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Research Article

Nephroblastoma: Profile and Management Outcome in a Tertiary Hospital in a Developing Country - a

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ABSTRACT

Objective: The objective of this study was to evaluate the profile and management outcome of children treated for Wilms' Tumor (WT) in a developing country.

Methodology: This was a retrospective study of children that were treated for WT at the pediatric surgery unit of Enugu State University Teaching Hospital (ESUTH), Enugu, Nigeria. Medical records of children who underwent treatment for WT over a 5-year period were evaluated.

Results: Twenty one cases of WT were treated during the study period with an age range of 3-12 years (median 4.5 years) and male to female ratio of 1:1.3. The median duration of symptoms prior to presentation was 6 months and the mean duration of hospital stay was 24.2 days. All the patients presented with abdominal mass and they all had abdominal ultrasound and chest x-ray. Five (23.8%) patients had metastasis at presentation and majority of the patients were in stage 3. Surgery with adjuvant chemotherapy plus radiotherapy was received by most of the patients. Survival rate as at 5 years follow up period was 66.7%.

Conclusion: There is still significant morbidity and mortality associated with the management of WT in resource-constrained environment.

Keywords: Nephroblastoma; Outcome; Pediatric; Resource-limited; Wilms' tumour

INTRODUCTION

Nephroblastoma, or Wilms' Tumor (WT), is an embryonal tumor of renal origin and is the most common genitourinary malignant tumor in children [1]. Overall, WT accounts for 7% of all childhood cancers and 90% of all pediatric tumors of the kidney [2]. WT is mostly unilateral however bilateral WT occurs in about 5% to 8% of patients [3]. In adults, WT accounts for less than 1% of all renal tumors [4]. Clinical presentation of WT typically involves an asymptomatic abdominal mass that is discovered incidentally by the parent, caregiver or primary care physician. Other clinical features, which are nonspecific, include microscopic or gross hematuria, hypertension, abdominal pain and fever [5]. Imaging investigations for WT entail abdominal ultrasound, Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI). However, CT scan should be performed with caution in children because of the long term adverse effects of radiations in children. Treatment of WT includes surgery, chemotherapy with or without radiotherapy. There are two treatment protocols for WT: The Children Oncology Group-National Wilms' Tumor Study Group (COG-NWTSG) protocol of upfront surgery and International Society for Pediatric Oncology (SIOP) protocol of upfront chemotherapy. We follow the COG-NWTSG protocol for the management of our patients. For best results, treatment of WT should be multidisciplinary involving the surgeon, pediatrician, radiologist, oncologist and pathologist [6]. Risk stratification of patients with WT fine tunes management and minimizes treatment toxicity [1]. Although there are many studies on WT conducted globally, there is paucity of studies on WT in Enugu, Nigeria. Hence, we conducted this study to evaluate the profile and management outcome of children treated for WT in a teaching hospital in Enugu, Nigeria.

METHODS

This was a retrospective study of children aged 15 years and below that had treatment for WT (histologically confirmed) between September 2007 and October 2012 at the pediatric surgery unit of Enugu State University Teaching Hospital (ESUTH) Enugu, Nigeria. Patients with incomplete medical records were excluded from the study. Patients who have had laparotomy for WT in a peripheral hospital and presented with a histological report of WT for further treatment were included in the study. ESUTH is a tertiary hospital located in Enugu, South East Nigeria. The hospital serves the whole of Enugu State, which according to the 2016 estimates of the National Population Commission and Nigerian National Bureau of Statistics, has a population of about 4 million people and a population density of 616.0/km2. The hospital also receives referrals from its neighboring states. The research and ethics committee waived ethical approval because of the retrospective nature of the study. This research conforms to the principles of the Declaration of Helsinki. The author certifies that they have obtained patient consent forms. In the form the patients have given their consent for their data to be reported in a journal. The patients understand that their names will not be published and due efforts will be made to conceal their identity.

Pre-operative protocol

On presentation, the patients were clinically evaluated and appropriate investigations requested. The investigations included full blood count and chest x ray. Abdominal and chest computed tomography scans were also requested for those that can afford them. The investigations assisted in preoperative staging of the WT. We follow the NWTSG protocol in managing WT patients.

Intraoperative protocol

Access was through a generous transverse supraumbilical incision. Through a meticulous dissection and early vascular control, the tumor was removed in bulk avoiding tumor spill as much as possible. Any tumor rupture/spill makes the tumor at least stage 3. Intra-operative staging was performed based on the operative findings.

Post-operative protocol

Surgical wound was examined on the 4th day and post-operative chemotherapy started on the 14th day if there is adequate wound healing. The number of courses of chemotherapy and drug combinations depended on the intra-operative tumor stage.

Data collection

Information was gotten from the case notes, operation notes, operation register, and admission-discharge records. The information obtained are the age, gender, presenting symptom, duration of symptoms before presentation, time interval between presentation and treatment, treatment offered, complications of treatment, duration of hospital stay, histological type and outcome of treatment. The mean period of follow up was for 60 months.

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Data analysis

IBM Statistical Package for Social Science (SPSS) for windows version 23 (IBM Corp., Armonk, NY) was used for data entry and analysis. Data were expressed as percentages, median, mean, and range.

RESULTS

Patients' demographics

Twenty three cases were treated during the study period but only 21 cases have complete case records and formed the basis of this report. The demographics are depicted in table 1.

Clinical features

All the patients presented with abdominal mass. In addition to abdominal mass, the patients presented with abdominal pain, fever, hematuria and hypertension in various combination (Table 2). Associated abnormalities such as aniridia and hemihypertrophy were not found in any of the patients. Although WT can occur as part of some syndromes such as WAGR syndrome, Denys-Drash syndrome and Beckwith-Wiedemann syndrome: Chromosomal analysis for the genetic mutations of these syndromes was not done due to absence of the necessary facilities.

Laboratory and imaging investigations

Fifteen (71.4%) patients had a hemoglobin level of less than 10 grams per deciliter (g/dl) whereas 6 (28.6%) patients had hemoglobin level of greater than 10 g/dl. All the patients had abdominal ultrasound and chest/abdominal x ray. Five (23.8%) patients had CT scan. None of the patients had MRI. Figures 1,2 shows radiograph and CT scan of one of the patients.

Metastasis at presentation

Based on the clinical evaluation and investigation results, 5 (23.8%) patients had evidence of metastasis. Three (14.3%) metastasis were to the lungs, one (4.8%) each to the spine and tibia bone.

Stage and side of the tumors

Using the NWTSG staging system, 7 (33.3%) patients were in stage 2, 9 (42.9%) patients were in stage 3 and 5 (23.8%) patients were in stage 4. There was no stage 1 tumor. Twelve (57.1%) tumors were left sided while 9 (42.9%) tumors were right sided. There was no bilateral tumor.

Table 1: Demographic characteristics of the patients.

Gender	
Female	12 (57.1%)
Male	9 (42.9%)
Median age of the patients	4.5 years (range: 3-12)
Median duration of symptoms prior to presentation	6 months (range: 2-10)
Median duration from presentation to treatment	3 days (range: 1-5)
Mean duration of hospital stay	24.2 days (19-35)
Mean interval between operation and tumor recurrence	16 months (8-23)

Table 2: Clinical features of the patients.

Clinical features	Number of patients (%)
Abdominal mass + abdominal pain	7 (33.3)
Abdominal mass + hematuria	6 (28.6)
Abdominal mass + abdominal pain + fever	4 (19.0)
Abdominal mass +abdominal pain + hypertension	3 (14.3)
Abdominal mass + hematuria + hypertension	2 (9.5)

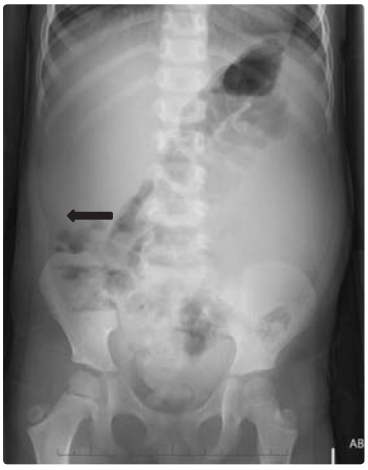

Figure 1: Plain radiograph (anterior-posterior view) of the abdomen of one of the patients showing left Wilms' tumor. The left tumor mass show as soft tissue shadow on the left flank (black arrow) and displaces the bowel (white arrow) towards the right side.

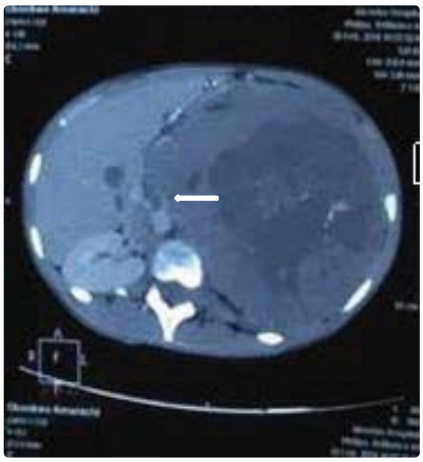

Figure 2: Coronal helical image slice Computed Tomography (CT) scan of the abdomen of one of the patients. CT scan showed a left Wilms' tumor (white arrow) affecting the upper pole and pushing the rest of left kidney to the periphery.

Treatment received to the patient

Nephroureterectomy was the surgery performed on the patients. All the patients had surgery and chemotherapy. Vincristine and dactinomycin were the first line drugs used for chemotherapy. Cyclophosphamine and Adriamycin were added when there was tumor anaplasia and when tumor is advanced (stage 3 and above). The number of courses of chemotherapy and the combination of therapy depended on the stage and histology of the tumor. Radiotherapy was administered in cases of stage 3 and stage 4 tumors. The combination of therapies received by the patients is shown in table 3.

Complications of treatment

Some of the patients had more than one complication. The predominant complications developed by the patients are shown in

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figure 1. For the purposes of this study, excessive bleeding was defined as loss of more than 50% of the patient's blood volume requiring blood transfusions.

Histopathological sub-types

WT is triphasic and consists of variable proportions of blastema, stroma and epithelial elements. One element may be more or less than the other. The predominant histopathological sub-types and favorable/unfavorable types of the patients' WT are shown in table 4.

Outcome of treatment

Out of the 21 patients, 14 (66.7%) patients completed their treatment and had no tumor recurrence as at 5 years follow up period. The tumor histopathological type of these 14 patients was of favorable type. Two (9.5%) patients were lost to follow up after surgery and could not complete their adjuvant chemotherapy. Five (23.8%) patients developed tumor recurrence and expired. Unfavorable (anaplastic) type was characterized by the presence of large atypical multipolar mitotic figures and enlarged and hyperchromatic nuclei (Figure 4). Tumor recurrence was discovered through clinical examination and confirmed by abdominal ultrasound. Out of the 5 patients that died, all of them had unfavorable histology and were in stage 4 Wilms' tumor. Currently, there is an improvement in the survival rate of children with Wilms' tumor; the exact data is being collated.

Table 3: Treatment.

Treatment	Number	Percentage
Surgery plus adjuvant chemotherapy	7	33.3
Surgery plus adjuvant chemotherapy plus radiotherapy	14	66.7

Table 4: Histological sub-types of WT in the patients.

Predominant Histological type	Number	Percentage
Stromal	9	42.9
Blastemal	7	33.3
Epithelial	5	23.8
Favorable/Unfavorable Histology		
Favorable	14	66.7
Unfavorable	7	33.3

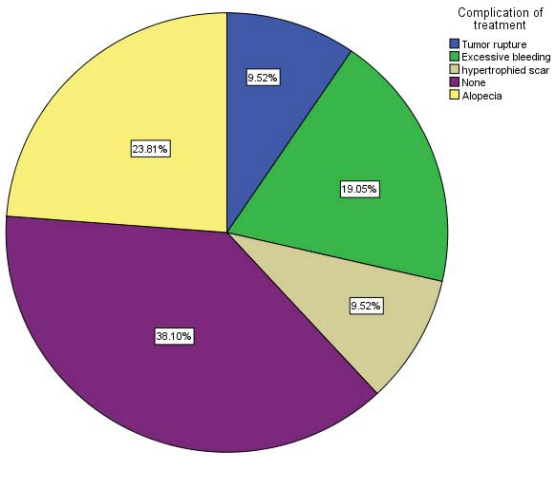

Figure 3: Pie chart showing complications of treatment.

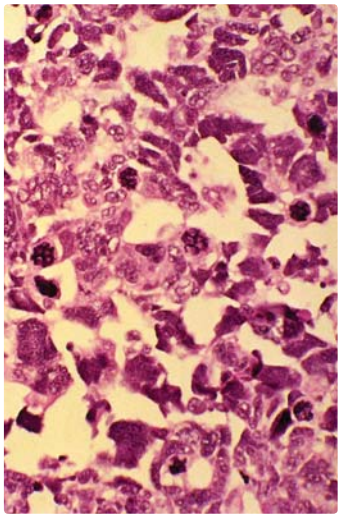

Figure 4: Photomicrograph of Wilms' tumor showing enlarged hyperchromatic giant nuclei (white arrow) of anaplasia and stromal cells (black arrow) (H &E, X100 magnification).

DISCUSSION

WT is the second most common intra-abdominal malignant tumor in children after neuroblastoma and WT arise from foci of persistent metanephric cells referred to as nephrogenic rests [5,7]. Formation of collaborative study groups and multimodal therapy has made dramatic advances in the management of WT [8]. However, in developing countries, late presentation, malnutrition, poverty and lack of multidisciplinary collaboration affect the treatment outcome of children that have WT [9,10]. The two comprehensive collaborative groups that have studied WT are the Children's Oncology Group (COG) and International Society of Paediatric Oncology (SIOP).

Female predominance recorded in the present study is consistent with the report of other studies [11,12]. However, other studies are not in agreement with this finding [10,13]. The male/female predominance may depend on geographical area of study. WT has no significant gender predilection; its incidence and median age at diagnosis are 1 in 10,000 and 3.5 years respectively [11]. This is at variance to the median age of 4.5 years reported in the present study. Elayadi, et al. [14] reported a median age of 5.25 years. Again, Chukwubuike et al reported a case of Wilms' tumor in a 12-year-old Nigerian female [15]. These differences may be explained by differences in race. It took an average of 6 months from the time the abdominal mass was noticed to when the parents presented to the hospital. This late presentation may explain why none of our patients presented with stage 1 Wilms' tumor. Poverty and ignorance that is prevalent in developing countries could account for this late presentation. A study performed in Lagos, Nigeria reiterated the late presentation of patients that have WT in developing countries [16]. The length of time the patients stayed in the hospital was dependent on the stage of the disease and nature of treatment. Ezomike, et al. [17] reported a mean duration of hospital stay of 31.78 days. This is not in agreement with the finding in the present study. The discrepancies in duration of hospital stay may be explained by the cohorts of patients recruited for the different studies. The interval between operation and tumor recurrence recorded in the present study is in accordance with the report of Wilde, et al. [18]. Most recurrent cases of WT usually occur in the first 2 years following treatment. However, Lee et al

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reported a case of WT recurrence 25 years after radical nephrectomy [19].

Like in the present study, abdominal mass is a consistent feature of WT. Other clinical features such as abdominal pain, hematuria and hypertension were also reported by other studies [1,5,18]. Left WT may also present as left scrotal varicocele [20]. More than two-thirds of our patients had a low hemoglobin level. Anemia in WT may result from hematuria or bleeding into the tumor. Howbeit, there are reports of polycythemia occurring in WT as a paraneoplastic syndrome and could be the only finding at presentation [21]. The presence or absence of pulmonary metastasis is an important consideration in WT staging and treatment. CT scan has been found to be more sensitive than x rays in detecting pulmonary metastasis because of its high spatial and contrast resolution. However, Wootton-Gorges, et al. [22] reported that chest x ray is adequate for the diagnosis or exclusion of pulmonary metastasis in patients with WT. In the present study, there were more chest x rays than CT scan. The cost of CT scan makes it non-affordable to most patients in low-income countries.

Metastasis in WT may depend on the time of patient's presentation. Metastasis to the lungs is the most common site as recorded in the present study. Metastasis to the bone is not common. Majority of our patients presented with stage 3 Wilms' tumor similar to other studies conducted in developing countries [23,24]. Late presentation of the patients may explain the high incidence of stage 3 WT. We found more left sided WT than right sided tumor. This finding is similar to the report of Ledlie, et al. [25]. However, Wilde et al in their series reported more right WT than left WT [18]. The reason for these differences is unknown.

The best treatment outcome of WT is achieved through multimodal treatment which includes surgery, chemotherapy with or without radiotherapy. Surgery is pivotal in the entire treatment protocol: All of our patients had surgery and chemotherapy. In cases of very large and inoperable tumors, chemotherapy was administered to downstage the tumor before surgery. The options of surgery are nephroureterectomy and radical nephrectomy. Treatment of a malignant tumor such as WT may have complications. Tumor rupture/spillage is one complication of WT surgery which should be avoided by careful dissection and mobilization of the tumor mass. Tumor rupture/spillage increase abdominal tumor recurrence by up to 20% [26]. Most children who have WT will receive chemotherapy at some point. Alopecia (hair loss) is the result of the chemotherapy. Qureshi et al reported that 100% of their patients with WT who underwent chemotherapy had alopecia [27]. Excessive bleeding during surgery for WT may be due to acquired von Willebrand disease [28]. As at the 60 months follow up period, the survival rate of the patients was 66.7%. This is comparable to the reports of other researchers in resource-constrained setting like ours [18,23]. This low survival rate is far from what is obtainable in developed countries [2]. Late presentation, inadequate treatment, non-compliance with prescribed treatment and loss to follow up may have contributed to the low survival rate recorded in our patient.

Comparison of clinical characteristics and management outcome of WT in developing and developed countries

In developed countries, children with WT present much earlier with a small impalpable Wilms' tumor that is discovered by imaging investigation. This is unlike what is obtainable in developing countries where the patients present with large tumors (advanced stage tumor) occupying almost the entire abdomen. Lack of awareness and enlightenment on the part of the parents may account for the differences in clinical state of the tumors at presentation. This finding is consistent with the report of Stone, et al. [29].

Management outcome of WT in developing country like Nigeria is different from the outcome gotten from developed country. The overall 5 year-survival in the current study is 66.7%. In contrast, the overall 5 year-survival in developed outcome is approaches 90% [30]. Late presentation and absence of treatment facilities may explain the discrepancies in treatment outcome between developing and developed countries.

In developed countries, the 5 year survival with respect to the stage of the tumor (unfavorable histology) is as follows: Stage 1: 83%; Stage 2: 83%; Stage 3: 65%; Stage 4: 33% [31].

Limitations of the study

This study was limited by the small number of cases. A larger number of cases would have availed better analysis.

This was a retrospective study. A prospective would have provided more information.

Gene analyses of the patients were not done due to non-availability of the necessary facilities.

CONCLUSION

WT is still associated with significant morbidity and mortality in resource-limited environments. Unlike in developed countries where treatment outcome has dramatically improved, outcome in low income setting has remained poor. Improved financing of the health sector by both government and private sector is required for better outcome.

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