Clinical characteristics and outcome of surgical treatment of childhood rhabdomyosarcoma: A 7-year experience

Francis A. Uba, Lohfa B. Chirdan

ABSTRACT

Background: The aim of this study was to describe the outcome and determine the prognostic factors of outcome of childhood rhabdomyosarcoma in a tertiary hospital in a developing country. **Patients and Methods:** This was a retrospective review of the clinical presentation, investigation, intervention, and treatment outcomes of children with rhabdomyosarcoma in our hospital over a 7-year period. Statistical analysis was performed using Chi-square test. **Results:** A total of 18 patients were identified with two-thirds being males (n = 12) with median age of 7 years. Most of the children were below 10 years of age. Lower limbs tumour predominated (n = 6) followed by the upper limbs and head and neck (n = 4 each). Other sites included perianal/perineal (n = 3) and the orbit (n = 1). Two patients were Intergroup Rabdomyosarcoma Study (IRS) group I, four group II, five group III, and seven group IV. Lymph node involvement was the commonest site of metastasis. Clinical group and stage was significantly more advanced in patients older than 10 years compared to younger than 10 years (P = 0.010, P = 0.008, respectively). There were 12 patients with alveolar disease while six had embryonal type of rhabdomyosarcoma. Treatment was by combination chemotherapy, and surgical excision which was done primarily in 11, after chemotherapy in four, and after radiotherapy in one. Two had biopsy only. Five patients are alive, two of them without evidence of disease at average follow-up period of 2 years. **Conclusion:** Mortality from rhadomyosarcoma in our setting is still unacceptably high. Late presentation may be the major contributor to high mortality. A more aggressive multimodality treatment approach may improve the outcome.

Key words: Children, outcome, rabdomyosarcoma, surgical treatment

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INTRODUCTION

Rhabdomyosarcoma is the most common soft tissue sarcoma and represents 10-15% of all malignant solid tumours in children.[1] The tumour is biologically heterogeneous and the outcome depends on such factors as the primary site, extent of the disease, histology, and patient's age.[2] Previous studies showed that improvement of patient's outcome is enhanced by multidisciplinary treatment approach involving multiagent chemotherapy, surgery, and radiotherapy.[3,4] This study describes our experience with the characteristics and management outcome of childhood rabdomyosarcoma in a tertiary (teaching) hospital in Nigeria over a 7-year period.

PATIENTS AND METHODS

All children managed for rhabdomyosarcoma between September 2000 and August 2007 were reviewed at the Jos University Teaching Hospital, Jos, Nigeria. Data were collated from patients' case files, operation registers, and histology registers and analysed for patients' ages, gender, signs, and symptoms, IRS clinical groups and pretreatment stages,[5] metastatic sites, histology, surgical treatments and outcome of management. Statistical analysis was performed using the Chi-square test and differences between the two groups were declared to be significant when the P value < 0.05.

RESULTS

There were 18 patients, 12 (79%) were male patients and 6 (21%) were females (M:F = 2:1). Their ages ranged from 4 months to 14 years with a median of 7 years. Twelve patients (66.7%) and 6 (33.3%) were below and above 10 years, respectively [Figure 1]. The age distribution peaked at the ages of 2 and 5 years.

The most frequently affected site was the lower limbs in nine (50.0%) patients [Figure 2], followed by the upper limbs and head and neck in five (27.8%) patients each. The perianal and perineal regions, defined as areas of extrapelvic, nongenitourinary tissue located between

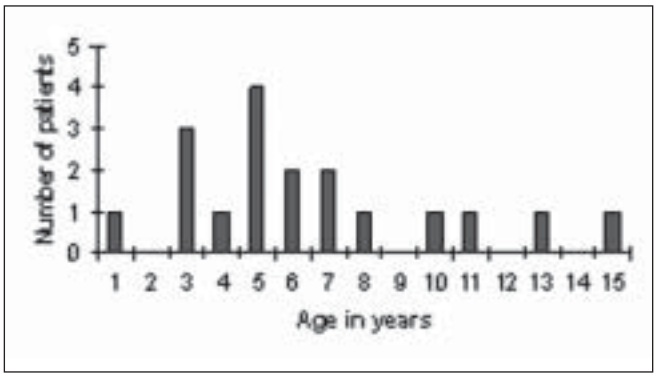


Figure 1: Age distribution of children with rabdomyosarcoma

the pubic symphysis anteriorly, the ischial tuberosities laterally, and the coccyx posteriorly, were involved in three patients (16.7%) [Figure 3] and the orbit was involved in one patient (5.5%).

The presenting features included local pain in 8 (44.4 %), swelling and ulceration in 8 (44.4%), palpable mass in 18 (100%), and constipation in 3 (16.7%). The patients' characteristics are summarized in Table 1.

Table 1: Characteristics of 18 patients with rhabdomyosarcomas

Age [4 months-14 years (median 7 years)]	Number of patients (%)
<10 years	12 (66.7)
>10 years	6 (33.3)
Gender	
Male	12 (66.7)
Female	6 (33.3)
Clinical features	
Palpable mass	18 (100)
Swelling and redness	8 (44.4)
Local pain	8 (44.4)
Constipation	2 (11.1)
Clinical group	
I	2 (11.1)
II	4 (22.2)
III	5 (27.8)
IV	7 (38.9)
Stage	
2	3 (16.7)
3	6 (33.3)
4	9 (50.0)
Regional lymph node metastasis	
+	15 (83.3)
NC	3 (16.7)
Distant metastasis	
+	12 (Distant lymph nodes, bone, liver, and lungs)
NC	6
Histology	
Alveolar	12 (66.7)
Embryonal	6 (33.3)

NC: Not certain

According to IRS clinical grouping, 2 (11.1%) patients were group I, 4 (22.2%) in group II, 5 (27.8%) in group III, and 7 (38.9%) in group IV. The pretreatment stage included stage 2 in 3 (16.7%) patients, 3 in 5 (27.8%), and 4 in 9 (50%) patients. The tumour metastasized to the regional lymph nodes in 15 (83.3%) patients. The inguinal lymph nodes were involved in 11 of the 15 patients while the axillary nodes were involved in four patients. Twelve (66.7%) patients had distant metastases including the liver in four patients, lymph nodes at distant sites and the lungs in three patients each, and bone in two. Histology was alveolar in 12 (66.7%) patients and embryonal in 6 (33.3%).

The characteristics of patients below 10 years of age (n = 12) were compared with those of patients above 10 years of age (n = 6) [Table 2]. In both groups, there was male predominance: 8 out of 12 (66.7%) patients in the former group and 4 of 6 (66.7%) patients in the latter group. The clinical group and the stage were more advanced in patients older than 10 years compared to those in patients younger than 10 years and the difference between the two was significant (P = 0.010 and 0.008, respectively).

Table 2: Relationship between the patients' characteristics and age

Characteristic	Age		P2
	<10 years (n = 12)	>10 years (n = 6)	
Gender			
Male	8 (66.7)	4 (66.7)	0.143
Female	4 (33.3)	2 (33.3)	
Clinical group			
I	2 (16.7)	-	0.010
II	1 (8.3)	3 (50.0)	
III	2 (16.7)	3 (50.0)	
IV	2 (16.7)	5 (83.3)	
Stage			
2	3 (25.0)	-	0.008
3	1 (8.3)	5 (83.3)	
4	2 (16.7)	5 (83.8)	
Histology			
Alveolar	7 (58.3)	5 (83.3)	0.026
Embryonal	4 (33.3)	2 (33.3)	

Figures in parentheses are percentage

Table 3: Surgical treatments and outcomes

Surgical treatment	
Primary excision or primary re-excision	15 (42%)
Second-look operation	1 (33%)
Biopsy only	2 (13%)
Outcome	
Alive at 2 years	5 (27.8%)
DF at 2 years	2 (11.1%) (2 and 4 years of age)
DOD	13 (72.2%)

DF: Disease-free, DOD: Died of disease

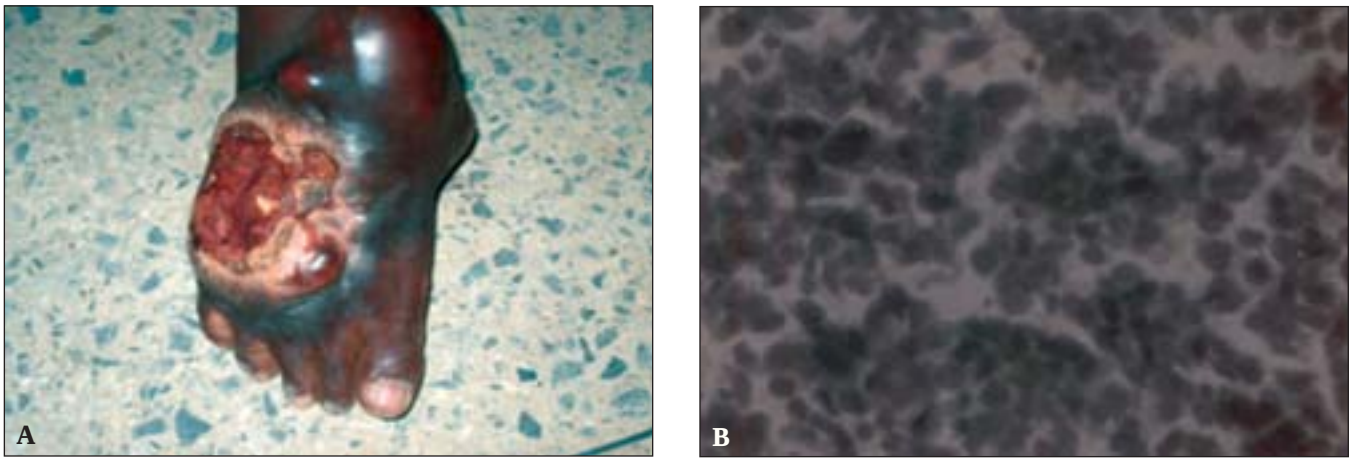


Figure 2: (A) Clinical photograph of embryonal rhabdomyosarcoma involving the right foot of a 7-year old boy. (B) Photomicrographs of a lower limb embryonal rhabdomyosarcoma from a 7-year old child demonstrating stroma infiltrated by solid sheets and nests of tumor cells

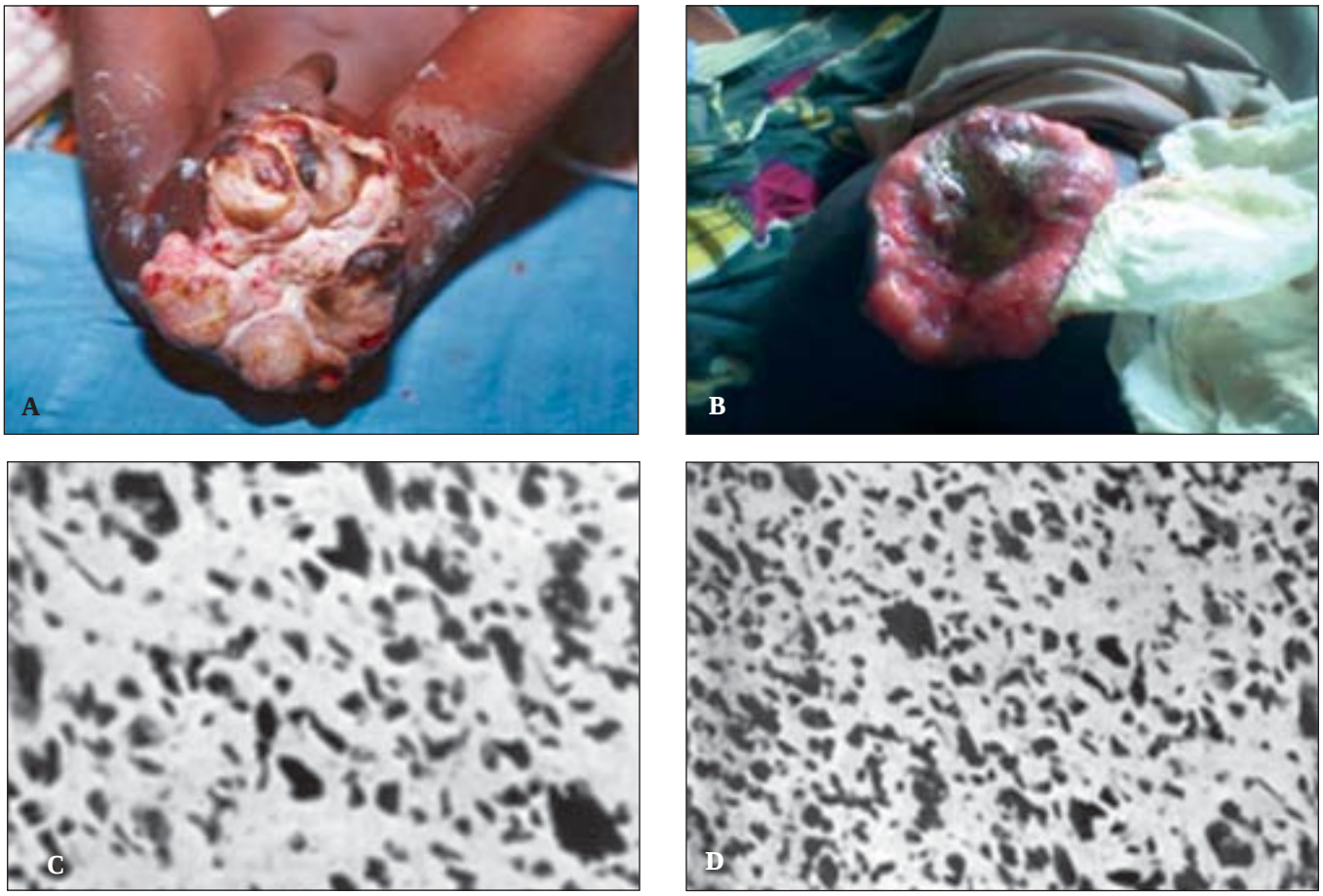


Figure 3: (A and B) Clinical photographs showing ulcerated perineal rhabdomyosarcoma in a 5-year boy and a 3-year old girl, respectively. (C) and (D) Photomicrograph of a perineal alveolar rhabdomyosarcoma from: (A) a 5-year old boy, and (B) from a 3-year old girl demonstrating stroma infiltrated by solid sheets and nests of tumor cells (original magnification: ×100), and demonstrating patchy expression of Desmin

Biopsy was either incisional, excisional, or by tru-cut method. All patients had histological confirmation of rhabdomyosarcoma and had combined chemotherapy with vincristine, actinomycin D, and cyclophosphamide. Fifteen patients underwent surgical treatments [Table 3], including primary excision or primary re-excision of tumours in 11 (61.1%) patients and excision after a systemic chemotherapy in 4 (22.2%). Three patients declined to have surgery after the initial biopsy.

Macroscopically, the tumour was completely removed in 7 of the 11 patients who had primary excision; four

other patients had some residual tumours. Macroscopic complete resection was achieved in three of the four patients who first had systemic chemotherapy.

Thirteen (72.2%) patients died on treatment, including 10 who had operative treatment and three that declined surgical treatment. These later patients who declined surgical treatment and were lost to follow up were considered died. Mortality rate was 83.3% (5/6) in the patients with embryonal rabdomyosarcoma, but in those with alveolar rabdomyosarcoma, mortality rate was 66.7% (8/12), $P = 0.04$.

Five of those who had surgical treatment were alive at the time of audit; 2 (22.2%) of them aged 2 and 4 years had no evidence of the disease 2 years after follow-up. In the two patients who were disease-free, primary surgery consisting of a wide resection was successful for complete excision of the tumour; this patient had a clinical group I, stage 2 tumour. The other patient had a group II, stage 3 tumour at the time of treatment, with no observed metastasis to the regional lymph nodes; he had re-excision because of a local recurrence. The remaining three patients, who still have inguinal node involvement, are stable on chemotherapy.

DISCUSSION

The incidence of 2% of rhabdomyosarcomas in the perianal or perineal regions in this study agrees with an earlier report by the third Intergroup Rabdomyosarcoma Study Group (IRSG).[6] This study showed a clear male preponderance in contrast to the Japanese report in which there was a prominent female predominance (female/male ratio was 4:1)[7] and the IRSG which showed an equal sex ratio.[6]

Majority of the patients were below 10 years; their age distribution showed two peaks at 2 and 5 years with a median of 7 years. A study by Okamura *et al*.[7] also showed a similar twin peaks, but the age distribution of their patients peaked at 2 and 15 years with a median 14 years. The age of 10 years appeared to be a watershed, defining clearly two phases in the biologic behavior of rhabdomyosarcoma. The higher incidence of distant metastasis and regional lymph node involvement was predominant in patients above the age of 10 years in this report, and was associated with poorer outcomes.

The findings in this study differ from those published in western literature in many respects, especially with regards to the very high mortality rate (approximately 72%). First, majority of the patients in our setting presented late with advanced or metastatic diseases (involving the lymph nodes, bone, lungs, and the liver). About two-thirds of the tumours were in clinical groups III and IV, and more than three-quarter were in stages 3 and 4, at presentation. The advanced or metastatic nature of the disease is directly related to late presentation. Patients with metastatic disease at the time of diagnosis have a very poor prognosis.[8-11] It is interesting to note that the only patients who survived for more than 2 years with no evidence of disease presented with a group I/stage 2 and group II/stage 3 tumours with associated lymph node metastasis.

Second, most of our patients had less than desired diagnostic workup before treatment. In most cases, the true extent of tumour spread was unknown due to lack of modern imaging techniques like computed tomography (CT) scan and magnetic resonance imaging (MRI). Ultrsonography, though available, is limited in complete diagnostic workup of a patient with advanced rabdomyosarcoma. The current improvement in survival in the developed countries resulted from (1) the determination of the extent of disease at the time of diagnosis by staging criteria, (2) the categorization of tumour histology into favorable and unfavorable types, (3) the appreciation of the natural history of the tumour from specific sites, and (4) the prompt referral of patients to paediatric cancer centers with experience in the management of childhood tumours.[8,9,12,13]

Third, complete tumour resection prior to chemotherapy should be the goal; and suspected involved lymph nodes should be at least sampled because nodal involvement is closely associated with prognosis.[7] When complete resection of the invading tumour is not feasible, initial biopsy and second-look operation following intensive chemotherapy and local irradiation is recommended to achieve a complete clinical response.[14]

Relapse at a local or regional site is usually an ominous sign;[15] this observation indicates that adequate margins of resection are far preferable to leaving behind microscopic tumour or gross residual disease.[16] In most cases complete excision of tumours without leaving behind microscopic tumour or gross residual disease was impossible in this study because of (1) the large tumour size and its areas of involvement, and (2) lack of frozen section services in our center.

Fourth, the treatment modalities in our setting are more limited. The introduction of multidisciplinary treatment programs utilizing operative resection, local or regional radiotherapy, and intensive prolonged courses of

multiagent chemotherapy has significantly improved the outcome of management of rabdomyosarcoma in the developed countries.[3,4,6] This cannot be said of our setting with scarce multiagent chemotherapeutic agents and complete absence of radiotherapy services. Even when the multiagent chemotherapeutic agents are available, the cost is prohibitive for most of our patients, thus making compliance erratic.

In conclusion, late presentation, advanced disease and embryonal tumour histology were poor prognostic factors on the outcome of management of childhood rhabdomyosarcoma in our setting. Poverty and scarce health facilities are contributory. Public enlightenment/ awareness campaign program on this deadly disease may improve the outcome of management childhood rabdomyosarcoma. A multicenter study group in countries with similar settings is needed to characterize the disease and set out management protocol.

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