Original Article

Clinical characteristics and outcome of rhabdomyosarcoma in South African children

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ABSTRACT

AIM To review a series of 33 children, treated for rhabdomyosarcoma at Tygerberg Children's Hospital between 1983-2005, with emphasis on age, gender, clinical presentation, site, histological subtype, TNM stage, treatment modalities and survival.

METHOD A retrospective study based on data obtained from the Tygerberg tumour registry.

RESULTS The age at diagnosis ranged from 7 days to 13 years; males 57% and females 42%. More than half of cases presented with a mass at varying sites. Almost a quarter had pressure symptoms due to bladder tumours. The predominant complaint in 9% was pain. The primary site of disease was the head and neck in 45% and the pelvis in 42%. The most common histological subtype was in 45% embryonal rhabdomyosarcoma. At the time of diagnosis, 63% of patients were TNM stage 3. Most patients received multimodality therapy (radiotherapy, chemotherapy and surgery). The survival rate from diagnosis to subsequent demise was poor – between 13 days and 3.5 years. The overall 5-year survival rate was 45%, which is partially explained by delay in diagnosis and advanced stage of disease

CONCLUSION The clinical characteristics of rhabdomyosarcoma at Tygerberg Children's Hospital are similar to those of first world countries. The majority of presentations were in the advanced stages of disease but sensitive to multimodal therapy. Recognition of early warning signs and public awareness could lead to earlier presentations and improve outcome. Further multicentre studies are needed in Africa to better report our experiences with rhabdomyosarcoma.

Keywords: Rhabdomyosarcoma, South Africa, Africa, Outcome assessment

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children under 15 years of age. It accounts for 6% of all childhood cancers.[1] In South Africa, where only around 650 cases of cancer are reported per year, RMSs represent the 5th most common cancer.[2]

Since 1987 there have been 33 cases of RMS, diagnosed annually within South Africa. At Tygerberg Hospital, a tertiary academic referral centre in the Western Cape, rhabdomyosarcoma is the 6th most common cancer and accounted for 50% of all soft tissue sarcomas diagnosed in children from 1983 till 2005. There have been 1-2 cases of

rhabdomyosarcoma diagnosed per year at Tygerberg Children's Hospital since 1983. There has not been a progressive annual increase in this figure and this trend has remained steady.[2]

The variable nature and uncommon occurrence of these tumors has made studies at single institutions or regional centers more difficult to do. Most of the literature reflects experiences in first world countries. Most advances in RMS knowledge, prognosis and treatment have resulted from major international collaborations. There is very little data or co-operative studies available from developing countries, notably Africa. There is a need for larger, collaborative descriptive studies in Africa to better report our experiences related to rhabdomyosarcoma. This study aimed to outline the clinical characteristics of rhabdomyosarcoma at Tygerberg Children's Hospital, Paediatric Oncology unit, between 1983 to 2005, with emphasis on the age, gender, clinical presentation, site, histological subtype, TNM stage, treatment modalities and survival.

METHODS

This was a retrospective, descriptive study to review a series of 33 children diagnosed and treated for rhabdomyosarcoma at the Paediatric Oncology unit at Tygerberg Children's Hospital, over a 22-year period (1983 to 2005). The medical records of all the patients admitted to the Oncology Unit and diagnosed with rhabdomyosarcoma from 1983-2005 were obtained and reviewed. The demographics and clinical details of these patients were routinely entered into the tumor register and updated with regard to their progress in the ward. Therefore the data included their admission history, inpatient course and treatment as well as outpatient visits and follow up. The data was collected and entered into Excel. The appropriate statistical techniques were finalized via consultation with a statistician, on a regular basis during the study. The Research Ethics Committee of the Faculty of Health Sciences, Stellenbosch University, approved the study.

RESULTS

There were 33 cases identified from the tumor registry and included in this study. The age at diagnosis ranged from 7 days to 13 years with a median age of 5 yrs. There was a male predominance with 58% (19 patients) and females accounting for 42% (14 patients).

Most of the children presented with a mass (67%) at varying sites, which was noticed 3 days to 3 months before consultation with 1 case presenting as late as 6 months. There were 9 out of the 22 patients who presented early, within 2 weeks. The rest of the 22 patients presented late over a time period of 2 months to 6 months. There were no differences between early and late presentation with regard to ethnicity or cultural characteristics, as these are important factors to take into consideration.

A number of cases presented with pressure symptoms (21%) especially due to bladder tumors with associated dribbling, urgency, poor stream and incomplete voiding. Intracranial tumors presented with pressure symptoms such as ptosis, proptosis, and cranial nerve palsies. Pain was the predominant complaint in 9% of cases - mostly as abdominal pain, leg pain (myalgia) and a painful eye. One patient presented with vaginal bleeding.

The primary site of disease was the head and neck in 45% (15 patients) and the pelvis (bladder, vagina, testicular and anal canal) in 42% (14 patients, Figure 1). Less frequent sites included the abdomen, upper limb, lower limb and thorax (right lung mass).

Embryonal rhabdomyosarcoma was the most common histological subtype in 15 patients (45%). The alveolar subtype accounted for 21% (7 cases) and botryoid for 6% (2 cases). The histological subtype was not identified in 27% (9 cases). Sixty-seven percent of patients (22 cases) were stage III at time of diagnosis. There were 24% (8 cases) at stage IV. Only 9% (3 patients) were stage II when diagnosed and there were no stage I cases. The mean age of stage III patients was 6 years and in stage IV patients it was 7 years. There were 76% males in stage III and 24% males in stage IV. Females accounted for 69% of stage III and 31% of stage IV.

Delay in diagnosis was found in 8 of the 33 cases. Half of the cases had a period of delay of 3 weeks

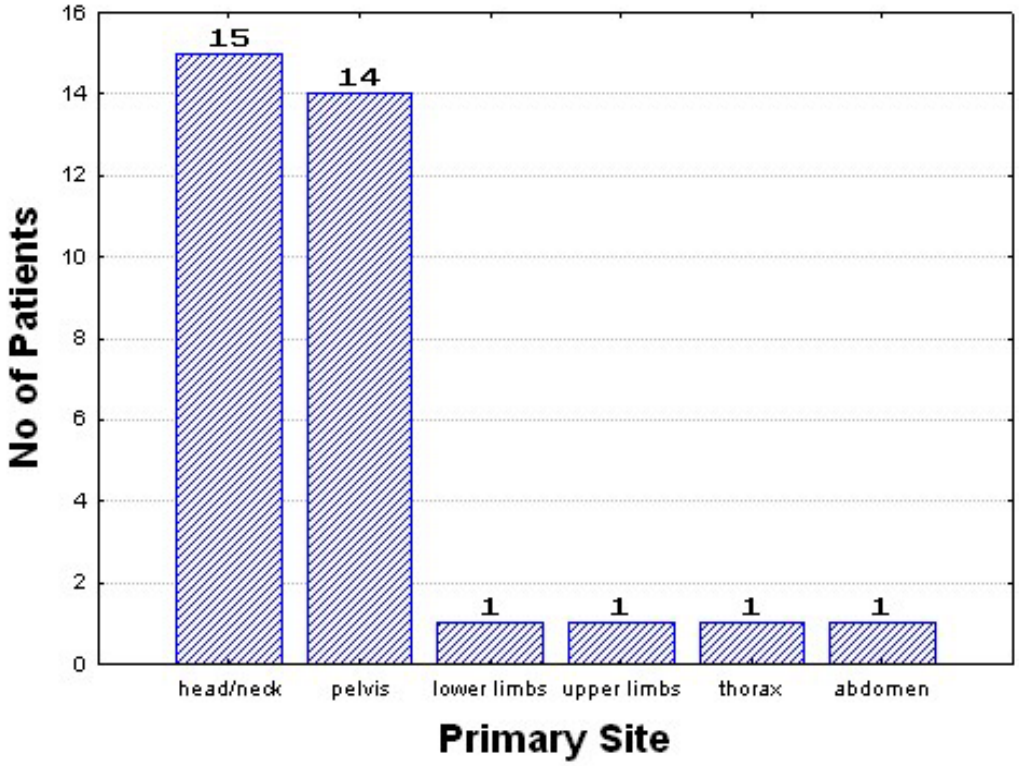

Figure 1. Primary sites of disease.
The commonest primary site of disease was the head and neck in 45% (15 patients) followed by the pelvis (bladder, vagina, testicular and anal canal) in 42% (14 patients).

to one month. The rest had periods of delay of 6 weeks, 2 months to 5 months and the longest being 6 months. Most of them presented and were treated as common pediatric problems namely, otitis media, sinusitis, urinary tract infections.

The histological subtypes in stage III were embryonal 79%, alveolar 50% and unspecified 75%. The stage IV subtypes were embryonal 21%, alveolar 50% and unspecified 25% (Figure 2).

More than half of the patients (58%) received multimodal therapy, as shown in Figure 3. This entailed surgery (biopsy or resection where possible) chemotherapy and radiotherapy (for patients with residual disease or as palliative care). There were 33% (11 patients) who received surgery and chemotherapy and 6% (2 patients) who received radiotherapy and chemotherapy only.

Survival duration was poor - between 13 days and 3.5 years from diagnosis to subsequent demise. The overall 5-year survival rate was 45% as shown in Figure 4. This constituted 58% male and 29% female. The correlation between stage and survival is shown in Figure 5 with fifty-five percent of survivors in stage III and 13% in stage IV. Co-morbidities such as malnutrition, infection, HIV and TB were considered but there was not enough information to be studied.

DISCUSSION

Intensive multimodal therapy, which involves a combination of surgery (primary or secondary excision of the tumor), chemo- and radiotherapy, is the ideal treatment for RMS. [1,3-6] Over the last 30 years, the use of a multimodal therapeutic approach has resulted in a cure rate of 70% for patients with localized disease. Despite advances in therapy, 30% of children with RMS experience progressive or relapsed disease, which is often fatal.[7]

Despite the fact that 58% of the patients in this study received multimodal therapy, the overall 5-year survival rate was only 45%. There was a higher male survival rate of 58% and a higher female mortality rate of 71%. We investigated the correlation between survival and stage and found that stage III patients had a higher survival rate at 55%. Stage IV had a poorer prognosis with a survival rate of only 13%.

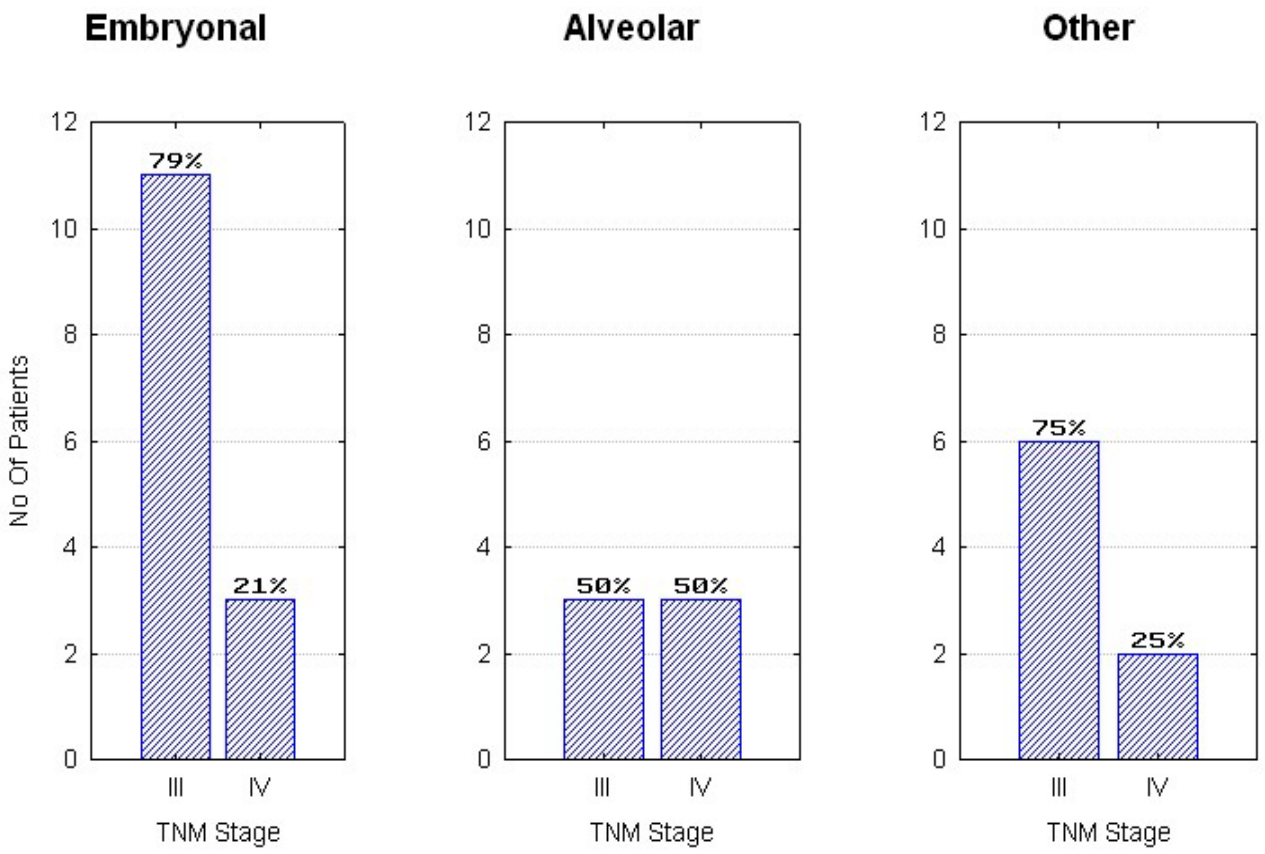

Figure 2. Correlation between stage and histology. The majority of embryonal and unspecified histological types were stage III disease. Alveolar histological types had equal numbers of stage III and stage IV disease.

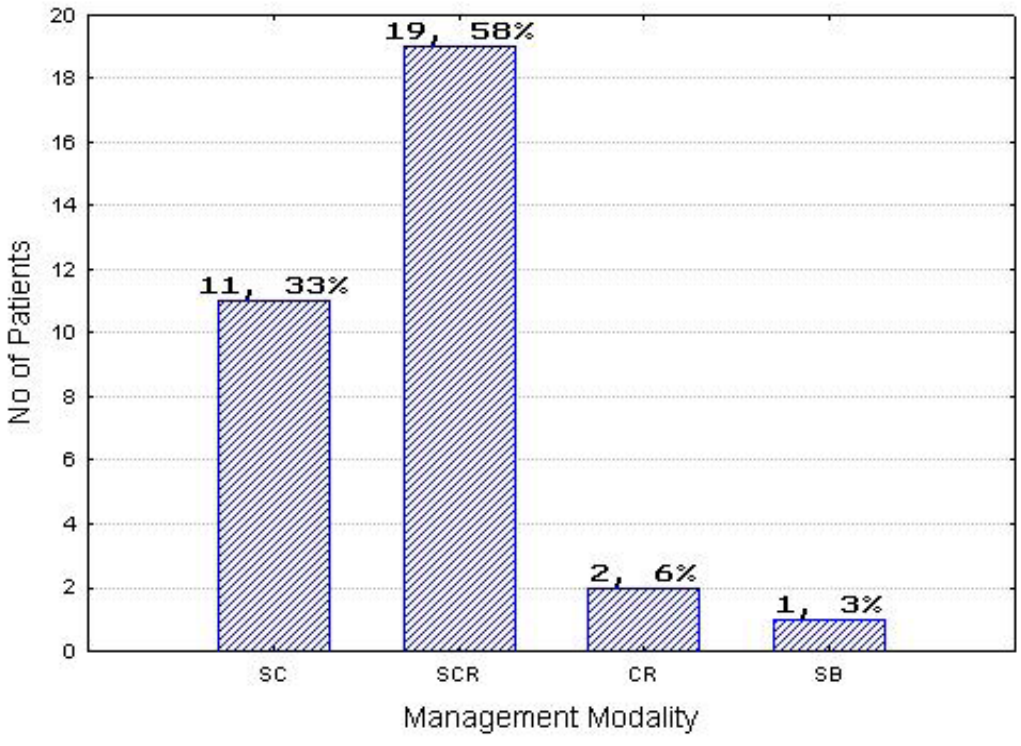

Figure 3. Treatment modalities. SC, surgery and chemotherapy; SCR, surgery, chemotherapy and radiotherapy; CR, chenotherapy and radiotherapy; SB, surgery and biopsy. More than half of the patients, 19 (58%), received multimodal therapy.

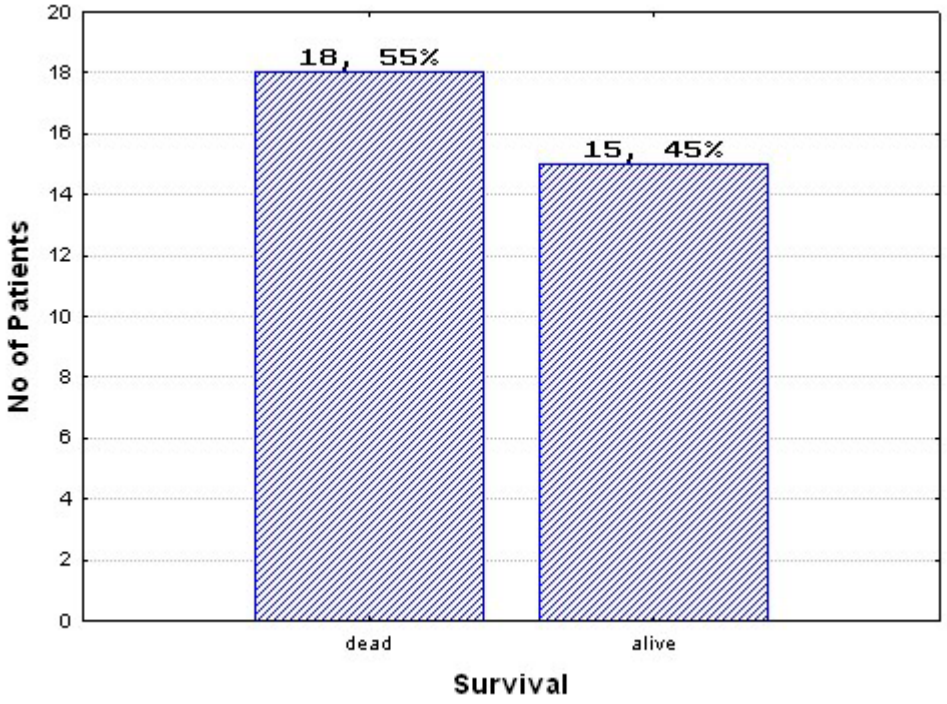

Figure 4. Overall 5-year survival rate. The overall 5-year survival rate was poor (45%)

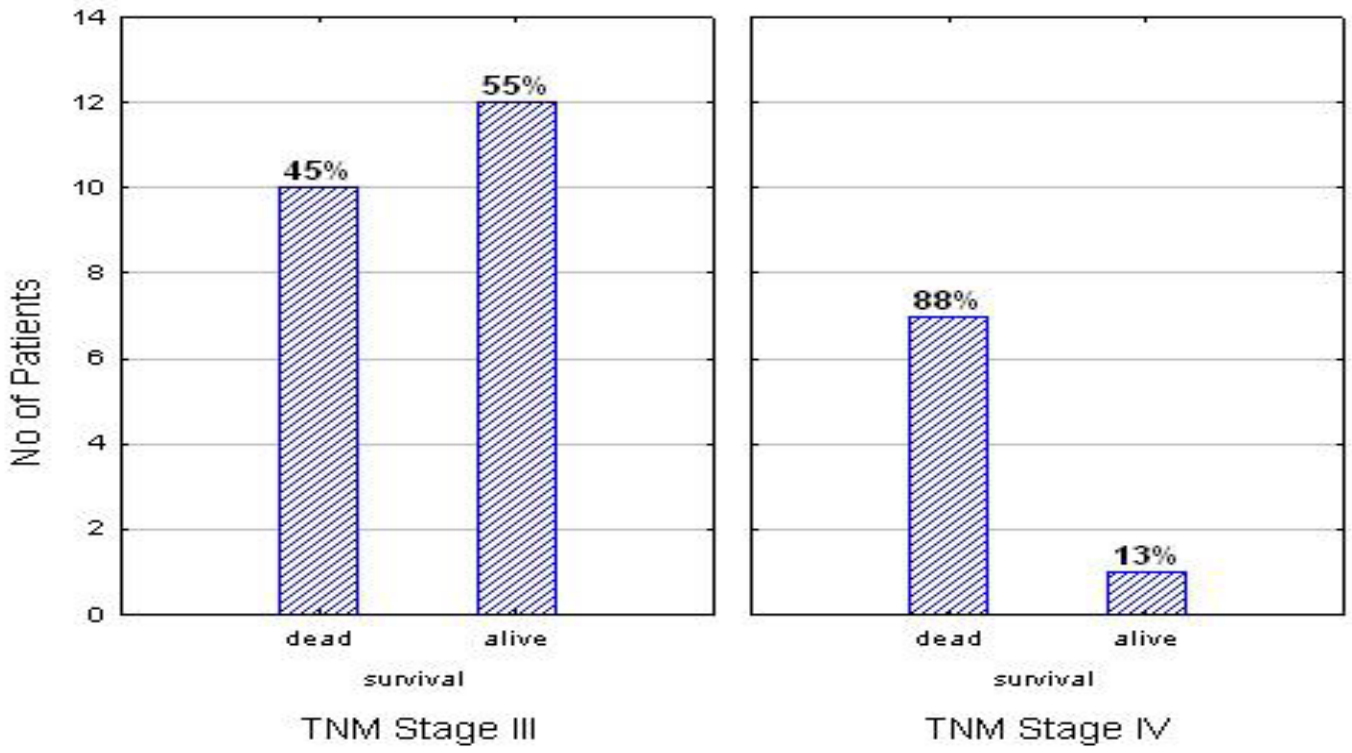

Figure 5. Correlation between stage and survival. The more advanced stage IV was associated with worse survival than stage III.

Rhabdomyosarcoma (RMS) has several distinct histological subtypes: embryonal rhabdomyosarcoma (ERMS), alveolar RMS, botryoid and spindle cell variants of ERMS, and undifferentiated sarcoma. The two most common subtypes, embryonal and alveolar, account for at least 80% of all rhabdomyosarcomas.[8-9]
Recent studies in the literature have reflected that embryonal RMS was three times more common than alveolar RMS.[1,4] Our results show that embryonal RMS was indeed the more common histological subtype at 45% but the unspecified RMS subtype was the second commonest at 27%. Alveolar RMS was the third and represented 21%. This confirms reports in the literature regarding the most common histological subtype. At the same time it differs from most of the western literature where alveolar has been the second most common RMS following embryonal type.

These histological subtypes have prognostic significance as well. Embryonal RMS tends to be a localized cancer that responds well to treatment and rarely spreads. [8,10-11] Alveolar RMS tends to be aggressive and harder to treat with a poorer prognosis. [10-12] Our correlation between stage and histology indicated that 79% of the embryonal types were stage III as were 75% of the unspecified and 50% of the alveolar types. As mentioned earlier the stage III patients had a higher survival rate than stage IV, which does concur with the findings of the The Intergroup Rhabdomyosarcoma Study Group (IRSG) in the literature. Half the alveolar subtype (50%) was Stage IV disease, with an overall 13% survival rate. These results further confirm the reports in the literature, which suggest a poorer outcome for alveolar RMS.

Tumor histology is an important predictor of 5-year survival. IRSG III – IV found that alveolar RMS or undifferentiated sarcomas had a worse outcome with a 5-year failure free survival rate (FFS) of 5%.[7,13] The 5-year survival rate for botryoid tumor was 64% and 26% for patients with embryonal tumors. [7,10] The IRSG further identified prognostic factors within histological subtypes. The earlier the presentation and therefore, the earlier stage or group, within the embryonal tumors, the better the prognosis.[7,10]

Soft tissue sarcomas most commonly present as asymptomatic masses, which was the case in this study. The majority of patients (67%) presented with a mass at varying sites (head and neck, pelvis, abdomen and extremities.) This study found a delay time to diagnosis ranging from 3 days to 6 months. The presenting symptoms can often mimic common childhood illness, which is another factor delaying diagnosis. [1,5,8] This correlates well with our Nigerian counterparts who showed that 100% of their study group also presented with a mass.[14]

Early stages of disease (stage I and II) have survival rates of 70%. [15] Delay in presentation accounted for almost 48% of cases in this study leading to the majority of presentations being in the advanced stages of disease. Delay in diagnosis accounted for 24% of cases. Most of these cases presented and were treated as common pediatric problems namely otitis media, otorrhoea, sinusitis, and urinary tract infections. The case with the longest delay in diagnosis was a lower limb fracture with subsequent subcutaneous mass noticed 2 months thereafter. The excision biopsy was delayed for 3 months when the patient had an upper respiratory tract infection. There was no reason given for the long delay in follow up excision date. Hessisen et al (2009) in their retrospective study in Morocco stated that 81% of cases had a 6-month or less delay in diagnosis. [16]

The remainder of patients, presented in advanced stages of disease (stage III and IV), without any delay in presentation. There were no differences found in those presenting early in advanced stages of disease and late presentations. There were no causative factors such as cultural characteristics, ethnicity, lack of transport or lack of medical facilities etc, found in the available medical records.

Ismail et al had similar findings, and stated that advanced stage of disease at presentation and delay in presentation was the norm in their clinical practice. [17] At the time of presentation, the tumors were so large that they could perform open biopsy to confirm the diagnosis. [17] Delay in presentation and hence advanced stage of disease at diagnosis, appears to be a shared finding and persistent problem for African countries. Parents and health care workers in day hospitals, clinics and general

practitioners need to be educated about the warning signs of oncological diseases.

Most (87%) of the rhabdomyosarcomas are found in the under 15-year age group. [8] Age related differences are observed for the different sites of primary disease. [8] The head and neck and genitourinary systems are most often involved in the 2 to 6 year age groups. [8]

The median age of 5 years found in this study group of less than 15 years corresponds with Brown et al, which yielded similar results. [9] Their age ranged from < 1 year to 14 years and their median age was 6.2 years. [6] The primary site of disease in our study, as well as with Brown et al, was the head and neck, followed by the genitourinary system. This correlates positively with the age and primary site association as found in western literature. Francis et al differed with the literature and found that the extremities (50%) were the most common sites of disease. [14] They also had a predominance of alveolar RMS, which together with this site signifies a poor prognosis. We only had 2 patients with this site of disease.

There was a slight male predominance in our study, which correlated positively with other reports in the literature. Francis et al in Nigeria had a two-thirds male predominance. [14] Further associations between gender and stage indicated that stage III had an almost equal male to female ratio at 76% compared to 69%. Stage IV had a female predominance of 31% compared to 24% male. We found the median age for stage III was 6 years and Stage IV was 7 years.

The histological findings of our study differ from Western countries in that our second commonest histological subtype was the unspecified type. This may be due to earlier pathology services not being as advanced as modern day services, available at our tertiary hospital. Or it may be that unspecified truly is the commonest after embryonal in our institution.

In the retrospective Moroccan study by Hessisen et al, the main problems regarding treatment were lack of availability of chemotherapeutic agents leading to chemotherapy substitutions. [16] Most of the available drugs were donated either by parents or volunteer groups. Therapeutic abandonment constituted a major problem and occurred at a rate of 37% with 89% of these abandonments occurring during chemotherapy. Abandonment was not a factor in this study but remains a pertinent problem in other African countries with reasons ranging from lack of finances and transport to lack of understanding by parents, which is dependent on level of education.

Approximately 91% of our patients were stage III and IV at time of diagnosis. This was due to late presentation in advanced stages of disease, which played a major role in the poor outcome of the patients in this study subsequently leading to an overall 5-year survival rate of 45% in the availability of multimodal therapy.
There are many factors that have to be considered as a reason for the delay in presentation: lack of awareness of signs and symptoms of oncological diseases, by the public and medical practitioners, cultural differences amongst the population related to cancer, residence in rural areas, with lack of finances and lack of transport to primary or secondary hospitals and many other reasons.

Delay in diagnosis occurred in 8 patients and was due to delay in referral to an oncology centre for appropriate diagnostic work up. There was no delay in making the diagnosis. In contrast to other African centers, the unit has access to diagnostic work-up services including full access to radiological imaging which is essential to diagnosis and staging. The unit had also access to multimodal treatment which was provided to 58% of our patients with this treatment. The unavailability of pathology services, radiotherapy and other modalities in African countries is a major contributing factor to the poor outcome shown in available African data.

CONCLUSION

The characteristics of rhabdomyosarcoma at Tygerberg Children's Hospital are similar to those of first world countries. Pediatric RMS has the same site predilection, age distribution, histological subtype and (prognostic factors) as in Western countries. We have late presentation in advanced stages of disease and higher mortality rates in common with other African countries. In contrast,

we have access to diagnostic facilities and multimodal therapy. Recognition of early warning signs and public awareness could lead to earlier presentations and improve outcome. Further multicentre studies are needed in Africa to report our experiences with rhabdomyosarcoma.

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FOOTNOTES

Conflicts of interest: The authors declare no competing conflicts of interest

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