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WILMS' TUMOUR: AN 18-YEAR TREATMENT OUTCOME AND CHALLENGES FACED IN MANAGING THIS TUMOUR IN DEVELOPING COUNTRIES.
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ABSTRACT

Background: **The survival rate of nephroblastoma (Wilms' tumour) has significantly improved, but the outcome of managing it in developing countries leaves much to be desired, mortality and morbidities still are high.**

Objectives: **The aim of this study is to review the treatment outcome of nephroblastoma in Nigerian children and to identify factors that play a role in the poor outcome in our setting.**

Materials and Methods: **This is an 18-year retrospective study of children aged 15years with Wilms' Tumour (WT) in two federal tertiary hospitals in northeast Nigeria. Data was obtained from patients' medical records and the operating registers. Kaplan-Meier test was used to estimate the 2- and 5-year survival rate and the Log Rank analysis employed for the significance of survival rate according to the stage of the tumour.**

Results: **There were 44 children, 25 (56.8%) boys and 19 (43.2%) girls in a ratio of 1.3:1 with a median age of presentation of 4 years, and only 3 (6.8%) patients presented in less than 2 months of onset of symptoms. Painless abdominal swelling was the most prominent symptom in 35(79.5%) children followed by weight loss in 15(34.1%). All the patients were managed according to the International Society of Paediatric Oncology (SIOP) protocol. Twenty-five patients (25, 60.9%) had a full course of post operative chemotherapy out of whom 11 (44.0%) of them were referred for radiotherapy. Eight (19.1%) patients defaulted post-operative chemotherapy. Twenty-one (47.7%) patients died; 14(66.7%) of their tumour, and 7(33.3%) from treatment related complications. Thus the overall survival rate was 52.3% after a median follow up of 24.5 months. Two- and 5-year survival rates were 43.2% (CI 28.5-57.8%) and 11.4% (CI 2.0-20.7%) respectively.**

Conclusion: **Our study revealed poor treatment outcome from WT, probably because of associated late presentation and incomplete treatment.**

INTRODUCTION

Wilm'stumour (WT) is anembryonal renal neoplasm in which blastemal, stromal and epithelial cell types appear in different proportions.[1]It was first described by

Wilms' in 1899 and is considered one of the most common malignant abdominal tumours in children and adolescence.[2] Prior to the 1930s when surgery was the only modality of treatment, the outcome was poor.

Over time the treatment outcome improved significantly due to an understanding of the biological characteristics of this tumour and also as a result of the introduction of multidisplinary approach to management of the tumour.3-5.

There is nowhere the impact of multidisplinary management and collaboration between different professional interest study groups is most obvious than in developed countries, where about 90% of patients with WT can now survive for 5 years.6 Unfortunately, survival rates for WT are still very low in developing countries, because the synergy of multidisplisnary management and spirit of collaborative study is still not well established.7.

This may be as a result of lack of dedicated children's oncology centers, insufficient professionals, poor financial support and other social setbacks in most tertiary hospitals in developing countries. Moreover, much of the budgets for health in developing countries are channeled towards prevention of communicable diseases as a priority8and not for treating non-communicable diseases. Our study is focused on the outcome of management, complications, challenges and the 2- and 5-years survival rate of WT in two federal tertiary hospitals in northeast Nigeria from a the perspective of a developing country.

MATERIALS AND METHOD

This is a retrospective study of children below 15-years of age, managed with Wilms' tumour from two tertiary hospitals in north-eastern Nigeria, University of Maiduguri Teaching Hospital and Federal Medical Centre, Yola between January 1999 and December 2016. Data collated from the patients' hospital records and operating register included patients' age, gender, duration of symptoms, clinical features, associated congenital anomalies, tumour stage at presentation according to the International Society of Paediatric Oncology (SIOP) protocol, and imaging reports.

Also collated were the type and the duration of chemotherapy, findings at operation and histology reports complications, and outcomes. The overall 2- and 5-years survival rates were calculated using the Kaplan-Meier test. Notable difference in survival rate based on stage of the tumour was verified with Log Rank test assuming 0.05.

RESULTS

Patients' demography

In all we had 44 cases o Wilms' tumour during the 18years retrospective review. Excluded was a patient with rhabdiod tumour. Thirty-eight (38, 86.4%) patients were from the University of Maiduguri Teaching Hospital, (6, 13.6%) from Federal Medical Centre Yola.

There were 25 (56.8%) boys and 19 (43.2%) girls, in a male to female ratio of 1.3:1. Fifty-two (52.7%) of the patients were under the age of 5-years and the median age of diagnosis was 4years, ranged 7-months-10-years.

CLINICAL PRESENTATION

The average duration of symptom was 4.7months. The duration of abdominal distension was 3months in 10(22.7 %) patients, 4 months in 14(31.8) patients, 5months and above in 20(45.4%) patients. Painless abdominal distension was the most frequent symptom in 35(79.5%), followed by

weight loss in 15(34.1%) of the patients. Other details of the clinical features are shown in Table 1

Table 1

Frequency distribution of clinical features.

Symptoms/signs	No of patients	Percentage
Abdominal swelling	44	100
painless	35	79.5
with pain	9	20.5
Additional features		
weight loss	15	34.1
anorexia	13	29.5
anaemia	11	25.0
constipation	9	20.5
hepatomegaly	8	18.2
ascites	7	15.9
cough	6	13.6
malaise	5	11.4
hypertension	3	6.8
fever	2	4.5
hematuria	2	4.5
Leftvaricocele	1	2.3
convulsion	1	2.3

One, child with WT had sickle cell disease; and no other associated congenital anomalies were found.

Five (11.4%) patients had stage I disease, 9(20.5%) -stage II, 16(36.4%) -stage III, 13 (29.5%) -stage IV, and 1(2.3%) child had stage V disease. Regarding tumour site, 26(59.1%) occurred in the right kidney, 17(38.6%) in the left kidney, and bilateral in 1 (2.3%) patient. Abdominal ultrasound scan was obtained in all the patients. Ultrasonography was capable of localizing the site of the tumour, giving accurate dimensions, revealing any evidence of tumour extension into the right renal vein in 4(9.0%) patients, detecting metastatic deposits in the liver in 9(20.5%) patients, and para-aortic lymph node enlargement in 2(4.5%) patients.

Of the 44 children, only 7(15.9%) had computerized tomography (CT) of abdomen done. Not many could afford to have CT done of the abdomen because of its high cost. Intracaval involvement by tumour was seen on CT of the abdomen in 5(71.4%) patients. There were 6(13.6%) patients with features of pulmonary involvement on routine plain chest X-ray. Intravenous urography (IVU) was available for all the patients; non-excretion of contrast was node sampling, and1(2.4%) patient had bilateral partial nephrectomy.

From the observed in all the tumorous kidneys, except in 2 (4.5%) patients who had prompt excretion of contrast despite the presence of tumour in their kidneys. Supportive heamatological parameters were also obtained in all the patients.

TREATMENT MODALITY

Patients with stages I-II had pre operative vincristine 1.5mg/m2 (maximum dose of 2mg) weekly for 4-weeks and dactinomycin 45ug/kg at week one and three. Those with stages III-IV had pre operative vincristine 1.5mg/m2 weekly for 8-weeks and dactinomycin 45ug/kg (maximum dose of 2mg) at weeks 1, 3, 5 and 7.

Two-thirds of the original dose of chemotherapeutics was administered to 15 patients with body weight less than 70% of the expected. In terms of clinical response to preoperative chemotherapy, in 29 (65.9%) patients tumour shrunk in size by more than 75%, in 11(25.0%) patients, it shrunk by 50%, while no appreciable response was observed in 4(9.1%).

Eventually, 41(93.2%) patients had nephro-ureterectomy performed after 2-weeks of rest from pre operative chemotherapy, while 2(4.5%) patients who had stage III disease died from pre-operative chemotherapy related complications. In one patient the parents declined surgery with the belief that cancers should not be operated and abandoned treatment against medical advice. Total nephro-ureterectomy incorporating lymph node clearance was performed in 35(83.3%) patients, 5(12.2%) patients had debulking surgery with lymph specimens taken during surgery, 32 (78.0%) patients had a favorable histology (i.enon anaplastic, triphasic-epithelial, stromal, blastemal components),and 9(21.9%) had unfavorable histology characterized by pleomorphic, and large hyperchromatic nucleus, abnormal multipolar mitotic figures.

Of the 9 (21.9) patients with unfavorable histology, 7(77.8%) were localized and 2(22.2%) diffused anaplasia. Concerning postoperative chemotherapy, the first dose of chemotherapy was administered 2-weeks after surgery when the wound had healed. In 5(12.3%) patient's post-operative chemotherapy was delayed because the platelet count was low (50×109/l). Patients thathad stages I-II favorable histology received vincristine 1.5mg/m2 on the 1st and 7th day weekly, a total of 12 doses and dactinomycin 15ug/kg every 3weeks, a total of 9 doses.

Total duration of postoperative treatment was 24 weeks. Patients who had stages III-IV disease with favorable histology received dactinomycin 45ug/kg, vincristine 1.5mg/m2 and in addition adriamycine 50mg/m2in 4-6 hours infusion every 6weeks, a total of 5 doses. Total duration of treatment was 28-weeks. Patients who had stages I-IV unfavorable histology received post-operative vincristine, dactinomycin and adriamycin(6doses every 6weeks) for a duration of 35 weeks.

The patients who had diffuse anaplasia had addition of cyclophosphamide 450mg/m2daily for three days. Overall (25, 60.9%) received full course of chemotherapy. Eleven (11) of them received additional radiotherapy. Six (6) patients defaulted because of financial problems, and two patients relocated to a different city. There was recurrence in 4 patients within 26 weeks of completion of post-operative chemotherapy. One of them was only a local recurrence; the others were both local and distant metastasis to the liver and the lungs. Twenty-one (47.7%) patients died; 7(33.3%) from chemotherapy related complications, and 14(66.7%) from tumour related complications (Table 2)

Table 2.

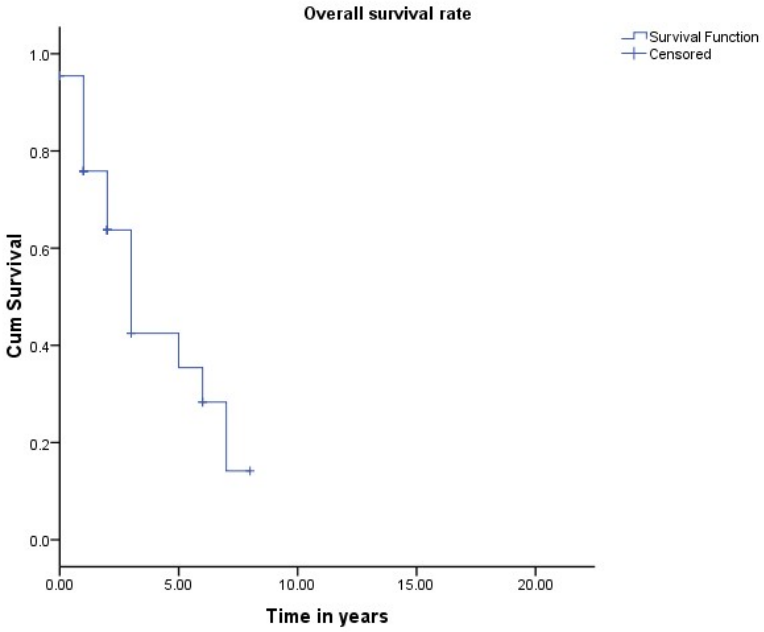
Treatment related complications and outcome

No of patients	Complications	Outcome
7	Diarrhea + Vomiting due to chemotherapy	Survived
5	Thrombocytopaenia due to chemotherapy	Survived
5	Cardiopulmonary failure tumour related	Died
4	Pneumonia + respiratory distress + pleural effusion tumour related	Died
3	Congestive cardiac failure chemotherapy related	Died
2	Renal failure chemotherapy related	Died
2	Hepatic failure+ ascites tumour related	Died
2	Dehydration chemotherapy related	Survived
2	Anaemia + septiceamia chemotherapy related	Died
1	Renal failure due to bilateral nephrectomy	Died
1	Internal hemorrhage tumour related	Died
1	Intestinal obstruction due to abdominal metastases	Died

The median follows up was 24.5 months. The overall survival rate was 52.3% among our patients. The 2- and 5-year survival rates were 43.2% (CI 28.5-57.8%) and 11.4% (CI 2.0-20.7%) respectively (Fig: 1).

Figure 1.

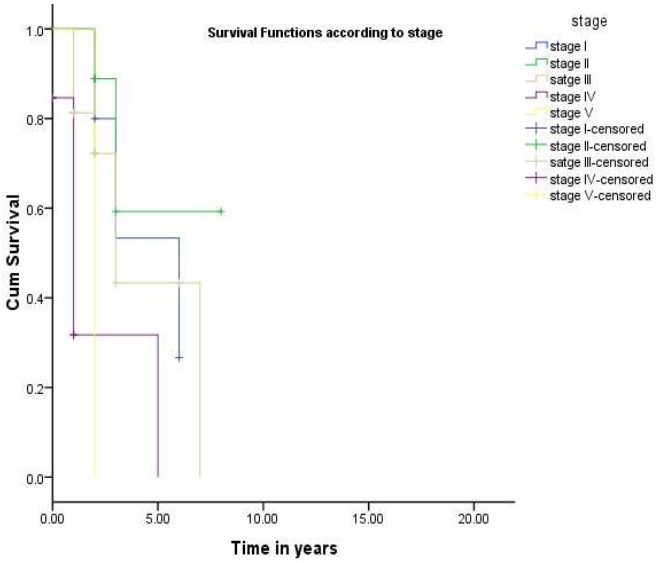
Overall survival curve of the whole study population



Analysing the survival rates according to the stage of the tumours the following results were obtained: 40.0% survived stage I, 77.8%- stage II, 56.2%- stage III, and 38.5%- stage IV. There was no survival in children with stage V tumours (Fig 2).

Figure 2

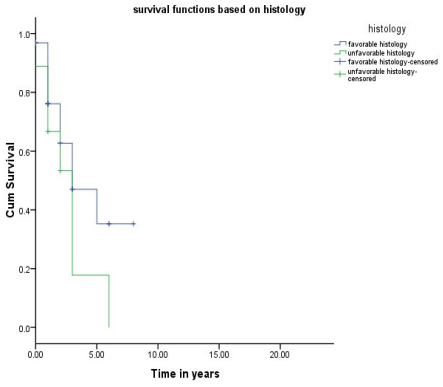
Survival proportions of the individual stages



A significant difference in survival rates was observed among the different stages (P<0.003),but not in the two histologicaltypes (favorable/unfavorable) (P> 0.174) (Fig. 3).

Figure 3

Survival curve of the histological types



DISCUSSION

Wilms' tumour (WT) is one common childhood tumour that continues to generate the interest of researchers. This interest has helped in the development of different study groups and also the formation of multimodal approach to treatment of WT with very good results.

With the multimodal approach to the treatment of WT those that used to be considered as inoperable can now be operated, thus improving the 2-year survival rates of WT from below 50% to nearly 80% in most settings where there are established management protocols. This achievement could also be attributable to early presentation, readily available facilities and finances. Overall, there was a total survival rate of 52.3% observed in the study.

But the 2-and 5-years survival rates were 43.2%, and 11.4% respectively, similar to most reports on outcome survival rates of WT in developing countries. Thus, the outcome survival rate of WT in developing countries is still below the 71% and 79% 2- and 5-years survival rates reached by patients in the developed countries.

The overall low long term survival outcome in this study, as also reported by other studies in the sub-region,16,17 is explained by the advanced stage disease in quite a number of our patients. An estimated survival rate of 40.0% was observed in stage I, 77.8% in stage II, 56.2% in stage III, and 38.5%in stage IV. One Turkish study had about 51.1% of 327 patients with advanced disease which culminated in a survival rate of 54% in stage III disease and 30% in stage IV disease, a finding almost similar to our report.18 Most of our patients presented late, with an average duration of presentation of 4.7 months. As a result, we had 36.4% of the patients with stage III tumour and 29.5% patients with stage IV tumour. The fact that majority of the patients had a painless abdominal swelling makes it easy for the tumour to grow bigger without attracting attention resulting in patients presenting with advanced disease.

There were several reasons for the low survival outcomes in this study. These included late presentation, incomplete treatment, poor financial background, and also loss to follow up as observed in some of the patients.

Though not common in this study, some parents are with the preconception that if a cancer is operated death is imminent, thus causing unnecessary delay in instituting management. One of the parents refused consent based on such belief. Thus, it is possible for social beliefs to influence the survival outcome of WT in our sub-region.19.

In a different study, late presentation and financial constraints were considered the fundamental setbacks for favorable outcome from WT in their patients.20 Hence, the challenges are similar concerning childhood tumours in developing countries, that apart from the inherent unfavorable biological factors in a tumour, late presentation, loss to follow up, inadequate treatment, poor financial capability and lack of collaboration among researchers negatively affect the outcome of childhood tumours.21 We regard ultrasound scan and intravenous urography essential for diagnosis in our setting as majority of our patients could not afford CT because of its cost. All the patients had pre-operative chemotherapy based on the SIOP protocol without pre-operative biopsy.

Pre-operative chemotherapy was initiated because most of the patients had advanced tumours at presentation, as according to the SIOP protocol. 22. The SIOP 6study recommends pre-operative chemotherapy once WT has been clinically diagnosed, being cautious, of the fact that 1% of the children are most likely to have a benign tumour.23We have not had any case of non-cancerous tumour in this study.

The preoperative chemotherapy was safe as it was given in pulses and for a short period and its clinical effect was obvious in two-thirds of the patients. Intra-operatively, there were no significant inadvertent scenarios: i.e. no incidence of intra-operative tumour spillage, and intra-operative bleeding was also minimal as most of the peri-tumoural vessels had shrunken thus reducing the chance of intra-operative transfusion.

Lemerleet al24 considered the effectiveness of preoperative chemotherapy in preventing tumour rupture above radiotherapy. In line with the current concept of the SIOP treatment protocol that minimizes dose of postoperative chemotherapy in order to reduce morbidity but at the same time improving outcome, the postoperative chemotherapy in our patients was regimented based on the stage of the tumour and post-surgery histology. Patients with unfavorable histology had an extended duration of postoperative chemotherapy with addition of cyclophosphamide to minimize the risk recurrence after surgery.25There was recurrence in 4(16.9%) patients 26 weeks after completion of post-operative chemotherapy.

The operative bed was involved in all of them. The failure of these patients to receive radiotherapy to the renal bed might have modified the risk of recurrence especially in patients with poor tumour biology. Finally, the survival outcome of WT is still low in our environment and so also in most developing countries; we look forward to improving the outcome of this tumour through collaboration among researchers in Africa, government support and partnership between technologically developed countries to cushion the setbacks of achieving appropriate treatment of WT.

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