

Pediatric Rhabdomyosarcoma in Child's Central Teaching Hospital: An Eight-Year Experience

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Abstract

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in the first two decades of life. There is, however, a paucity of reports on the pattern of its occurrence in Iraq. **Aim:** To determine the demographic characteristics, clinical presentation, and survival among children with RMS treated at Child's Central Teaching Hospital (CCTH). **Patients and Methods:** A retrospective study was on 48 patients of histologically proven RMS, in previously untreated children aged <15 years old at the CCTH in Baghdad, during the period from January 2009 to December, 2017. **Results:** Forty-eight patients with confirmed RMS were included. The mean age (standard deviation) was 4.9 (3.5) years. Thirty-four patients (70.8%) were <6 years, male 22 patients (46.8%), female 26 patients (54.2%), male:female ratio of approximately 1:1.2. Histopathology was embryonal in 38 case (79.1%). Incisional biopsy was done in 21 patients (43.8%), while excisional biopsy in 18 (37.5%) patients. The head and neck was the most common site of involvement at presentation, (nonorbital) 16 (33.3%) of cases. The estimated 4-year event-free survival (EFS) was $26.3\% \pm 7\%$. Twenty-one (43.8%) patients abandoned treatment. Among the cases who completed their treatment in the center, eight cases (16.7%) relapsed. In univariate analysis using log-rank test, nodal involvement was found to significantly influence the EFS at 4 years ($P = 0.01$). The estimated 4-year overall survival was $41.4\% \pm 9\%$. Nodal involvement significantly reduces overall survival at 4 years ($P = 0.006$). **Conclusions:** Clinical features and epidemiology of RMS in Iraqi children treated at CCTH somewhat resembles those of other countries. However, the EFS at 4 years and overall survival at 4-years are lower than that reported elsewhere.

Keywords: Excisional biopsy, rhabdomyosarcoma, the head and neck

INTRODUCTION

Rhabdomyosarcoma (RMS) represents the most common soft tissue tumor among children. It is responsible for approximately one-half of all soft tissue sarcomas. In this age group,^[1] RMS may occur at virtually any anatomic site, but the head and neck are usually account (25%), orbit (9%), genitourinary tract (24%), and extremities (19%), retroperitoneal and other 7 sites account for the remainder of primary sites. RMS is divided into histologic subtypes. Embryonal RMS (ERMS) and alveolar RMS (ARMS) are major subtypes accounting for approximately 60% and 20% of cases, respectively. There are three histological variants of RMS, which are ERMS, ARMS, and pleomorphic RMS. The ARMS and ERMS being the most frequent childhood forms. Now, the WHO includes spindle cell/sclerosing RMS as a distinct entity.^[2,3] The typical signs and symptoms of RMS in children are soft-tissue mass and are often described as painless masses found in the extremities, head and/or neck

region, the signs and symptoms can be due to mass effect on adjacent organs or neurovascular tissues or associated with a visible mass protruding from an orifice^[4] ERMS often occurs in areas of very little skeletal muscle, such as the orbit, pharynx, sinuses, vaginal wall, and paratesticular tissues. ARMS has a greater tendency to occur in the area of skeletal muscle such as the trunk and limbs. There may be palpable regional lymphadenopathy and, occasionally (with alveolar histology tumors), distant involved nodes and metastases to the skeleton or marrow. RMS may disseminate

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early and cause symptoms of pain or respiratory distress associated with pulmonary metastases.^[5] RMS is diagnosed by direct analysis of tumor tissue from either an incisional or excisional biopsy sample or core needle biopsy sample that is subjected to a series of histology and molecular pathology studies.^[3] Curing RMS, first requires eradication for the gross primary tumor by the use a combination of surgery and/or external beam-ionizing radiation. The systemic chemotherapy is important to eradicate disseminated disease that is assumed or proven to exist in most children with RMS.^[6] RMS disease status can be described in terms of both stage and clinical group. RMS is divided into four Stages (1–4), depends on the anatomical site of the primary tumor, tumor's size, presence or absence of regional lymph node involvement, and presence or absence of distant metastasis.^[7] Clinical Group (I to IV) applies surgical and/or pathological features including the degree of resection of localized or regionally spread tumor and the presence or absence of distant metastasis.^[8]

Aim of the study

To determine the demographic characteristics, clinical presentation, and survival among children with RMS treated at Child's Central Teaching Hospital (CCTH).

PATIENTS AND METHODS

Study design

A retrospective descriptive study conducted in the Pediatric Hematology-Oncology unit in the CCTH, Baghdad, over a period of 1 year from the February 1, 2019 to the January 1, 2020. Including 48 patients of histologically-proven diagnosed RMS among children aged <15 years old who had been diagnosed since January 2009 to December 2017 with a period of follow-up till December 2019.

Data collection

A systematic review was done on the medical records for demographic data, date of the diagnosis, duration of treatment, presentation, investigations, site, size, staging, and outcome.

Diagnosis

The diagnostic evaluation focused on delineating the extent, of the primary tumor, and the location and extent of metastatic disease and consisted of the following: (1) Complete history and physical examination including measurements of the primary tumor and assessment of regional lymph nodes. (2) Laboratory tests including complete blood count, comprehensive metabolic panel including liver and renal functions and urinalysis. (3) Assessing the primary tumor and metastatic disease by imaging included Abdominal and pelvic ultrasound, chest computed tomography (CT) magnetic resonance imaging (MRI). (4) Metastatic workup of lung metastasis. MRI/CT of draining lymph nodes. All patients had a histological confirmation of RMS, and were classified as embryonal, alveolar or undifferentiated subtypes. The site of primary tumor was classified into five groups; head and

neck nonorbital, orbital, genitourinary tract, extremities, and other localizations.

Staging

The staging of the tumor was classified according to the clinical group classification system for RMS^[9] into (I-IV). Patients were also classified according to site, size, LN and whether distant metastasis was identified upon presentation. The outcomes were mainly analyzed over a minimum period 3 years follow-up: alive, dead, or loss of follow-up. Overall survival (OS) is defined as the duration from the date of diagnosis to the date of death from any cause, with patients last known to be alive censored at the date of last contact.^[10] Event-free survival (EFS) is defined as a duration from the date of diagnosis to the date of the first of completion or going off treatment protocol without complete remission (CR), relapse from CR, or death due to any cause.^[10] Patients last known to be alive without an event were censored at the date of the last contact. OS and EFS were calculated using the Kaplan–Meier method (K–M) can estimate how long after starting a particular treatment that the studied event (e.g., death, relapse, etc.) occurred for individuals, who were not otherwise lost to the sample or until the study has ended.^[11] Events were defined as relapse or resistance and death. The patients that abandoned treatment were censored in the analysis at the time of loss follow up.^[10]

Management

Treatment of the patients started by chemotherapy according to third group high-risk protocol for RMS. Relapse protocol for relapsed cases. Surgery accordingly and lastly by radiotherapy for indicated cases.^[12]

Statistical analysis

The normality of distribution of continuous variables was tested by the one-sample Kolmogorov–Smirnov test. Means and standard deviations (SDs) were given for the normally distributed variables, while median, minimum, and maximum values were given for variables that were not normally distributed. Frequencies and percentages were used to present categorical variables. Chi-square test was used to test whether the final outcome of treatment occurred the independent of the presence of distant metastasis upon presentation. Survival analyses are statistical methods used to examine changes over time to a specified event. Kaplan–Meier can estimate how long after starting a particular treatment that the studied event (e.g., death, relapse, etc.) occurred for individuals, who were not otherwise lost to the sample or until the study has ended.^[11] The log-rank test calculates Chi-squares (χ^2) for each event time, which are summed to calculate an ultimate Chi-square for each arm.^[13]

RESULTS

A demographic characteristics of RMS patients are demonstrated in Table 1, 48 patients, with confirmed RMS were included; in this study. Mean age (SD) was 4.9 (3.5) years. Thirty-four patients (70.8%) were <6 years. The median duration of

symptoms onset was 2 months. Twenty-six patients (54%) were females with a male:female ratio of approximately 1:1.2. Incisional biopsy was done in 21 patients (43.8%). Histopathology was embryonal in thirty-eight cases (79.1%), immunohistochemistry (IHC) was done in 21 patients (43%).

The most common site of involvement at presentation was head, and neck (nonorbital) in 16 patients (33.3%) as in Table 2.

Thirty-seven patients (77%) had late presentation (Stage III or VI). Moreover, thirty-six cases (75%) had tumors larger than 5 cm [Table 3].

Table 4 shows the outcome of RMS cases according to tumor localization. Twenty-one patients (44.1%) were lost to follow-up during the study period. Eleven patients (23.1%) had long-term remission.

Nineteen cases (39.6%) were from Baghdad, while 12 cases (25%) were from Al-Hilla province. The number of patients and finale outcome in each province is shown in Table 5.

The estimated 4-year EFS was $26.3\% \pm 7\%$. Twenty-one patients (43.7%) abandoned treatment, however, six patients were contacted: five (17.1%) are dead, one (2.9%) are still alive. Among the cases who received their treatment in the center, eight (16.7%) relapsed, three (18.8%) are still alive, and five (20.8%) died during the follow-up period. The EFS for patients without nodal involvement was $38\% \pm 10\%$, while for patients with nodal involvement, it was $6.7\% \pm 6\%$ [Table 6]. In univariate analysis using log-rank test, nodal involvement was found to significantly influence the EFS ($P = 0.01$). The presence of metastatic disease at the start of treatment did not significantly influence the EFS ($P = 0.08$).

The estimated 4-year overall survival was $41.4\% \pm 9\%$. The estimated OS at 4 years was $57.8\% \pm 12\%$ for patients without LN involvement and $10\% \pm 9\%$ for patients with LN involvement. In univariate analysis using log-rank test, nodal involvement was found to significantly influence OS ($P = 0.006$), while the presence of metastatic disease at the start of the treatment did not significantly influence the OS ($P = 0.18$). The final outcome of 48 patients 14 patients (29.1%) while the dead patients were 13(27%) and loss of follow up 21 patients (43.7%) [Table 7].

DISCUSSION

This study examines the demographic characteristics and survival among RMS patients treated in CCTH in Baghdad from 2009 through 2017. Almost two-thirds of patients were diagnosed before the age of 6 years with a slight female predominance, consistent with Gurney *et al.*^[14] Nonetheless, it is well known that RMS has a slight male predominance. The intergroup RMS study IV, which involved 1.016 patients, the male:female ratio was 1.6:1.^[15] The Egypt study of 190 children with RMS reported that male:female ratio was 2:1. A median age at presentation was 6 years and 60% were younger than

Table 1: Demographic characteristics and laboratory findings of rhabdomyosarcoma patients

Characteristics	Value
Number of cases	48
Mean age (years) (SD)	4.9 (3.5)
Median duration of symptoms (minimum value, maximum value)	2 months (7 days, 2 years)
Gender, n (%)	
Male	22 (46.8)
Female	26 (54.2)
Investigations (SD)	
Mean PCV	32.6 (6.7)
Mean WBC (cell/mm ³)	11.226 (4.998)
Mean platelet count (cell per mm ³)	365 (170)
Biopsy, n (%)	
Incisional biopsy	21 (43.7)
Excisional biopsy	18 (37.5)
FNAC	6 (13)
Not recorded	3 (6.3)
Histopathology, n (%)	
Embryonal	38 (79.1)
Alveolar	4 (8.3)
Unclassified	6 (12.5)
Immunohistochemistry, n (%)	
Done	21 (43.8)
Not done	27 (56.3)

FNAC: Fine needle aspiration cytology, PCV: Packed cell volume, WBC: White blood cells, SD: Standard deviation

Table 2: Site of rhabdomyosarcoma upon presentation

Characteristics	n (%)
Site of involvement at presentation	
Head and neck; non orbital	16 (33.3)
Extremities	11 (22.9)
Bladder	9 (18.8)
Orbital with bone erosion	4 (8.3)
Orbit without bone erosion	4 (8.3)
Genital	2 (4.2)
Other*	2 (4.2)

*A case presented with a retroperitoneal mass and another with pelvic mass

Table 3: Stage and size of rhabdomyosarcoma upon presentation

Characteristics	n (%)
Stage	
I	6 (12.5)
II	1 (2.1)
III	19 (39.6)
IV	18 (37.5)
Not recorded	4 (8.3)
Size (cm)	
<5	8 (16.6)
>5	36 (75)
Not recorded	4 (8.3)

Table 4: Outcome of cases according to tumor localization

Localization	No	Alive, n (%)		LOF, n (%)	Death, n (%)
		Remission	Relapse		
Nonmetastasis	32	9 (18.9)	2 (4.2)	13 (27.3)	8 (16.8)
Metastasis	14	2 (4.2)	1 (2.1)	7 (14.7)	4 (8.4)
Not recorded	2	0	0	1 (2.1)	1 (2.1)

LOF: Loss of follow-up

Table 5: Final outcome across Iraqi provinces

Province	n (%)	Outcome		
		Alive, n (%)	Dead, n (%)	Lost to follow-up, n (%)
Baghdad	19 (39.6)	5 (10.4)	8 (16.7)	6 (12.5)
Al-Hilla	13 (27.1)	6 (12.5)	1 (2.1)	6 (12.1)
Al-Anbar	5 (10.5)	2 (4.2)	1 (2.1)	2 (4.2)
Al-Diwaniyah	3 (6.3)	0	1 (2.1)	2 (4.2)
Najaf	2 (4.2)	0	1 (2.1)	1 (2.1)
Karbala'a	2 (4.2)	1 (2.1)	0	1 (2.1)
Nasiriyah	1 (2.1)	0	0	1 (2.1)
Muthanna	3 (10.5)	0	1 (6.3)	2 (4.2)
Total	48	14 (29)	13 (27)	21 (43.7)

Table 6: 4-year survival as a function of lymph node involvement and metastasis

Factor	EFS±SE (%)	P	OS±SE (%)	P
LN involvement				
Negative	38±10	0.01	57.8±12	0.006
Positive	6.7±6		10±9	
Metastasis				
Nonmetastatic	31.3±9	0.086	50.3±11	0.18
Metastatic	19±11		29.1±16	

EFS: Event-free survival at 4 years, LN: Lymph nodes, OS: Over-all survival at 4 years, SE: Standard error

Table 7: Final outcome of 48 patients

Outcome	n (%)
Dead	13 (27)
Alive	14 (29.1)
Loss of follow-up	21 (43.7)

10 years.^[16] Moreover, the study was done by Abd El-Aal *et al.*^[17] showed 55 new patients of RMS treated at the pediatric unit clinic of Kasr El Aini Center of Radiation Oncology. Males comprised (63.6%) of the patients and the median age was 6 years. In an earlier report from Children's Welfare Teaching Hospital (CWTH) in Iraq, the median age was 4.2 years, and the male:female ratio was 1.5:1. Histopathology is not always sufficient for an unequivocal diagnosis, necessitating ancillary studies, including IHC. However, in this study, IHC was done in almost half of patients, because it is not widely available in Iraq during the treatment period. Moreover, a small 27 portion of patients, especially in the early period of

the study, had fine-needle aspiration cytology done instead of the biopsy required for IHC to be performed. This could be attributed to the lack of cooperation from the surgical team in these cases. The IHC results are in agreement with other studies that demonstrate the high sensitivity and specificity of IHC in RMS.^[18] The most common site of involvement was nonorbital head; and neck in a third of patients, which can rise to almost half of the cases if we account for orbital tumors. The extremities and genitourinary tract were equally the next mostly involved sites three consecutive intergroup RMS study group international rubber study group (IRSG) trials which included more than 2,700 patients, 35% of them had head and neck tumors. The next most common site was the genitourinary tract (24%).^[19] Embryonal subtype was the most common histopathology, accounting for 79.1% of cases. In a report from Morocco by Hessissen *et al.*, the most frequent subtype was embryonal subtype (73%), while the most common site of disease was head and neck, followed by the genitourinary tract and limbs.^[20] Another study from CWTH in Iraq obtained similar findings with the head and neck involved in 64% followed by the genitourinary tract (14%) and embryonal subtype was the most common pathology.^[18] Shouman *et al.*^[16] found that the primary site of tumor was highest in the head and neck (36.4%), followed by abdominal sites (23.6%). Embryonal type was the most common one (87.3%). Similar results were obtained by Unuvar A *et al.*^[21] the primary site of tumor was highest in the head and neck (31.4%) followed by genitourinary tract (21.6%), embryonal type was the most common type (80.4%). The three main treatment modalities of children with sarcomas are surgical removal (if feasible), radiotherapy for local control, and chemotherapy for systemic control.^[22] Patients are usually referred for other centers outside the hospital for histopathology, radiotherapy, ophthalmology, and orofacial surgery. Coordination between these institutions in this regard is difficult, and there is a risk of abandonment; when the patients are transferred between institutions. Most of the chemotherapeutic drugs available, at the unit are donated by nonprofit institutions and volunteer associations, and some drugs are not regularly available. The forementioned reasons could explain the high abandonment rate (41%) seen in this study. Other studies from Morocco and Turkey revealed comparably high rates of abandonment.^[21] Many patients seek medical care in other institutions outside the country once the diagnosis is confirmed or at early stages of treatment. Loss of follow up is a very real problem throughout the developing countries. Malignant diseases associated with poor prognosis seem to have a high abandonment rate. It is also related to the socioeconomic and educational status of. Parents and travel time to treatment centers. Linking between public hospitals in developing countries and established cancer centers elsewhere, which includes several preventative interventions, has clearly been shown to work.^[23]

Most of patients in this investigation (83%) had clinical Groups III and IV disease, which is higher than the rate found by the IRSG I, II, and III studies.^[10,11,24] These findings are

consistent with the CWTB study in Iraq. In extensive analysis reported by Al-Hadad *et al.* investigated the various difficulties in cancer diagnosis and management in Iraq. In this report, the significant delay between the disease manifestation and referral to specialized centers could be caused by delays in the diagnosis or the problems of transportation; faced by families who live in distant provinces. A relatively high fraction of patients are lost to follow-up because of economic and security problems, financial and psychological, exhaustion as they cannot afford the prolonged treatment cost.^[25] These findings highlight the need for an early detection program to be employed. Such programs can involve physician training abroad and assessing the feasibility of modern treatment protocols as in certain campaigns.^[26] More than two-thirds of the cases had large tumor size upon presentation, which parallels the results obtained by IGRS IV.

Most patients were from Baghdad and to a lesser extent, Babel. The other study in CWTB had almost half of patients from Baghdad, reflecting the high population density and easy referral from the capital.^[18] With combined modality therapy, the OS of children with nonmetastatic RMS has dramatically improved from 25% before 1970 to more than 75% in 2001 (IRSG IV). The survival obtained in this study lags behind these numbers remarkably. However, abandoning treatment can have a huge influence on the estimated survival rate. Lymph node involvement negatively influenced patient's survival in this study, while metastasis does not. These findings are in line with the results of the IGRS IV. While the number of metastatic sites is found to be correlated with survival in the later study, the analysis in our study did not differentiate between patients according to the number of metastatic site and were grouped according to whether distant metastasis existed upon presentation. However, the survival among patients with metastasis was lower but did not reach the level of significance. This study has several weaknesses. First, the high abandonment rate in the analysis could largely influence the survival analysis. Some of these patients could have a favorable outcome and yet are considered an event in the survival analysis. Secondly, the retrospective design has its merits. In such type of research, the researcher obviously relies heavily on records and observations made by other observers. The number of cases enrolled in this analysis is not sufficient to make powerful group analyses. The rarity of RMS despite the long observation period and the single-center design are two apparent reasons.

CONCLUSIONS

1. Over-all survival and EFS of patients with RMS in CWTB is considerably lower than that seen in other developed countries
2. A substantial number of patients abandon treatment at various points in time
3. Nodal involvement upon presentation has a negative impact on survival among RMS patients.

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Conflicts of interest

There are no conflicts of interest.

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