died, *n* (%)	Lost to follow up	Discharged	Relapse/progression	*P*
Disease stage					
Low**	2 (5)	14 (35)	14 (35)	1 (2.5)	0.001*
High$^{\infty}$	7 (17.5)	1 (2.5)	1 (2.5)	0 (0)	
Duration of symptoms prior to presentation (months)					
<3	1 (2.5)	9 (22.5)	14 (35)	0 (0)	0.001*
>3	8 (20)	6 (15)	1 (2.5)	1 (2.5)	
Health insurance status					
Has NHIS	0 (0)	1 (2.5)	3 (7.5)	0 (0)	0.161
No NHIS	9 (22.5)	14 (35)	12 (30)	1 (2.5)	

*Statistically significant, **Stages 1 and 2 tumor, $^{\infty}$Stages 3-5 tumors. NHIS: National Health Insurance Scheme

contributes to the primary delay. There is a role of ignorance and the vicious cycle of poverty and the effect of catastrophic out of pocket spending among parents who often have a large family size worsens the health-seeking behaviour. The role of a poorly developed referral system may have contributed to the late presentation in our environment.

Osuoji *et al*.[15] reported similar mean duration of symptoms probably because their institution and ours are both government hospitals located in the same city and possibly serving the same socioeconomic class. However, Atanda *et al*.[16] from Northern Nigeria reported a mean duration of about 9 months with Ekenze *et al*.[17] from Eastern Nigeria reporting 4.7 months.

The pre-dominant stage of WT seen in HICs is Stage 1 and 2, but most reported studies from Africa shows a pre-dominance of Stages 3 and 4 at presentation.[18] Two-thirds of our patients had Stage 3 disease which was associated with poor outcome (P = 0.001). This is similar to the finding in the UKW3 trial.[19]

The development of a hospital multi-disciplinary treatment pathway for diagnosis and treatment of patients has positively improved treatment compliance and outcome. These units were functioning mutually exclusive of each other in the past and as such, there were few communication gaps in galvanising scarce resource optimally. The institutionalising of treatment protocol through the development of a hospital Wilms' multi-disciplinary team which meets to discuss individual patients' treatment plan and pathway of care resulted in a more inclusive care from the units and ultimately an improvement in the outcome of patients. Those who have completed treatment and are disease free now works as advocates who motivate new patients' relatives for enhanced treatment compliance and therapy completion. This used to be a major challenge with patients management in the past.

The disease-free survival rate at 5-year post-treatment was 31.48%[8] in a previous study from this institution with only about 50% of patients completing their treatment schedule. Sixty-three per cent of our patients now complete their treatment. This could be due to the elaborate multidrug therapy, involvement in counselling of caregivers prior to commencement of therapy. We have also been able to secure some grants from non-governmental organisations which has enabled completion of chemotherapy and ultimately improved outcomes.

We adapted a modification of the SIOP regime in that for Stage 1 disease with a moderate size tumour, we operate upfront then follow with adjuvant chemotherapy, while the other stages are managed strictly according to the SIOP protocol.[20] This strategy has enabled the patients to get the benefit of having all members of the team outlying treatment sequence with the allocated time sequence for each segment. Thus, most patients have been completing therapy with this strategy. This approach has also improved the outcome of WT in our centre as 75% survival at the end of therapy was recorded in this study compared to only 11% in the previous study.[10]

Follow-up of patients has been through telemedicine which includes phone calls and creation of WT WhatsApp chat room for dissemination of information. The lessons learnt using telephone as contact tracing tool during the Ebola and more recently COVID-19 pandemic has been adapted to our patient follow up care.

Conclusion

In the management of WT, a synergistically coordinated institutional protocol directly improves patients' outcome, increase patients' compliance to chemotherapy and sustain follow-up. There is however an urgent need for reduction in pre-hospital delay through community awareness programmes with support groups.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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