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Wilms' tumour: Determinants of prognosis in an African setting

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ABSTRACT

Background: The few studies available in the literature on Wilms' tumour (WT) from sub-Saharan Africa have reported a dismal outcome for children with the tumour. This study evaluated the risk factors that have been correlated with outcome in the literature and compare these with outcome among our patients. **Materials and Methods:** Cases of histologically confirmed WT between 2009 and 2013 in a tertiary hospital in Northwestern Nigeria were evaluated for gender, age, laterality, symptoms, duration before presentation, stage at presentation, histologic subtype and p53 mutation. These were then correlated with outcome. **Results:** Totally, 30 cases of WT were diagnosed with mean age of 4.8 ± 1.9 years; and male:female ratio of 2:1. No statistically significant relationship with outcome was found for gender ($P = 0.138$) or histologic subtype ($P = 0.671$). The most significant variables which positively influenced the outcome were presentation at earlier stages ($P = 0.007$) and completion of therapy ($P = 0.0007$). p53 mutation was seen in 3 (16.7%) of 18 cases and was not associated with a poor outcome ($P = 0.089$). However, 2 of the 3 cases presented in Stage IV and none of them survived the 1st year. **Conclusion:** This study shows that even though p53 mutation was associated with a more aggressive phenotype, the most significant determinants of a good outcome among patients in a developing country like ours is non-blastemal dominant histologic subtype, early stage at presentation and completion of therapy.

Key words: Blastema, outcome, p53, Wilms' tumour

INTRODUCTION

Wilms' tumour (WT) is one of the most common childhood malignancies of the kidney worldwide with racial differences being described.[1] Unpublished analysis of the cancer registry in our centre shows an incidence rate of 9 per million populations of children aged 0-9 years. This is in the upper limit of the range 4-10/million reported in the literature.[2] The outcome for affected children in developing countries has also been poor, with survival rates being between 0% and 52.7%.[3-5]

Studies have identified malnutrition, inability to optimize therapy and lack of health insurance as some of the factors associated with poor outcome among children with WT in sub-Saharan Africa.[3-5] Researchers from this region have variously suggested that molecular factors may also play a significant role in determining this dismal outcome. Unfortunately, these molecular factors have been poorly studied mostly because of lack of resources to undertake such studies and loss of patients to follow-up. Molecular studies that have been done have mostly been from Eastern and Southern Africa[6,7] as well as North Africa.[8] Important molecular factors identified have included p53 and WT1 among others and these and have been associated with metastatic disease and recurrence.[9-11]

There is a dearth of studies from Nigeria, which have attempted to correlate clinical and histomorphologic

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features of this tumour with outcome. The aim of this study, therefore, is to evaluate the clinico-morphologic profile of these tumours and correlate them with the outcome among children diagnosed with the disease in Northwestern Nigeria.

MATERIALS AND METHODS

Oncology notes, histological request and report forms and slides of cases of nephroblastoma that were diagnosed and managed in a teaching hospital over a 5 year period between 2009 and 2013 were reviewed. Data retrieved included age, duration of symptoms before presentation to the hospital, stage at presentation, completion or otherwise of chemotherapy, duration of follow-up and outcome of the patient. Histological slides made for the cases were also reviewed and graded using the schema by the International Society of Paediatric Oncologists (SIOP). A histomorphologic variant was assessed as being dominant when 66% or more of the surface area of histologic sections made for that case showed that morphology.

For the p53 immunohistochemical staining, tissue sections of 3 micron thickness were cut and mounted on sialinised slides. Antigen retrieval was done, and endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Sections were incubated with monoclonal antibody p53 (DAKO Denmark DO-7 Thermo-Scientific) followed by wash in phosphate-buffered saline.

Antibody binding was detected using envision Dual link system (Dako Denmark) for 45 min followed by 3,3'-aminobenzidine chromogen diluted in the ratio 1:50 with 3,3' diaminobenzidine substrate buffer after wash. Sections were counter-stained by Meyer's haematoxylin and mounted with distyrene plasticizer xylene. Sections of breast carcinoma known to stain for p53 was included in the run as positive controls, and N-universal negative control mouse (Dako) was utilised as negative control. A case was classified as p53 positive when nuclear staining for p53 was observed in 5% or more of the cells in 10 high-power fields as adopted in a similar study.[8]

RESULTS

In the 5 years study period, there were 30 cases of biopsy-proven WT. Complete data including outcome were available in 18 (60%) cases and incomplete data in the remaining cases most of which were not managed in our centre or lost to follow-up.

As shown in Table 1, the 30 cases comprised 20 males and 10 females (ratio 2:1) with a mean age of 4.8 ± 1.9 years respectively. Only a case of bilateral tumour was seen; and even though 19 (63.3%) of the cases were left sided, with a $P = 0.767$, there was no statistically significant laterality. The data also show that apart from abdominal mass, which was seen in all the patients, together with weight loss (56% of cases) and abdominal pain (32% of cases) the trio constituted the most common presenting symptoms. A case presenting as varicocele was also seen.

Information on staging was available in 25 of the 30 cases as shown in Table 1. Two (8%) of the children presented in Stage I; 1 (4%) in Stage II; 16 (64%) in Stage III; and 5 (20%) of the remaining children presenting in Stage IV as well as a bilateral Stage V case accounting for the remaining 4% of cases. There was no statistically significant relationship between gender and stage ($P = 0.309$). Mean duration of pre-clinical presentation was 9 ± 5.0 months.

Submitted nephrectomy cases ranged from 230 g to 2500 g (mean 874 ± 743 g) maximal tumour diameter ranged from 8 cm to 21 cm (mean 11.9 ± 3.9 cm). Histologically, blastema dominant (46.7%) and epithelial dominant (36.7%) constituted the most common variants. Only one each of the regressive and necrotic pattern was noted, and both were in male patients. However, no gender-related pattern was noted

Table 1: Clinical and morphologic features of Wilms' tumour cases

Clinical and morphological features	Male (n = 20)	Female (n = 10)	Total (%)	P
Laterality (n=30)				
Left	11	8	19 (63.3)	0.704
Right	6	4	10 (33.3)	
Bilateral	1	—	1 (3.4)	
Symptoms at presentation (n=25)				
Weight loss	9	5	14 (56)	
Abdominal pain	4	4	8 (32)	
Haematuria	2	2	4 (16)	
Side-effects of chemotherapy (n=25)				
Anaemia	11	7	18 (72)	
Alopecia	8	8	16 (64)	
Nausea and vomiting	6	5	11 (44)	
Stage (n=25)				
I–II	2	1	3 (12)	0.309
III	9	7	16 (64)	
IV-V	3	3	6 (24)	
Morphology (n=30)				
Blastemal	11	3	14 (46.7)	0.196
Nonblastemal	9	7	16 (53.3)	

for the blastema dominant or non-blastema dominant variants ($P = 0.196$). Only a case of anaplastic tumour (unfavourable histology) was seen with the remaining 96.7% of cases being of favourable histology. Based on the SIOP 2001 schema, 21 (84%) of the cases were stratified as intermediate risk, 2 (8%) as high risk and 2 (8%) as low risk.

Table 2 also shows outcome for the 18 cases which had complete records. These comprised 10 males and 8 females (male:female = 1.3:1). Results show that with a $P = 0.138$ gender was not associated with outcome, nor was the outcome related to histomorphologic variant ($P = 0.671$). Significant correlation with a better outcome was however found to stage ($P = 0.007$) and completeness of chemotherapy ($P = 0.0007$). p53 was positive in 6 (26.1%) of the 23 cases stained (5 males and 1 female) but complete oncology records were available for only 18 of them from our centre. As shown in Table 2, of the 18 cases, 3 (16.7%) showed positivity for p53 but was not associated with poor outcome ($P = 0.089$). However, 2 of the 3 cases presented in Stage IV and none of them survived the 1st year.

Ten (55.6%) of the 18 completed therapy and 8 (80%) are alive at periods ranging between 1 and 4 years. Two of the 10 died of complications of therapy rather than from the tumour. Average duration of symptoms before presentation for the 3 p53+ cases was 3.3 months and average duration of survival was about 8 months.

Table 2: Relationship of clinical and morphologic features with outcome

Feature	Alive	Dead	Total (%)	*P*
Gender				
Male	6	4	10 (55.6)	0.138
Female	2	6	8 (44.4)	
Age				
<4 years	2	2	4 (22.2)	0.799
≥4 years	6	8	14 (77.8)	
Duration of symptoms				
<5 months	3	6	9 (50)	0.342
≥5 months	5	4	9 (50)	
Stage				
I-III	8	4	12 (66.7)	0.007
IV-V	0	6	6 (33.3)	
Histologic subtype				
Blastemal	4	4	8 (44.4)	0.671
Nonblastemal	4	6	10 (55.6)	
P53 status				
Positive	0	3	3 (16.7)	0.089
Negative	8	7	15 (83.3)	
Chemotherapy				
Completed	8	2	10 (55.6)	0.0007
Incomplete	0	8	8 (44.4)	

DISCUSSION

Results show that the average age of cases in our study was 58 months. This age is higher than the mean, and median ages reported in studies from outside[1,12] and within Africa[8] which have ranged from 35 to 44 months. However, locally in Nigeria as well as from Malawi, such higher ages have been documented.[3,4,13] Of the 18 cases in our study 14 (77.8%) were at least 4 years old. Such advanced ages have been associated with poor outcome.[14,15] Our study, similar to others,[16] however, failed to show any statistically significant relationship of the outcome to age at presentation. This may be a consequence of smaller sample size of children less than 4 years of age in our series. However, survival rate among younger children was higher than among older children (50% vs. 33%).

Predominant gender of affectation by WT has shown variation in the literature. Studies from Nigeria, apart from those by Abubakar *et al*.[17] in Maiduguri, Northeastern Nigeria, have demonstrated a male predominance.[3,4,18] Those from other African countries and outside have reported the differing gender preponderance as well; though, just like ours, no statistically significant association has been made with outcome.[13]

Late presentation to appropriate healthcare facilities for cancer-specific therapy has been well recognised as a common denominator among WT patients in developing countries. We found no statistically significant association between interval before presentation with outcome among our patients ($P = 0.342$). Possible explanations for this have included parental negligence, poverty, and inadequacy of diagnostic facilities among others.[4,13,19] Similarly, most parents would have taken the children primarily to non-orthodox medical practitioners, only showing up when no solution has been found. This is reflected in the mean duration of 9 ± 5 months before hospital presentation by our patients. Ekenze *et al*. in Nigeria[4] also reported an average duration of 4.7 months. Other researchers in Africa have also highlighted this tendency for late presentation of children with paediatric malignancies.[3,13,17,19,20]

In contrast to findings from developed countries where their cases present mostly in Stages I and II, most reports from Africa have documented a predominance of Stages III and IV at presentation.[3,4,6,8,17,18] Advanced stages (IV and V) in our study were significantly associated with poor outcome ($P = 0.001$). Similar conclusion was

drawn by Pritchard-Jones *et al*. in the United Kingdom Wilms' study-3.[21]

Nephrectomy specimens received for our patients were quite bulky with an average weight of 874 ± 743 g and average maximal tumour diameter of 11.9 ± 3.9 cm. This average weight falls within the 500-1000 g weight range recorded in 40.9% of children studied in a tertiary centre in Lagos, Southwestern Nigeria.[22] It is higher than the average of 334 ± 359 g described in the NWTSG.[23] Such bulky sized tumours suggest late presentation and/or rapid proliferation; and is a risk factor for tumour rupture. Such tumour rupture was seen in 4 (16%) of our patients. Average maximum tumour diameter recorded in our study is higher than the 10 cm recorded in a study[24] from China. Zugor *et al*.[25] found out that in their series, all complications noted were in patients with tumour diameters >5 cm, and this was associated with adverse outcome.

Even though only 2 (11%) of our cases had pre-operative chemotherapy, blastema dominant variant (44.4% of cases) was the most frequent histomorphologic subtype in our immediately operated cases. Blastemal dominant histology was found in 49.2% in the Egyptian study[8] and 53.3% in the Kenyan study.[6] This contrasts with the finding by Weirich *et al*.[26] where mixed variant was the most predominant followed by blastemal dominant for immediately operated cases. Our blastema dominant cases, however, did not correlate with outcome by simple Chi-square ($P = 0.671$). This differs from the report by Weirich *et al*.[26] which showed a statistically significant poorer outcome for blastema dominant WT cases in their series. On multivariate analysis, our blastema dominant cases showed slight correlation with male gender ($P = 0.0128$) but not stage ($P = 0.604$) albeit with a low R^2 value. This partly differs from the observation by Salama and Kamel in Egypt[8] who documented no significant relationship of tumour histology with gender or stage. However, they found blastemal subtype was associated with poorer prognosis compared with other subtypes.[8] The importance of the blastema dominant subtype is reflected in the re-assignment of this subtype under high-risk subgroup in the 2001 revised SIOP classification for pre-treated cases. Another possible implication of this is that nephrogenic rests, which are derived from embryogenic residual blastema[1] and which Beckwith *et al*.[27] has described as precursors for WT, may be common in our setting. However, more research is required to ascertain this.

Results from our study also show that 26.1% of our WT cases exhibited p53 mutation. The pattern of p53 mutation in cases reported from developed countries of Europe and the Americas have shown rates ranging between 0 and 13.4,[28,29] while in the African series, the rates have ranged between 8.3% and 60.3%.[6-8] This wide range of the positivity for p53 would suggest not only a role for the mutant gene in the biology of the tumour but also a racial variation; with Africans exhibiting a higher frequency for the mutation.

Apart from the single case of diffuse anaplasia in our study which showed the most intense and diffuse staining for p53 (Figure 1; not included in this study because of incomplete data), the 3 (16.7%) of our 18 cases that were positive for the stain were of favourable histology. This is higher than the 3.5% reported from South Africa,[7] but less than the 31% reported in the Kenyan study,[6] and the 52.9% reported in the Egyptian study.[8] Positivity for this mutation in cases with favourable histology has been associated with more clinically aggressive disease.[30] This is corroborated by our finding that 2 of the 3 p53+ cases with favourable histology presented in Stage IV and all died even though the duration of symptoms before presentation was 3.3 months. This is suggestive of tumours with an aggressive phenotype.

Finally, outcome of our patients was most statistically correlated with completion of therapy ($P = 0.0007$). Multivarate analysis shows that a favourable outcome was most significantly correlated with completion of therapy. Chemotherapy regimen is based on the SIOP-9 protocols. Vincristine and actinomycin D are given for 4 weeks pre-nephrectomy. Nephrectomy is then done within 1-week. For those that have immediate nephrectomy and pre-treated cases, vincristine and actinomycin D are given for 18 weeks for Stage I, while doxorubicin is added and given for 27 weeks for other

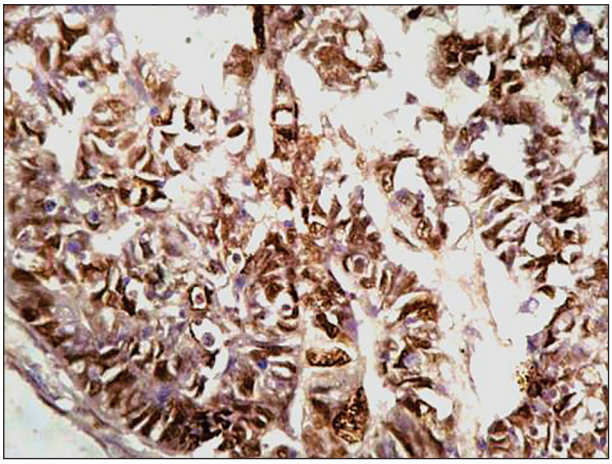

Figure 1: A nest of neoplastic cells with positive nuclear stain for p53 antibody immunostain (×20)

stages, including radiotherapy, where finance is not a constraint, for Stage III and above.

Ten (55.6%) completed therapy and of these 8 are alive; 2 died of chemotherapy-related complications rather than the disease. The best clinical presentation, representing 5 (50%) of the 10 cases that survived the 1st year, were children older than 3 years of age presenting in Stage III or earlier with non-blastema dominant histology and who completed treatment. One-year event-free survival was achieved irrespective of age of patient, histologic subtype, duration of symptoms, stage and p53 status if treatment was completed ($P = 0.0047$).

Inability to ensure completion of therapy has been identified by several reports from Nigeria.[3,4,17,18] The challenge therefore for oncologists practicing in developing countries is how to facilitate chemo-, radio-and surgical therapy for patients in such resource-constrained countries. One of the solutions that have resulted in improved outcome has been demonstrated in the Kenyan experience where collaboration was formed between Kenyan high-volume hospitals and the Vanderbilt University Medical Centre, Nashville Tennessee. This collaboration has resulted in not only improvement in patient outcome, but also in molecular characterisation of their tumours as well as the establishment of a WT registry.[6] Such collaborative efforts are worthy of emulation for other centres in Africa where such is non-existent.

CONCLUSION

Our study has shown that even though p53 mutation was associated with a more aggressive phenotype, the most significant determinants of a good outcome among patients in a developing country like ours is non-blastema dominant histologic subtype, early stage at presentation and completion of therapy. It also becomes clear the need for formation of national WT consortia, improvement of record keeping in our hospitals and a need to begin optimised individualised therapy of WT cases.

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Conflicts of interest
There are no conflicts of interest.

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