

Original Article

Clinicopathological characteristics and treatment patterns in children with Rhabdomyosarcoma at Tikur Anbessa Specialized Hospital, Ethiopia

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Abstract

Background: Rhabdomyosarcoma (RMS) is the most common type of soft tissue sarcoma in children and adolescents, making up almost half of all cases. The clinical presentation of rhabdomyosarcoma varies on the site of involvement and the histological subtypes vary based on the age and site of occurrence. This study aimed to summarize pediatric RMS patients' clinical profiles and histological subtypes.

Methods: This retrospective study was conducted at Tikur Anbessa Hospital in children diagnosed with RMS between March 2017 to March 2022. The collected data comprised the socio-demographic profile of patients, the clinical characteristics, the histological subtypes, and treatment patterns of RMS. The collected data were analyzed using a statistical package for social sciences (SPSS) version 25. A chi-square test was performed to assess the association between variables.

Results: Fifty histopathologically confirmed RMS patients met the inclusion criteria. Most patients (66%) were under five years old, with a median age of three years (range: 1 month to 14 years). Time from symptom onset to pediatric oncology presentation ranged from 1 week to 2 years, with a median of five months. Swelling was the most common symptom (90%, n=45), and the head and neck were the most frequently affected sites (56%). One-fifth (20%) had distant metastasis at diagnosis. Embryonal RMS was the most common histology subtype (53.7%), followed by alveolar RMS (41.5%). Nearly all patients (96%) received systemic chemotherapy, while 52.1% underwent combination therapy, including surgery and radiotherapy.

Conclusion: Most pediatric patients diagnosed with rhabdomyosarcoma were younger than five years old and experienced delayed presentation of more than three months from the onset of symptoms. Emphasis has to be given to improving early diagnosis of pediatric rhabdomyosarcoma and the practice of local therapy measures has to be strengthened.

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Introduction

Rhabdomyosarcoma is the predominant type of soft tissue sarcomas accounting for 40% of all pediatric soft tissue sarcomas and it is the third most common extracranial solid tumor (1,2). It has a slight male predominance, and the majority of pediatric soft tissue sarcomas occur sporadically, though association with certain familial syndromes has been reported (1-4).

The clinical presentation of RMS varies based on the site of involvement; Head-neck and genitourinary sites are commonly involved in children under 10 years of age and adolescents usually present with swellings on the extremities, trunk, and para testicular sites. Pediatric RMS may present with a swelling, or proptosis in the head and neck region; urinary obstruction, hematuria, constipation, vaginal bleeding, or vagina discharge in genitourinary RMS (2,4-7).

A study done in Nigeria in children with rhabdomyosarcoma revealed that the age range was from 1 to 14 years with a mean of 6.2 years, and the male: female ratio was 1.5:1. The majority of RMS tumors were in the head, and neck region (50.6%) (8). A retrospective analysis of Pediatrics RMS in Egypt showed that the Head and Neck region were the most common site of involvement, and most patients presented with an advanced stage IV and stage

III (9,23).

A descriptive retrospective review of pediatric patients aged less than 18 years in Tanzania showed swelling was the commonest presentation and most patients presented with large tumors greater than 5 cm. The review also revealed that most patients presented with stage IV disease, and the lung was the most common site of distant metastasis (10).

A multicenter study done in Dakar, Senegal showed extremity RMS was the most frequent, followed by Head and Neck RMS, and most patients had tumors greater than or equal to 5 cm (11). A multi-center analysis of pediatric rhabdomyosarcoma patients treated in four LHEAR countries (Slovenia, Slovakia, Croatia & Romania) showed all patients received systemic chemotherapy, 57% had radiotherapy, and 63% had surgery as local control. The five-year OS for patients with localized disease was 72% compared to 24% for metastatic disease(12).The treatment of rhabdomyosarcoma is complex and requires a multidisciplinary treatment with systemic chemotherapy, surgery, and radiotherapy is the mainstay of treatment in children and adolescents with rhabdomyosarcoma (12-22). Despite the multimodal therapy, some rhabdomyosarcoma (RMS) patients achieve less than a complete response and may develop acute toxicity during the treatment course (20-24).

Based on Estimates of Cancer Incidence in Ethiopia in 2015, soft tissue sarcoma accounted for 5% of all childhood cancers (7). However, there was no well-documented data about pediatric RMS's clinical presentation and treatment profiles. Thus, this study aimed to provide a detailed analysis of the clinical characteristics, histopathological subtypes, and treatment profile patterns in children with rhabdomyosarcoma at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Methods

Study design, setting and period

A hospital-based cross-sectional study was carried out and the data were collected from October 1, 2022, to October 30, 2022. The study was conducted at the Pediatrics Haemato-Oncology Unit at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Tikur Anbessa Specialized Hospital is the biggest tertiary hospital in the country and is one of the largest pediatric haemato-oncology treatment centers in the county. The pediatric haemato-oncology unit provides both inpatient and outpatient services for an average of 8,000 pediatric hematology and oncology patients per year and an average of 700-900 patients per month.

Sampling

All radiologically and pathologically confirmed rhabdomyosarcoma in children under the age of 15 years from March 2017 to March 2022 were included in the study. Children with non-rhaboid soft tissue sarcomas, tissue biopsies revealing other solid cancers and benign

tumors, and patients with incomplete records were excluded. A total of fifty (50) patients met the inclusion criteria and were included in the study.

Data collection and data analysis

Data were collected by the principal investigator and trained general practitioners. The study questionnaires had four parts: Part I was about the socio-demographic characteristics of the study participants, Part II was about the clinical profile of patients at presentation, Part III was about the diagnosis and stages of the disease, and Part IV was about the treatment profiles of children diagnosed with RMS at Tikur Anbessa Specialized Hospital. After selecting the study cases, the data was collected from the registration log book, the patient card, and the follow-up chart by the data collectors. The administered questionnaire encompasses the socio-demography profile, clinical profile, and outcome. The collected data exported to SPSS version 25 for analysis. P-value <0.05 was considered to be statistically significant.

Data quality control

To ensure data quality, the structured questionnaire checklists were tested on 5% of the sample. Problems highlighted during the pre-test were corrected before the start of the data collection. Each question was properly coded; the principal investigator did continuous cross-checking during the pre-test and data collection period. The collected data were checked for completeness and consistency on each day of data collection.

Results

Socio-demographic profile of children diagnosed with Rhabdomyosarcoma

Data from all fifty histopathological confirmed rhabdomyosarcoma patients were successfully retrieved. More than half of the patients, 27 (54%) were males. The median age at diagnosis was 3 years with a range of 0.1-14 years.

Children below 5 years of age accounted for 66% of the patients and 18% of cases were between 5-10 years of age. [Table 1] The majority of patients; 46% (n=23) came from the Oromia region, and only 8% (n=4) came from Addis Ababa, the capital city [Figure 1]. Near half of the patients, 46% (n=23) came from rural areas for treatment.

Table 1- Socio-demographic characteristics of Children with Rhabdomyosarcoma, Tikur Anbessa Hospital, Addis Ababa, Ethiopia (n=50)

Variable	Category	Frequency	Percentage (%)
Age category	<5years	33	66
	5–10 years	9	18
	10–15 years	8	16
Sex	Male	27	54
	Female	23	46
Residence	Oromia	23	46
	SNNPR	13	26
	Amhara	7	14
	Addis Ababa	4	8
	Others	3	6

SNNPR: Southern Nations, Nationalities, and Peoples' Region

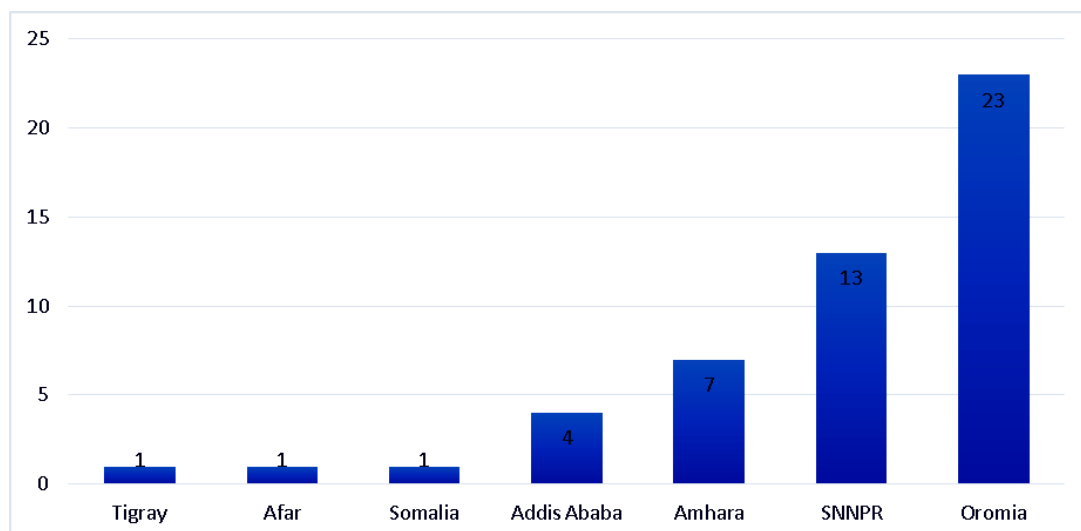


Figure 1- Geographical distribution of children with RMS at Tikur Anbessa Hospital (n=50)

Clinicopathological profile and Staging of Pediatric Rhabdomyosarcoma at the time of diagnosis

The majority of study participants; 45(90%) had swelling at their initial presentation. Pain and voiding complaints were found at the time of diagnosis in 10(20%) patients. About 8% of patients had difficulty of breathing at presentation. The time to presentation; the duration of

symptoms ranges from 1 week to 2 years with a median of five months with an IQR range of 2- 7 months.

The Head and Neck region was the commonest site of occurrence; the primary site was orbital in 30% (n=15) cases, Para-meningeal in 20% (n=10) cases, and genitourinary sites accounted for 16 % of cases. [Table 2].

Table 2- Sites of primary tumor in children with rhabdomyosarcoma at Tikur Anbessa Hospital, Addis Ababa, Ethiopia (n=50)

Variables	Site of involvement	Frequency	Percentage
Pediatric RMS patients (n=50)	Orbital	15	30
	Para meningeal	10	20
	Head and Neck - Other Sites	3	6
	Genitourinary (Non-prostate, Non-bladder)	5	10
	Genitourinar (Prostate or Bladder)	3	6
	Extremities	5	10
	Other Sites	9	18

The size of the primary tumor at initial presentation ranged from 1cm to 41cm with an average size of 8.85 cm. The size of the tumor is greater than 5cm in the majority of patients constituting 66% (n=33). About 40% of the patients had regional lymph node involvement at presentation, and one-fifth of children; 20% (n=10) had distant metastasis at the time of diagnosis.

The majority of the patients presented with Stage III disease accounting for 40% (n=20)

followed by Stage I disease constituting 36% [Figure 2].

Of all 50 patients who had histologic confirmed diagnosis of Rhabdomyosarcoma, only 41 (82%) had their histologic subtypes reported. Embryonal Rhabdomyosarcoma was the most common histologic subtype accounting for 53.7% (n=22) followed by the alveolar subtype rhabdomyosarcoma accounting for 41.5% as shown in Figure 3 and Table 3.

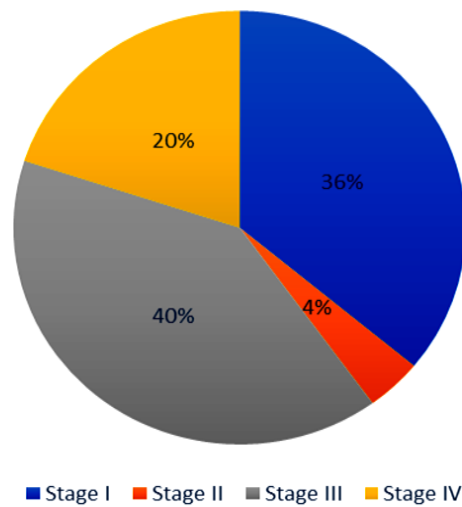


Figure 2: The stages of Childhood Rhabdomyosarcoma at the time of Diagnosis at Tikur Anbessa Hospital

Table 3: Clinicopathological Characteristics and Staging in Children with Rhabdomyosarcoma at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia (n=50)

Variables		Frequency	Percentage
Size of the Tumor(n=50)	≤5cm	17	34
	>5cm	33	66
Histologic Subtype (n=41)	Botryoid	1	2.4
	Embryonal	22	53.7
	Alveolar	17	41.5
	Spindle Cell	1	2.4
Major presenting symptoms	Swelling	45	90
	Pain	10	20
	Difficulty of breathing	4	8
	Difficulty of swallowing	3	6
	Voiding problem	10	20
	Constipation	2	4
	Nonspecific symptoms	31	29.5
Stage of the disease at presentation	Stage I	18	36
	stage II	2	4.0
	Stage III	20	40.0
	Stage IV	10	20.0
Regional Lymph node involvement	Yes	20	40.0
	No	30	60.0
Staging at the time of diagnosis	Localized	40	80%
	Metastasis	10	20%

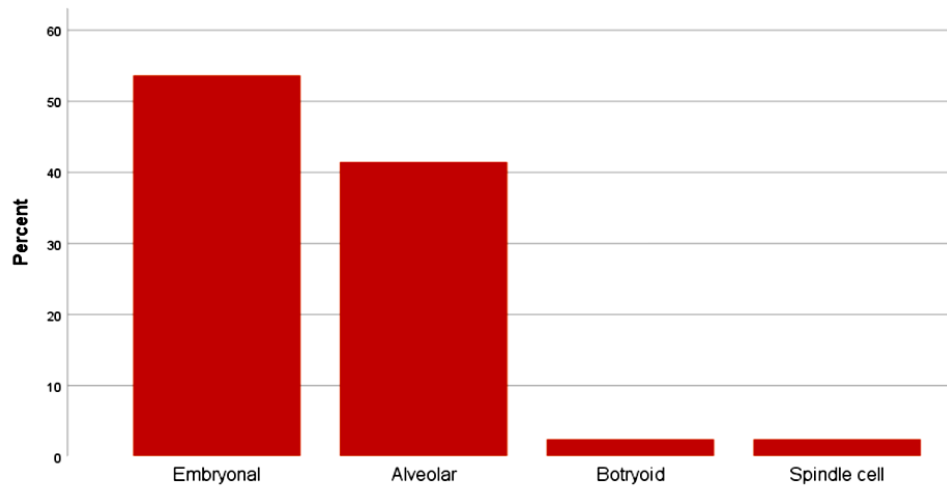


Figure 3: Histologic subtypes of Pediatric Rhabdomyosarcoma at Tikur Anbessa Hospital

Patterns of treatment profile in children with rhabdomyosarcoma

For children diagnosed with rhabdomyosarcoma, treatment was provided with a combination of systemic chemotherapy, and local control measures such as surgery and radiotherapy. About 96% (n=48) of patients were treated with systemic chemotherapy, 34% (n=17) had

surgery, and 24% (n=12) patients received radiation therapy. More than half of the patients (52.1%) had been treated with a combination of two or more types of treatment modalities. The mean duration of systemic chemotherapy was 26 weeks with a range of 1-42 weeks as shown in Figure 4.

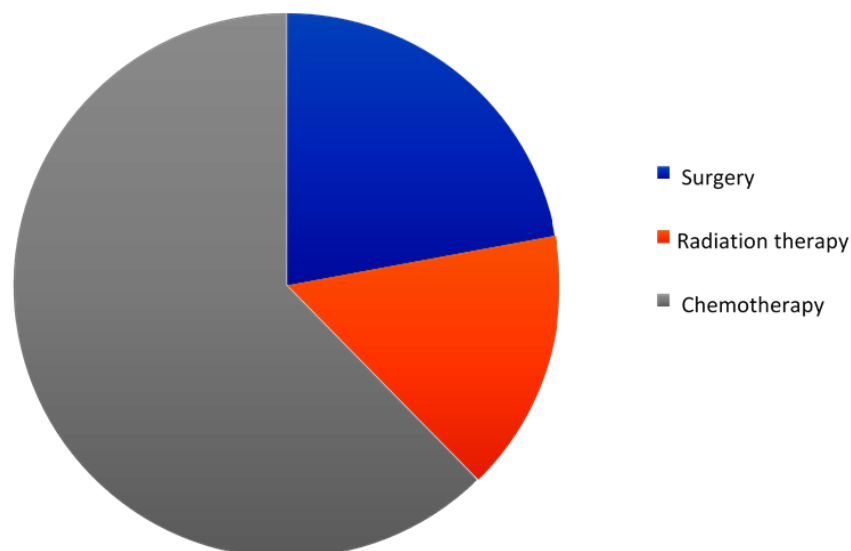


Figure 4: Treatment patterns profile in children diagnosed with rhabdomyosarcoma at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia (n=50)

Factors associated with the histologic subtype in pediatric Rhabdomyosarcoma

A chi-square test was performed to assess the association between age and histologic subtype

and histologic subtype with the primary site of tumor occurrence (Table 4). The associations were not statistically significant at a p-value of <0.05.

Table 4: Association between Histologic Subtypes and Primary Site of Occurrence in Pediatric Rhabdomyosarcoma at Tikur Anbessa Hospital, Addis Ababa, Ethiopia (n=41)

Category	Variables	Histologic Subtype				P value
		Botryoid	Embryonal	Alveolar	Spindle cell	
Age	< 5years	1(3.7%)	13(48.1%)	12(44.4%)	1(3.7%)	0.89
	5-9 years	0(0.0%)	5(62.5%)	3(37.5%)	0(0.0%)	
	10-15 years	0(0%)	4(66.7%)	2(33.3%)	0(0.0%)	
Primary site of occurrence	Orbital	0(0%)	6(50%)	6(50%)	0(0%)	.066
	Para meningeal	0(0%)	4(57.1%)	3(42.9%)	0(0%)	
	Head and Neck - Other sites	0(0%)	2(100%)	0(0%)	0(0%)	
	Genitourinary (Prostate or Bladder)	1(33.3%)	1(33.3%)	1(33.3%)	0(0%)	
	Genitourinary (Non-Prostate, nonbladder)	0(0%)	5(100%)	0(0%)	0(0%)	
	Extremities	0(0%)	1(20%)	3(60%)	1(20%)	
	Other sites	0(0%)	3(42.9%)	4(57.1%)	0(0%)	

Discussion

The study was done in one of the biggest tertiary referral hospitals, serving as the only center for the treatment of pediatric cancer patients till recently, and this study analyzed the clinical presentation, Clinicopathological Characteristics and Patterns of Treatment in Children with Rhabdomyosarcoma (RM) at Tikur Anbessa Specialized Hospital, Ethiopia. The study also analyzed the patterns of treatment profiles and the practice of local measurements in the study setting. Our findings have shown that pediatric Rhabdomyosarcoma is slightly more common in males and two-

thirds (66%) of the patients were diagnosed under 5 years of age, similar to other studies in Africa and the developed world (6,8). Swelling was the commonest clinical presentation; the median time to presentation to the oncologic center was five months with a range of one week to two years. About two-thirds of the patients had a tumor size of more than 5 cm at the time of diagnosis and most of the patients had late presentation similar to other low- and middle-income countries (9,11). The study revealed more than 50% of pediatric rhabdomyosarcoma occurred in the Head and Neck region, and the Orbit was the

commonest site of involvement and this was supported by other studies. Embryonal rhabdomyosarcoma was the most frequent histological subtype, constituting more than half of the cases (53.7%) followed by alveolar RMS (1,8,9,10,13).

Sixty percent of pediatric rhabdomyosarcoma patients presented with locally advanced disease (stage III) and distant metastasis (stage IV) at the time of diagnosis. One-fifth of the patients had stage IV disease at the time of diagnosis which was lower than studies done in Egypt, but higher than reports from Tanzania (9,10). A chi-square test was performed to assess the association between the factors and histologic subtypes, but the associations were not statistically significant at a set p-value of 0.05.

More than half of the patients (52.1%) had been treated with a combination of two or more treatment modalities. Systemic chemotherapy was administered for more than 95% of patients, and only nearly half of the patients got local control measures either surgery or radiation therapy. The mean duration of chemotherapy was 25.6 weeks with a range between 1 to 42 weeks. The local control measures in these settings were very low as only half of the patients had either surgery or radiation compared to other studies (14,15,23,24). Though systemic chemotherapy was administered in nearly all patients, the practice of local control measures with surgery, radiotherapy, or both was low and emphasis has to be given as local control is fun-

damental for the treatment of Rhabdomyosarcoma.

Limitations of the study

The limitation of this research is that the study didn't specifically investigate the overall survival status of children with rhabdomyosarcoma and the effects of local control measures such as surgery or radiotherapy in pediatric rhabdomyosarcoma. Furthermore, the study used small sample size and single center which hinder the generalizability of the findings.

Conclusion

Most of the pediatric Rhabdomyosarcoma occurred in children below five years of age. More than two-thirds of patients had delayed presentation and had a tumor size of more than 5 cm at the time of diagnosis. Though systemic chemotherapy was the main treatment modality, the practice of local control measures with surgery, radiotherapy, or both was low and emphasis has to be given as local control is fundamental for the treatment of soft tissue sarcoma.

Declarations

Ethical approval and consent to participate

Approval for the present study was obtained from the Research and Publication Committee of the Pediatrics and Child Health Department (DRCP), School of Medicine, College of Health Sciences, Addis Ababa University. The requirement for informed consent was waived because of the anonymous nature of the data.

Availability of data and materials

The datasets used and analyzed are available upon reasonable request from the corresponding author.

Contribution of Authors

B.Y.: Inception of the idea, data collection, data analysis, write-up; G.A.: Data analysis, review of the manuscript, and write-up; A.H.: Data analysis, review of the manuscript, prepared figures 1-6; A.M.: Data analysis, review of the manuscript, and prepared tables 1-5; All authors reviewed the manuscript and approved it for publication.

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Competing interests

We have no competing interests.

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