Original Research Paper

Volume-9 | Issue-9 | September - 2019 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Oncology

CLINICAL PRESENTATION AND OUTCOME IN CHILDHOOD RHABDOMYOSARCOMA--AN INSTITUTIONAL EXPERIENCE

Bhargab Jyoti Saikia	Professor, Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
Sreya Mallik	Senior Resident, Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.
Munlima Hazarika*	Professor, Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India. *Corresponding Author
P. S. Roy	Professor, Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India.

ABSTRACT **BACKGROUND:** Rhabdomyosarcoma is the most common soft tissue sarcoma in children constituting 3.5% of the cases of cancer among children aged 0 to 14 years. The aim of the study is to analyse demography, clinical characteristics and outcome of paediatric rhabdomyosarcoma in a cancer care center of North-East India.
METHODS: A retrospective analysis was performed on medical records of children with rhabdomyosarcoma who were treated at Dr. B. Borooah Cancer Institute from 2014 to 2017.
RESULTS: The median age of presentation was six years with male predominance. Head and neck was the most common primary site and embryonal was the most frequent histopathologic subtype with a favourable outcome. Lung was the most common site of distant metastasis. Overall survival rate at 1 year was 81.08% and at 2 year was 56.75%. Median progression free survival was 29.2 ± 5.3 months.
CONCLUSION: The epidemiological characteristics of our patients are quite near to the worldwide data, apart from the survival.

KEYWORDS : Children, Demography, Rhabdomyosarcoma, Survival

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. The annual incidence of RMS in children below 19 years is 4.9 cases per million [1] of which 50% of cases are seen in the first decade of life [2]. RMS accounts for approximately 3.5% of all cases of cancer among children aged 0 to14 years and 2% of the cases among adolescents and young adults aged 15 to 19 years [3]. In all age groups, the tumour is slightly more common in males and Caucasians [2]. RMS is the third most common extracranial solid tumour in children after neuroblastoma and Wilms tumour. However, in adults, RMS represents <1% of all solid tumour malignancies [4]. Several distinct histologic groups have prognostic significance, including embryonal rhabdomyosarcoma (ERMS), which occurs in two thirds of the patients [5] the botryoid type; alveolar type [6]; and "undifferentiated". type. Head and neck RMS are more common in younger children and extremity tumours are more common in adolescents. 15%-25% of newly diagnosed patients may have distant metastasis. The lung is the most frequent site of metastasis (40% - 50%) [7]. Approximately 35%-40% of all RMS arise from the head or neck region,15-20% from extremities and 20-25% from genitourinary tract (bladder and prostate, vagina and uterus, paratesticular) and remainder from truncal primaries and other sites (around 5-10% each)[8]. In patients with localized disease, overall 5-year survival rates have improved more than 80% with the combined use of surgery, radiotherapy, and chemotherapy [9]. 5-year event-free survival rate in metastatic disease is less than 30%. Those patients with metastatic disease without other high-risk factors (i.e. unfavourable site, more than 3 sites, bone marrow involvement and age younger than 1 year or older than 10 years) have a better prognosis [10]. But in Indian scenario the situation is different from the developed countries due to socioeconomic and logistic issues. There is not much published data on paediatric rhabdomyosarcoma in Indian population. So aim of the study is to evaluate the clinical presentation and outcome in a cancer care centre in North-East India.

MATERIALS AND METHODS

A retrospective observational analysis was performed on medical records of children with RMS who were treated and followed up in the Department of Medical & Pediatric Oncology, Dr. B. Borooah Cancer Institute (BBCI), Guwahati, Assam during the period from January 2014 to December 2017. Patients were followed up till December 2018. The follow up period ranged from 3 months to 41 months with a median of 25.3 months. Data were collected retrospectively from individual medical case records.

The medical records were reviewed for
(i) Personal data i.e., name, age, sex and residence
(ii) Presenting symptoms and signs
(iii) Primary site of the tumor
(iv) Histopathology of the tumor and immunohistochemistry
(v) Risk stratification
(vi) Treatment protocols including surgery, radiotherapy and chemotherapy
(vii) Treatment outcome.

Inclusion criteria: Children from 0 to 18 years of age group attending medical and pediatric oncology OPD of our Institution since 1st January, 2014 till 31st December, 2017 diagnosed as RMS by histological examination and confirmed by immunohistochemistry.

Exclusion criteria: Patients above 18 years and who had synchronous other malignancy or previously diagnosed and/or treated for other malignancy were excluded.

Stage was determined according to Clinical Group (surgico-pathologic), developed by Intergroup Rhabdomyosarcoma Study Group (IRSG) and the pretreatment site-modified TNM staging system. Survival status was determined from the date of registration for every patient. Chemotherapy protocol used was either IRS IV protocol (Vincristine, Etoposide, Ifosphamide and Actinomycin D) or VAC (Vincristine, Doxorubicin and Cyclophosphamide) alternating with IE (Ifosphamide and Etoposide).

Statistical Methods

Patient and demographic characteristics were analyzed using median/centiles and mean. Survival curve was estimated using the Kaplan-Meier method. Analyses were performed in SPSS 18.0 software. Two tailed p-values less than 0.05 were considered statistically significant at 95% confidence interval.

RESULTS

A. Demographic Characteristics

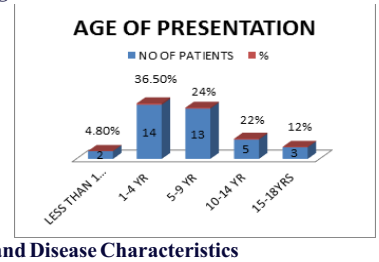
From 2014 to 2017, 48 patients of paediatric rhabdomyosarcoma were registered at BBCI, Guwahati, Assam. Among them 37 patients were analysed in this study. Twenty-nine patients (78.3%) were from rural background and eight (21.7%) were from urban locality.

The median age of presentation was 6 years (range 1-16 years) and twenty four patients (65.4%) were below the age of 10 years of age [Fig 1][Table 1]. Twenty one (56.7%) out of thirty seven patients was male and sixteen (43.3%) were female [Table 1]. The male to female ratio was 1.5:1.

Table 1.Demographic characteristics of the patients

Age in years	No. of patients (n=37)	(%)
< 10	24	65.4
>10	13	34.6
	No. of patients (n=37)	(%)
Male	21	56.7
Female	16	43.3

Figure 1. Age Distribution



B. Patient and Disease Characteristics

Head and neck was the most commonly "affected" primary site of tumour followed by extremities and genitourinary. Eleven (30%) patients presented with primary tumour at parameningeal site, eight (22%) presented with orbital disease and five patients (13%) presented with extremity tumour and four patients (11%) presented with genitourinary tumour. [Table 2]. The embryonal RMS was the most frequent histopathologic subtype. Twenty five out of thirty seven patients (67%) had embryonal subtype, followed by alveolar type (24%) and lastly the botryoid, spindle cell and anaplastic consisting of three percent for each subtype [Table 3],[Fig. 2]. Nineteen patients (51%) were non metastatic and ten patients (27%) had distant metastasis at presentation, lung being the most common site of distant metastasis(60%) followed by bone marrow (20%), bone(10%) and liver (10%). Eight (22%) patient presented with lymph nodal metastasis at diagnosis [Fig.3].Seventeen (46%) patients belonged to intermediate risk category, thirteen (35%) patients were in low risk category and seven (19%) patients were in high risk category [Table 4].

Table 2.

Primry site	No of patients (n=37)	(%)
Parameningeal	11	30
Orbit	8	22
Extremity	5	13
Genitourinary	4	11
Other Head and Neck	4	11
Trunk, Retriperitoneum	5	13

Table 3: Histopathological subtypes of tumour

Histopathology	No. of patients	(%)
Embryonal	25	67
Alveolar	9	24
Botryoid	1	3
Spindle cell	1	3
Anaplastic	1	3

Figure 2. Histopathological subtypes

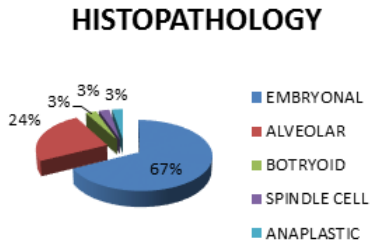


Figure 3. Site of Distant Metastasis

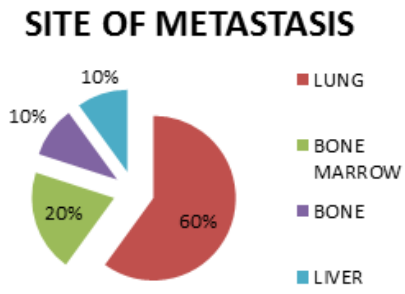


Table 4. Risk Stratification

Risk Classification	No of patients	(%)	Description
Low Risk	13	35	All favourable site non metastatic Embryonal RMS and Unfavourable site, resected non metastatic Embryonal RMS
Intermediate Risk	17	46	All non metastatic Alveolar RMS and Unfavourable site, unresected Embryonal RMS
High Risk	7	19	All metastatic RMS

C. Treatment Characteristics

Twenty seven (73%) out of total thirty seven patients were treated with radical intent. Out of all non-metastatic cases, 17 patients (63%) received radiotherapy as radical treatment modality and 10 patients (37%) underwent surgery as radical treatment. All patients received chemotherapy with either IRS IV [11] protocol or VAC/IE protocol. Thirty three (89%) patients received IRS IV protocol and four (11%) patients received chemotherapy with VAC/IE.

D. Treatment outcome and survival

The estimated overall survival (OS) rate at 1 year was 81.08% and at 2 year was 56.75%. The estimated progression free survival rate (PFS) at 1 year was 75.67% and at 2 year was 51.35%. Median progression free survival was 29.2 months ± 5.3 months [Fig. 4]. In our study lost to follow up patients are considered for events for analysis of progression free survival.

There was a significant relationship between metastasis and survival (p =0.0024), where 80% of patients who had distant metastasis at time of diagnosis died while 72.4% of patients without metastasis survived [Table 5]. There was a significant relationship between histological type and disease recurrence (p =0.013). Disease recurred in 6 patients out of 9 patients (66%) of Alveolar histology and 9 patients out of 25 patients (36%) of Embryonal histology.

Figure 4. Median progression free survival

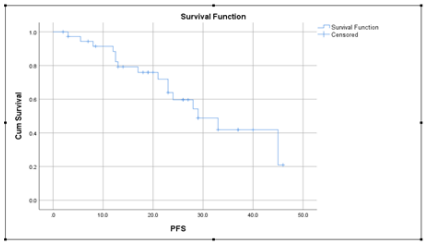


Table 5.

	OVERALL SURVIVAL RATE		PROGRESSION FREE SURVIVAL RATE
1 YEAR	81.08%		75.67%
2 YEAR	56.75%		51.35%
METASTASIS	SURVIVOR	DEAD	P Value
+ve (n=10)	2 (20%)	8 (80%)	0.0024
-ve (n=27)	20 (72.4 %)	7 (27.6%)	

DISCUSSION

Rhabdomyosarcoma (RMS) is a highly malignant and most common soft tissue sarcoma in the first two decades of life, with a peak incidence in very young children [3]. The median age of our patients was 6 years with 65.4% of patients were below the age of 10 years of

age. These results are similar to a study conducted by Badr et al. (2012) [12] who reported the same median age but with 80.4% of patients below the age of 10 years. It has also been reported by Shouman (2005) [13] as the same median age of six but with 60% of patients below the age of 10 years. The IRS IV reported that the median age of patients was 5-year, with 72% of patients below the age of 10 years [14]. In our study 56.7% of patients were males while 43.3% were females with male to female ratio of 1.5:1. IRS IV reported higher male to female ratio (1.6:1) [14].

In our study, head and neck was the most common affected primary site of tumor (63%), followed by extremities (13%) and genitourinary (11%).These results are different from IRS IV who reported that the genitourinary is the second most common affected site. Abd El Aal et al.,[15] also reported that the genitourinary is the second most common affected site (23.6%), after head and neck (36.4%), followed by extremities (16.3%).This difference can be explained by small number of our patients compared to these studies.

Our study showed that embryonal RMS was the most frequent histopathologic subtype (67%) while alveolar RMS represents 24% of patients. A study by Hessissen et al.showed that embryonal subtype represents 73% while alveolar subtype represents 13% of patients [16]. The IRS IV reported that 70% of the patients with embryonal type which is quite near to our results. In our study, 22% of patients had lymph node (LN) involvement at time of diagnosis. This result has some difference as compared to a study by Shouman [13] and the IRS IV who found that15% of patients had LN involvement. Hosoi et al.,(2007)[17] showed that 19% of patients had LN involvement. Our study showed that 27% of patients had distant metastasis at time of diagnosis. Koscielniak et. al. [18] reported that fewer than 25% of patients have metastatic disease at diagnosis. Patients with distant metastasis at time of diagnosis can be explained by the unawareness of primary health care physicians about early presenting symptoms and signs of the disease, together with the unavailability of diagnostic facilities which can allow earlier picking up of cases with localized disease.

In our study, there was a significant statistical relationship between histopathologic subtypes of tumor and outcome. Disease recurred in 6 patients out of 9 patients (66%) of Alveolar histology and 9 patients out of 25 patients (36%) of Embryonal histology. There was a significant relationship between metastasis and outcome (p =0.0024), where 80% of patients who had distant metastasis at time of diagnosis died while 72.4% of patients without metastasis survived. Study conducted by Badr et. al [12] showed similar type of result. Breneman et. al.[19] found that children with metastatic disease at diagnosis have the poorest prognosis.

In our study, the estimated overall survival (OS) rate at 1 year was 81.08% and at 2 year was 56.75%. The estimated progression free survival rate (PFS) at 1 year was 75.67% and at 2 year was 51.35%, which is quite less as compared to other reported in literature [12] [13]. The most likely reason is lack of long term follow up record and loss of follow up of the patients.

The major limitations of our studies are small sample size, retrospective data and short median follow up period. Our study provided some database for paediatric rhabdomyosarcoma as there is lack of data for the same in North –East India.

CONCLUSION

Rhabdomyosarcoma is the fourth most common solid childhood tumour in our Institution. Chemotherapy forms the integral part of the treatment however it also requires the local therapy (Surgery and/or RT). The epidemiological characteristics of our patients are quite near to the worldwide data, apart from the survival. Our study needs further long term follow up for better analysis of outcome.

REFERENCES

[1] Casillas J, Ross J, Keohan ML, et. al. Soft tissue sarcomas. In: Bleyer A, O'Leary M, Barr R, Ries LAG eds. Cancer epidemiology in older adolescents and young adults 15-29 years of age, including SEER incidence and survival: 1975-2000. Bethesda, MD: National Cancer Institute 2006, 81-96; NIH Pub No. 06-5767

[2] Ognjanovic S, Linabery AM, Charbonneau B and Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States,1975–2005.Cancer 2009;115:4218–26.

[3] Ries LA, Kosary CL, Hankey BF et al. SEER Cancer Statistics Review,1973–1996,National Cancer Institute,1999 Bethesda, MD, USA.

[4] Sultan I, Qaddoumi I, Yaser S. et. al. Comparing adult and paediatric rhabdomyosarcoma in the surveillance, Epidemiology and End Result program, 1973-2005:An analysis of 2600 patients. J Clin Oncol 2009;27:3391-3397

[5] Newton WA Jr, Gehan EA, Webber BL,et. al. Classification of rhabdomyosarcoma and related sarcomas: pathological aspect and proposal for a new classification. An Intergroup Rhabdomyosarcoma Study. Cancer 1995;75:1073-85.

[6] Rudzinski ER, Teot LA, Anderson JR, et al. Dense pattern of embryonal rhabdomyosarcoma, a lesion easily confused with alveolar rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Am J Clin Pathol 2013;140:82–90.

[7] Weiss AR, Lyden E, Anderson JR, et. al. Histologic and clinical characteristics can guide staging evaluation for children and adolescents with rhabdomyosarcom: a report from the Children's Oncology Group Soft tissue Sarcoma Committee. J. Clin Oncol 2013;26:3226-3232.

[8] Raney RB, Walterhouse DO, Mezza JL, et.al. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committeeof the Children's Oncology Group.J Clin Oncol 2011; 29(10):1312-1318.

[9] Punyko JA, Mertens AC, Baker KS, et al. Long-term survival probabilities for childhood rhabdomyosarcoma: a population-based evaluation, Cancer 2005; 103: 1475–83.

[10] Bou´e DR, Parham DM, Webber B, Crist WM, Qualman SJ. Clinico pathologic study of ectomesenchymomas from intergroup rhabdomyosarcoma study groups III and IV, Pediatric and Developmental Pathology 2000; 3:290– 300.

[11] Raney RB, Maurer HM, Anderson JR, et. al. The Intergroup Rhabdomyosarcoma Study Group (IRSG): Major Lessons From IRS-I Through IRS IV Studies as Background for the Current IRS V Treatment Protocols, Sarcoma 2001;5:9-15.

[12] Badr MA, Al-Tonbary YA, Mansour AK,et. al. Epidemiological Characteristics and Survival Studies of Rhabdomyosarcoma in East Egypt:A Five-Year Multicenter Study ISRN Oncology 2012;2012:1-8.

[13] Shouman T, El-Kest I, Zaza K et al. Rhabdomyosarcoma in childhood: a retrospective analysis of 190 patients treated at a single institution, Journal of the Egyptian National Cancer Institute 2005;17: 67– 75.

[14] Crist WM, Anderson JR, Meza JL et al. Intergroup Rhabdomyosarcoma Study-IV: results for patients with nonmetastatic disease, Journal of Clinical Oncology 2001; 19: 3091–3102.

[15] Abd El-Aal HH, Habib EE, Mishrif MM. Rhabdomyosarcoma: the experience of the pediatric unit of Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) (from January 1992 to January 2001), Journal of the Egyptian National Cancer Institute2006;18:51– 60.

[16] Hessissen L, Kanouni L, Kili A et al. Pediatric rhabdomyosarcoma in Morocco. Pediatric Blood and Cancer2010:54: 25–28.

[17] Hosoi H, Teramukai S, Matsumoto Y et al. A review of 331 rhabdomyosarcoma cases in patients treated between1991 and 2002 in Japan," International Journal of Clinical Oncology2007;12:137–45.

[18] Koscielniak E,Harms D,.Henze G,et al. Results of treatment for soft tissue sarcoma in childhood and adolescence: a final report of the German cooperative soft tissue sarcoma study CWS-86, Journal of Clinical Oncology1999;7:3706–19.

[19] Breneman JC, Lyden E, Pappo AS et al. Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma—a report from the Intergroup Rhabdomyosarcoma Study IV, Journal of Clinical Oncology2003;21:78–84.