

Spectrum of Rhabdomyosarcoma in a Tertiary Care Center – A 20 Year Study

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ABSTRACT

Background: Rhabdomyosarcoma (RMS) is a rare tumor. It is the commonest soft tissue tumor in children. It is the third most common extracranial solid tumor in children. Head neck region was the most common sites followed by extremities, orbit, vagina, bladder and etc. Most of the cases are diagnosed in first decade of the life. The commonest histological type is Embryonal Rhabdomyosarcoma (E RMS).

Aims and Objectives: The aim of our study was to see the distribution of RMS among children below 18 years of age. To note the distribution of age, sex of the children, site of the tumor, and the histological type of the tumor. It is classified as low, intermediate and high-risk group and the stage of the tumor also determined during presentation.

Materials and Methods: The study was carried out in a Tertiary Care Center over a period of 20 years (2001-2021). We took all the specimens came to the Department of Pathology with Clinical diagnosis of RMS. We then performed the histopathological processing of the specimens by standard technique. We also noted the history, investigations from the specimen request form.

We took the Ethics Committee approval from the Institutional Ethics Committee and took the informed consent from the patients and patient party.

Result and Analysis: There were 123 children in our study. The most common age group was 1-10 years. The most frequent site was Head Neck region. The most frequent histological type was E-RMS.

Conclusion: Early diagnosis, early implementation of management (Surgery, Chemotherapy and etc.) and patients' awareness are necessary for the better outcome.

KEY WORDS: Rhabdomyosarcoma, Embryonal Rhabdomyosarcoma, histopathology, soft tissue sarcoma, surgery, chemotherapy.

ARTICLE DETAILS

Published On:
14 September 2026

Available on:
<https://ijpbms.com/>

INTRODUCTION

Malignant tumors are rare in children. Malignant tumors in Pediatric age group comprise 1-3% of all malignancies [1-2]. Rhabdomyosarcoma (RMS) is a rare malignant tumor arising from skeletal muscle. According to United States National Cancer Institute the rare cancers have an incidence of less than 15/ one lakh people per year [3]. In Europe the rare cancers are defined as the incidence of less than 6 per one Lakh people per year [4]. RMS is the most common malignant soft tissue tumor in childhood [5-6]. It is the third most common extracranial solid tumor of Pediatric age group

after Neuroblastoma and Nephroblastoma [7]. The annual incidence of Rhabdomyosarcoma is 4.3 per million under the age of 20 years[8].

Head Neck region was the most common site followed by extremities[8]. More than 50% cases were diagnosed in the first decade of life[4-5]. The main histological types of RMS are of two types . 80 % are Embryonal variety and 20% are Alveolar type. Embryonal type usually carry better prognosis. Fusion of Transcription factor gene FOXO1 to PAX 3 or Pax 7 found in Alveolar variety of RMS (ARMS) [9]. Chromosomal translocations involving chromosomes 2 or 1

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and chromosome 13, t(2;13) and t(1;13)), are found in ARMS. It is detected by Cytogenetics [10]. Maximum RMS occurs in children within the age of 2-6 years and also in 14-18 age group.

The median age of diagnosis is 5 years [9-11]. In a study conducted by Ferrari A et al. 15 patients had congenital RMS out of 50 infants. The RMS diagnosed within 4 weeks of birth is known as congenital RMS [12]

Olga et al. conducted a study on RMS in infants and children. They showed that the prognosis of RMS in infants was better when compared to other children. But in previous studies it was concluded that the infants had worse prognosis [11]. Again according to some other studies the prognosis of infants and other children were same [11-12].

The differential diagnosis includes other small blue round cell tumor of pediatric age group and hematolymphoid tumors. Immunohistochemistry for Myo D1, Myogenin, Desmin, Vimentin are needed for confirmation of the diagnosis [13].

The prognosis of RMS depend on several features. The prognostic factors are age of the patient, sex of the patient, size of the tumor, site of the tumor e.g head and neck, orbit, extremities, retroperitoneum, stage of the tumor, and nodal status. Male sex, age more than 10 years, size more than 5 cm, sites like tumors on extremities and in retroperitoneum have worse prognosis [14].

The head and neck, orbit, vagina, para testis were considered as favourable sites. Rest were unfavourable [15].

The chromosomal number aberration can be seen in 20%-50% of cases of E-RMS. In 30% of E-RMS there is loss of chromosome pairs of 9,10,15. The gene amplification seen in chromosome region 12q13-q15. Mutation in oncogene and tumor suppressor gene is more common in E-RMS. The most common translocation seen in A-RMS in t(2;13)(q35;q14) and t(1;13)(p36;q14). The fusion gene *PAX3-FOXO1* and *PAX7-FOXO1* is formed. A-RMS has been divided into Fusion positive and fusion negative type [16-17].

The incidence of RMS is high in Africa and it is variable in different parts of Africa. Compared to Europe the incidence is low in Asia [16].

AIMS AND OBJECTIVES

The objective of our study was to find out the distribution of Rhabdomyosarcoma in pediatric age group, to find out the age and sex of the patients affected, site of the tumors, the histological type of the tumor, and the lymph node status of the patients affected by RMS.

MATERIALS AND METHODS

The study was carried out in the department of Pathology of a Tertiary Care Center over a period of 20 years (2001-2021). The Ethical clearance was taken from the Institutional Ethics Committee. Informed consent was taken from the patients and the patient party. We included all the clinically and radiologically diagnosed cases of Rhabdomyosarcoma,

whose core needle biopsy or excision biopsy were sent to the department of Pathology for histopathological examination. We noted the chief complaints of the patients, took the detailed history from the patients or patient party and noted site of the tumor and presence of any enlarged lymph nodes were also noted. All the investigation reports were compiled. After receiving of the specimen we examined the specimen and put the large specimens in 10% Neutral Buffer Formalin overnight. On the next day the grossing was carried out. During Grossing the specimens were inspected, measurements were taken. The sections from the tumor, surgical margins, deep margin and taken. Multiple sections were taken from the tumor. Usually one section per each cm of the tumor was taken. Then it was processed for histopathology by Leica automated tissue processor.

We included all the specimens received by the department of Pathology. The core needle biopsy, incisional biopsy and excised specimens were incorporated in the study. After receiving the small biopsy samples were fixed for at least 6-8 hours and then sent for processing by the standard technique. After processing Formalin Fixed Paraffin Embedded blocks (FFPE) were made in the tissue embedding station. Then tissue sections were cut at 4-5 micron using Digital Leica Microtome. All the sections were stained routinely by Hematoxylin & Eosin (H&E) stain. Most of the Pediatric RMS were of Embryonal variety. So there was always a differential diagnosis of Round Cell Tumor (RCT). So the application of Immunohistochemistry (IHC) was essential for confirmation. Alveolar variety and other types of RMS also needed IHC confirmation. So IHC was applied wherever needed for confirmation of the diagnosis.

RESULT AND ANALYSIS

In our study we came across 123 RMS patients over the period of 20 years (2001-2021). All the patients were below 18 year. The majority of the patients were in the age group of 1-9 years. In most of the cases the tumors occurred in 1 year to 5 year age group. There were 5 (4%) cases of Congenital RMS. Among infants there were 18 cases (15%). 90 cases were found in 1 to 9 year age. It is occasionally seen in 9-16 year age group and rarely seen after 16 year (Table no.1.). The males outnumbered the females. 66 (54%) patients were male and the rest 57 (46%) patients were female (1.2:1)

The most frequent site was head neck region (Fig. A & B) followed by orbital region, extremities, vagina, bladder and others (Fig.C). Intra abdominal and pelvic tumors were also noted (Table no.2.) Different histological types of RMS were found. The commonest variety was Embryonal RMS (Fig.D,E &F). Embryonal variety was found in 92 children comprising 75% of cases. Next common was Alveolar type in 20 patients (16%). Other types were Botryoid RMS found in 7 cases (6%). 4 tumors (3%) fell under Others. In others there are mixed tumors or RMS- NOS. IHC Myogenin show nuclear positivity in RMS (Fig. F).

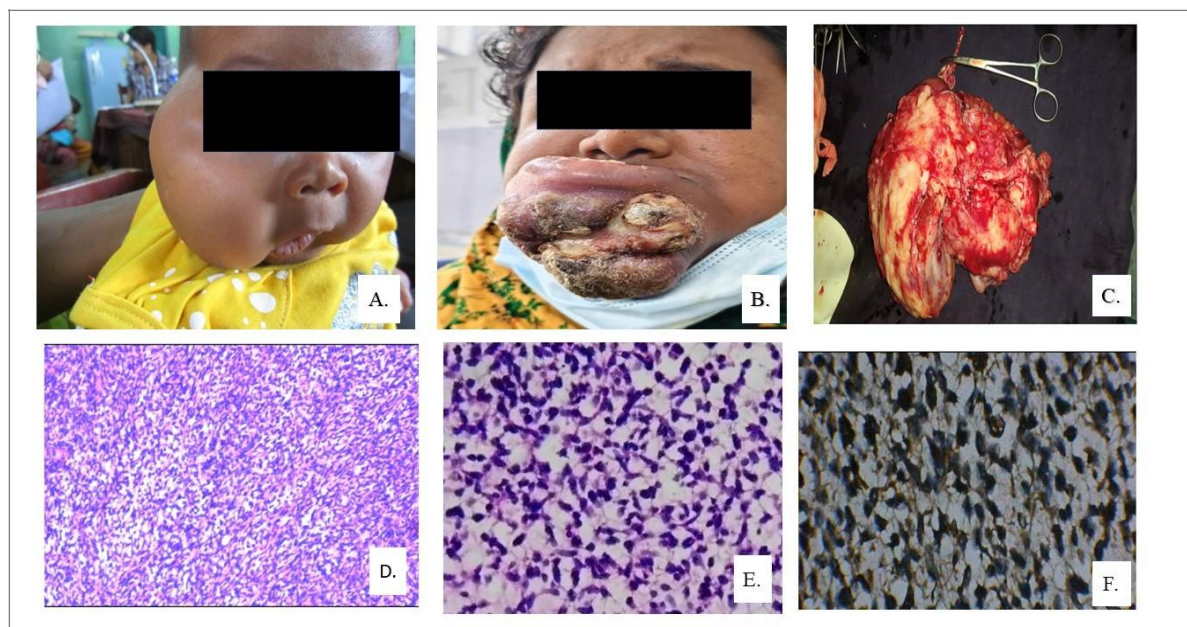
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Table no. 1. Distribution of age group

Age group	No of Cases	Percentage
Congenital	5	4%
Infants	18	15%
1 – 9 year	89	72.1%
9 – 16 year	10	8.1%
17 – 18 year	01	0.8

Table no. 2. Distribution of Sites

Site	No. Of cases	Percentage
Head Neck region	52	42.4%
Orbit	14	11.4
Extremity	30	24.4
Back	3	2.4
Vagina	4	3.2
Pelvic	8	6.5
Intra abdominal	7	5.7
Bladder	5	4



- A. Facial swelling in a case of rhabdomyosarcoma of head.
- B. Swelling in lower face and neck in a case of rhabdomyosarcoma of neck.
- C. Grey white, lobulated and nodular, fleshy omental mass showing areas of haemorrhage in a case of omental rhabdomyosarcoma.
- D. & E. H&E(100X) shows tumour composed of small round to oval and few spindle shaped cells with scant cytoplasm arranged in sheets in ERMS.
- E. IHC (Myogenin,400X) showing nuclear positivity in rhabdomyosarcoma.

DISCUSSION

This study consists of 123 children with RMS over a period of 21 years. Deepak Bansal et al found in their study in India that among 159 patients the median age was 4 years and 13% of them were infants [8]. Skapek SX et al. have shown that the commonest age group affected was 0-9 years. There were 20 infants and 5 congenital tumors [10]. RMS occurs in children within the age of 2-6 years and also in 14-18 age group [9-11]. Shern et al. found that their 50% of patients were in the age group of 01-10 years [7].

The children with RMS showed the male : female ratio was 2.7:1 [7]. In a study comprising 5656 patients showed that 55% of cases were within 1-9 years. There was 57% male and 43% were female [18]. Martin-Giacalone BA et al. showed the males were predominantly affected than females [16]. In a study comprising 124 patients Markiz SN et al. showed that the male to female ratio was 2.4:1[19]. Our study also showed the similar to above studies. The majority of the patients within the age of 1- 9 year. There was male predominance. Male : Female ratio was 1.2:1.

Among 123 patients 18 (15%) cases were infants and 5 (4%) congenital cases. These are similar to the studies by Skapek SX et al. The most common age group of 1-9 years is also identical with above studies. Dipak Bansal et al. found 15% infants in their series.[8]

Histological types of RMS were mainly Embryonal Rhabdomyosarcoma and Alveolar Rhabdomyosarcoma. Other types were mixed Pleomorphic and Spindle cell [19-21]. The most common type was Embryonal [21]. ERMS, the commonest variety, mostly occurs in head neck region.

ARMS is the next common tumor. It occurs usually in extremities and trunk [22].

In our series the commonest histological variety was ERMS followed by ARMS which are similar to the above studies.

The most common site of tumor was Head and Neck region followed by genitourinary system and extremities [21]. In another study the most frequent site was Head neck region [19].

Matthew T et al. showed that the most frequent site was Trunk followed by Head Neck and

Extremities and Genitourinary system [18]. In our cases, we also came across the similar result. The commonest variety was ERMS followed by ARMS. The most frequent site was Head Neck followed by extremities.

The children with Rhabdomyosarcoma can be classified into Low risk, Intermediate risk, High risk [23].

Prognosis of the patients depend on the site of primary tumor, histological type and clinical risk group. On the other hand unfavourable site, high risk group failure to response to initial therapy resulted in poor prognosis [19].

Intergroup Rhabdomyosarcoma Study Group (IRSG) along with Children's Oncology Group

(COG) Soft-Tissue Sarcoma (COG-STS) guided the risk stratification of RMS patients based on the residual tumor after surgery and lymph node involvement. Based on these factors the patients were divided into Group I, Group II, Group III and Group IV. (Table no.3). This group system can predict the survival of the patients [14]. Based on this system the low, intermediate and High risk group classification given (Table no.4) [23].

Table no. 3 Clinical Group Classification according to IRS

Group	Definition
Group I	Localized disease, completely resected
Group II	Total gross resection, with evidence of regional spread
A	Grossly resected tumor with microscopic residual disease
B	Involved regional nodes completely resected with no microscopic residual disease
C	Involved regional nodes grossly resected with evidence of microscopic residual disease
Group III	Biopsy only or incomplete resection with gross residual disease
Group IV	Distant metastatic disease (excludes regional nodes and adjacent organ infiltration)

Table no. 4 : The classification of Risk group

Risk Group	Stage	Clinical Group	Age
Low	1	I, II, III (orbit only)	Any
	2	I, II	
Intermediate	1	III (non-orbit)	Any
	1, 2, 3	I, II, III	
	2, 3	III	

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	3	I, II	
	4	IV	<10 years
High	4	IV	>10 years
			Any

FOXO1 fusion is not seen in more than 95% ERMS. On the other hand 80% of ARMS have FOXO1 fusion. Fusion negative ARMS in low risk group children has better prognosis than fusion positive low group Rhabdomyosarcoma [24].

In spindle cell RMS MYOD1 (L122R) mutation are found in older children and it leads to worse prognosis [25-26]. Presence of TP53 mutation in Fusion negative RMS come across dismal prognosis [23].

Immunohistochemistry(IHC) is also needed for confirmation of the different types of RMS. Myogenin and Myo D1, Desmin were positive for all the types of RMS. Other IHC like AP2 β , HMGA2, Nestin, and SIRT1 are also positive in RMS[27]. Cytogenetics and molecular technique are helpful for diagnosis of RMS [16].

Standard therapy of the tumor is surgery excision with wide margin 1.5 cm, followed by chemotherapy and radiotherapy. If the margins are negative there is less chance of recurrence. In case of positive margins chance of recurrence is there. In cases of recurrence radiotherapy is needed[21]. Prognosis of Head Neck RMS was better than RMS of other areas. without radiotherapy the prognosis was worse [27]. Neoadjuvant Chemotherapy usually given in North American Centers and some practise Surgery followed by Chemotherapy, with or without Radiotherapy. Multimodal treatment is beneficial for RMS. Neoadjuvant chemotherapy, complete resection and radiotherapy. The cure rate of RMS is about 70%. The treatment was done according to European paediatric Soft tissue sarcoma Study Group (EpSSG) and the Cooperative Weichteilsarkom Studiengruppe (CWS) [28]. Rijs Z. Et al showed that with the use of Real-time intraoperative Fluorescence-guided imaging can aid the complete resections by determining tumor tissue and tumor free resection margin during surgery [29]. Rhabdomyosarcoma must be differentiated from Wilms' tumor, Ewing sarcoma, neuroblastoma, pheochromocytoma, liposarcoma, osteosarcoma, acute myelocytic leukemia, acute lymphoblastic leukemia, and non-hodgkin lymphoma[17].

In our series, the most of the children presented within 1-9 year of age group. The commonest site of the tumor was Head Neck region. Mostly the histopathological variety was Embryonal Rhabdomyosarcoma. The patients were treated by Surgery, Chemotherapy and Radiotherapy. Five year survival rate was on and average was 70%. Our findings were corroborated with most of the above studies.

CONCLUSION

Rhabdomyosarcoma commonly occurs in the age group of 1-9 year. The most frequent site was Head Neck region. Most

of these tumors were Embryonal Rhabdomyosarcoma. Clinical suspicion, CT scan and histopathological examination of the surgical specimen needed for the final diagnosis. The standard treatment were Surgery, Chemotherapy and Radiotherapy. Early diagnosis, early management and close follow up can improve the outcome.

CONFLICT OF INTEREST STATEMENT

None. FUNDING

None declared.

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