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Original article

Rhabdomyosarcoma in Children in the Five-Year Period in Oncology Unit in a Pediatric Teaching Hospital

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SUMMARY

Introduction/Aim. Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in pediatric population and adolescents. Limited data is available on the characteristics of RMS in Iraqi pediatric patients. The aim of the study was to examine the clinical and histological aspects of RMS in Iraqi children, with a focus on their response to treatment, prognosis, and survival.

Methods. A retrospective cohort study was conducted at the Oncology Unit of Children's Welfare Teaching Hospital, Medical City, Baghdad, Iraq and included patients who were newly diagnosed with RMS and received treatment during the period between January 1, 2015, and December 31, 2019. The patients were followed up from the time of diagnosis until October 1, 2020.

Results. A total of 59 patients were included with a median age of 3.5 years ranging between 1–12 years, with a male-to-female ratio of 3.2:1. The most frequent clinical presentation was urine retention in 15 patients (25.4%), followed by proptosis in 14 (23.7%) patients.

However, the main sites of involvement were the head and neck in 23 (39%) patients, followed by the trunk and the genitourinary tract observed in 17 (28.8%) and 15 (25.4%) patients, respectively. The alveolar type, found in 11 (18.7%) patients, was the most prevalent histological variety, followed by the embryonal type reported in 42 (71.3%) patients, whereas six patients (9.7%) had other varieties. Of the 49 patients included in the prognosis assessment, 18 patients (36.7%) had a complete response, 20 patients (40.8%) died, and 11 patients abandoned treatment. The average duration of disease recurrence was 21.3 months, with a 7% recurrence rate. The overall survival rate was 36.7%, with a mean survival duration of 14.1 months.

Conclusions. Pediatric RMS in Iraq is primarily prevalent in males. There is a significant delay in disease diagnosis from the onset of the symptoms. A high rate of advanced-stage disease may relate to patients reluctant to discontinue treatment. The low disease-free survival rate is due to impediments that hindered the effectiveness of therapy.

Keywords: **rhabdomyosarcoma, follow up, pediatrics, Iraq**

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INTRODUCTION

Rhabdomyosarcoma (RMS) is mesenchymal tumor that can arise in nearly any part of the body; however, the trunk, extremities, and the head/neck regions are the most frequently affected. RMS is the most prevalent soft tissue sarcoma in pediatric and adolescent populations (1), with an estimated 350 new cases annually. The maximum incidence is observed in the 0–14 age group, where it accounts for 5.8% of all malignant solid tumors in this age group (2, 3). A diminished occurrence peak is observed during the early to mid-adolescent stage, with approximately 66% of cases being detected in individuals under the age of six. A marginal preference for males has been discerned, with a male-to-female ratio that is between 1.3 and 1.5. Male predication has been associated with the patient's race. It has been shown that RMS prevalence in African-American girls is approximately half that of Caucasian girls, while the prevalence in males is comparable between the two racial groups (4). In contrast to predominantly Caucasian population, the incidence of a specific phenomenon appears to be lower among individuals of Asian descent (4).

Although RMS can be observed in various regions of the body, there are identifiable patterns that link the primary site, histology, and age at which the diagnosis is made. Younger infants have a higher incidence of head and neck RMS. The embryonal subtype is the predominant subtype in cases where these malignancies manifest in the orbit. A unique variant of embryonal RMS predominantly observed in neonates is that it originates within the bladder or vagina wall. However, in older adolescents, it may have a manifestation in the nasopharynx. The alveolar histological subtype is frequently associated with tumors of the extremities, which are more prevalent among adolescents (5).

We have limited data on the characteristics of RMS in Iraqi pediatric patients. Without providing information about the particular incidence based on age, the Iraqi Cancer Registry listed RMS as the fourth most prevalent type of cancer affecting the urinary bladder of Iraqi males (6). The aim of this study was to examine the clinical and histological aspects of RMS in children from Iraq, with a focus on their response to treatment, prognosis, and survival.

METHODS

A retrospective cohort study was conducted at the Oncology Unit of Children's Welfare Teaching Hospital, Medical City, Baghdad, Iraq and included patients who were newly diagnosed with RMS tumor and received treatment during the period between January 1, 2015, and December 31, 2019. The study was approved by the Ethical Committee of Children's Welfare Teaching Hospital. Patients without histopathology reports or incomplete clinical or follow up information were excluded from the study.

A thorough examination of hospital and outpatient medical records, notes, and laboratory data was conducted to determine demographic information, including age, gender, place of residence, duration of symptom onset, clinical manifestation, date of diagnosis, and the results of diagnostic investigations. The patients underwent a variety of clinical investigations, such as complete blood count (CBC), renal function test (RFT), liver function test (LFT), chest x-ray (CXR), abdominal ultrasound, computed tomography (CT) of the thorax, CT of the primary site lesion, magnetic resonance imaging (MRI) of the primary site lesion, and (when feasible) bone marrow aspiration and biopsy. All patients were staged in accordance with the TNM staging system (RMS staging based on TNM classification) (7, 8) and were treated according to the standard United Kingdom Children's Cancer Study Group (UKCCSG) rhabdomyosarcoma protocol.

The patients were followed up from the time of diagnosis until October 1, 2020. Event-free survival (EFS) was defined as the duration from the start of treatment to the onset of disease progression/relapse, loss to follow-up, or mortality from any cause. The time from the commencement of treatment to mortality from any cause was referred to as the overall survival (OS).

Statistical analyses

An analysis of the data was conducted using Statistical Package for the Social Sciences (SPSS), version 13. Quantitative data was presented as mean and median, while qualitative data was represented in terms of frequency and percentage. The Chi-square test was employed to evaluate the relation-

ships between event-free survival and independent variables under investigation. The Kaplan-Meier method was employed to illustrate the survival curves. P-values that were equal to or less than 0.05 were considered significant.

RESULTS

The study comprised a total of 59 patients who met the inclusion criteria. The median age was 3.5 years, with a range of 1-12 years. The male population was predominant, with a male-to-female ratio of 3.2:1. The median duration from the onset of symptoms to diagnosis was three months, with a range of 0.5-24 months and a mean of 3.8 months (Table 1).

Table 1. *Demographic and clinical characteristics of rhabdomyosarcoma patients (n = 59)*

Characteristics	No.	%
Age (years)		
< = 1	3	**5.1**
1-5	42	**71.2**
> 5	14	**23.7**
Sex		
Males	45	**76.3**
Females	14	**23.7**
Duration from onset to diagnosis		
< 1 month	4	**6.8**
1-4 months	39	**66.1**
> 4 months	**16**	**27.1**

The largest number of patients were recorded in Baghdad (42.4%), followed by Karbala (11.9%), and Anbar (6.8%), as illustrated in Table 2.

The most frequent clinical presentation was urine retention, which was observed in 15 (25.4%) cases, followed by proptosis in 14 (23.7%) cases, as illustrated in Table 3.

However, the primary site of involvement was the head and neck in 23 patients (39%), followed by the trunk and the genitourinary tract in 17 (28.8%) and 15 (25.4%) cases, respectively, while extremities were affected in 4 (6.8%) cases, as indicated in Table 4.

The mean haemoglobin level was 10.2 g/dl, with a range of 4-14 g/dl. In 47 patients (79.7%), a chest x-ray of 10 patients (16.9%) revealed thoracic involvement. Only one patient underwent a bone marrow aspiration examination, which revealed bone marrow involvement, as shown in Table 5.

Table 2. *The residence of rhabdomyosarcoma patients (n = 59)*

Governorate	No.	Percent
Baghdad	25	**42.4**
Karbala	7	**11.9**
Anbar	4	**6.8**
Dyala	4	**6.8**
Dywania	3	**5.1**
Kurkok	3	**5.1**
Wasit	3	**5.1**
Babelyon	2	**3.4**
Basrah	2	**3.4**
Nasria	2	**3.4**
Salah Aldin	2	**3.4**
Samawa	1	**1.7**
Najaf	1	**1.7**
Total	**59**	**100.0**

* Mousal, Misan, Kurdistan—no referred cases

Table 3. *Clinical presentation of patients with rhabdomyosarcoma (n = 59)*

Main clinical presentation	No.	%
Urine retention or overflow incontinence	15	**25.4**
Proptosis	14	**23.7**
Local mass and pallor fever	11	**18.6**
Lymphadenopathy	9	**15.3**
Upper way obstruction	4	**6.8**
Abdominal mass	4	**6.8**
Scrotal swelling	1	**1.7**
Mass and ear discharge	**1**	**1.7**

Table 4. *The main sites involved by rhabdomyosarcoma (n = 59)*

Site	No.	%
Head and neck	23	**39**
Trunk	17	**28.8**
Genitourinary tract	15	**25.4**
Extremities	**4**	**6.8**

The diagnosis was established for all patients through histological examination of the mass. A histological examination by immunohistochemical study was conducted on 14 patients at the Department of Pathology at Rome University. Twelve patients had the same diagnosis as the histopathological study in Iraq. The diagnosis was modified in two of the fourteen patients. Embryonal type in 42 patients comprised the main histological variety, accounting for 71.3 percent. The alveolar type was found in 11 patients (18.7%), whereas other varieties were reported in and 6 (9.7%) patients. Four patients had soft tissue sarcoma, one patient had botryoid RMS, and one patient had undifferentiated RMS, as shown in Table 6.

We found that the largest number of patients were in stage III disease (23, 39%), followed by stage I (18, 30.5%), II (11, 18.6%) and IV (7, 7.9%), respectively, as shown in Table 7.

Of 59 patients, 10 were excluded from the treatment analysis. These patients had a histological type other than alveolar or embryonal, had been treated at other centers, refused treatment, or passed away before commencing treatment.

The UKCCSG protocol was implemented for all 49 patients. The mass was surgically removed from three patients, while only two patients underwent radiotherapy with chemotherapy.

The patient was followed from the time of diagnosis until October 1, 2020, with an average follow-up period of 16 months. The prognosis of 49 patients after treatment is depicted in Table 8. Of these, 18 patients (36.7%) had a complete response, 20 patients (40.8%) died, and 11 patients abandoned treatment (the majority of whom were lost to follow-up).

Sepsis was the primary cause of mortality in 10 patients, accounting for 50% of the cases, as illustrated in Table 9.

Table 5. *Initial laboratory results of rhabdomyosarcoma patients (n = 59)*

Item	No.	Percentage (valid %)
HB		
< 10 g/dl	23	**39 (39.7)**
> 10 g/dl	35	**59.3 (60.3)**
Not Recorded	1	**1.7**
CXR		
Normal	47	**79.7 (82.5)**
Metastasis	10	**16.9 (17.5)**
Not recorded	2	**3.4**
Bone marrow examination		
Normal	57	**96.6 (98.3)**
Involved	1	**1.7 (1.7)**
Not recorded	1	
		1.7

Table 6. *Histopathology types (n = 59)*

TYPE	No.	%
Embryonal	42	71.3
Alveolar	11	18.7
Others	6	9.7

Table 7. *Tumor staging of rhabdomyosarcoma patients (n = 59)*

STAGE	No.	%
I	18	30.5
II	11	18.6
III	23	39
IV	7	11.9

Table 8. *Outcome in rhabdomyosarcoma patients (n = 49)*

Outcome	No. of patient	%
Death	20	40.8
Alive	18	36.7
Lost	11	22.4
Total	49	100.0

Table 9. *Causes of death in rhabdomyosarcoma patients (n = 20)*

Cause of death	No.	%
Sepsis	10	50
Progressive disease—died at home	4	20
Fits and apnea	2	10
renal failure (obstructive uropathy)	2	10
Bleeding	1	5
Upper air way obstruction	1	5
Total	20	100.0

The average duration of disease recurrence was 21.3 months, with a 7% recurrence rate. The overall survival rate was 36.7%. Furthermore, the event-free survival was determined to be 16 months, as illustrated in Figure 1. The Kaplan-Meier study of the overall survival according to the clinical stage of the disease is depicted in Figure 2. The p-value is 0.23, indicating that there is no significant difference between clinical staging and survival time (not significant).

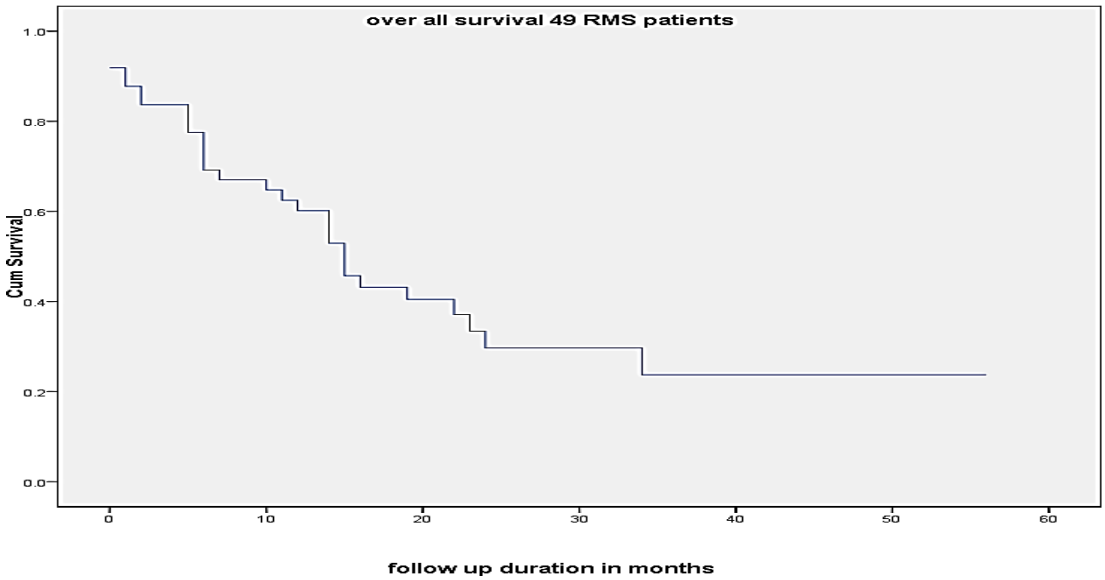

Figure 1. *Event-free rhabdomyosarcoma patients (n = 49)*

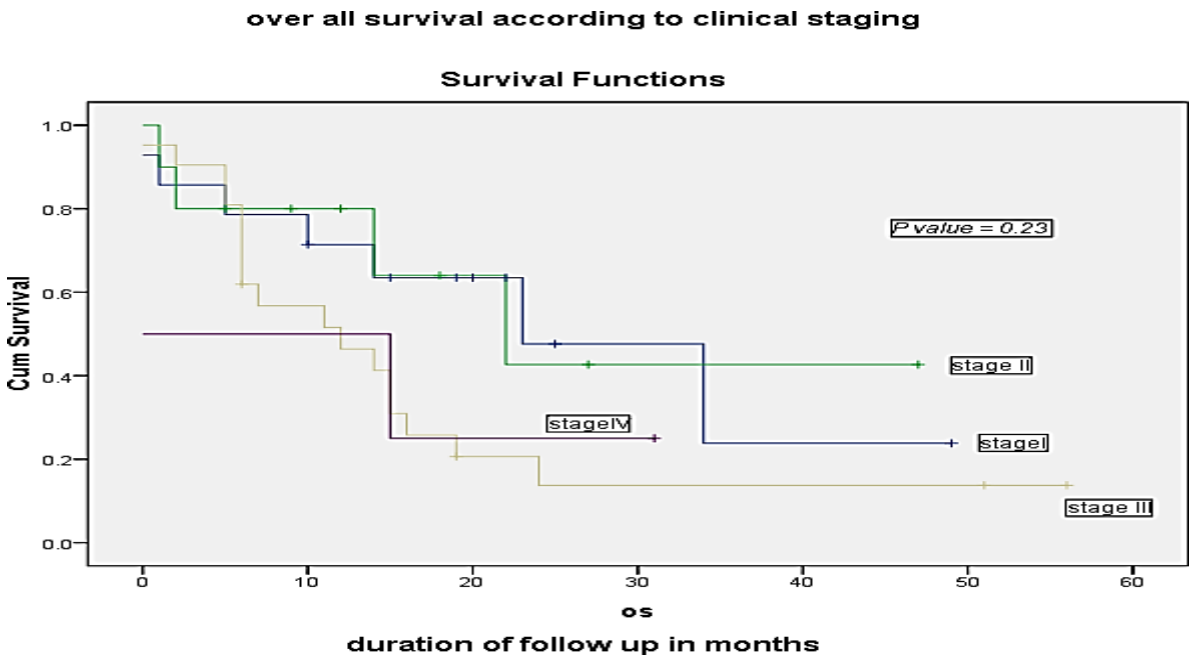

Figure 2. *Overall survival according to clinical staging of RMS patients*

DISCUSSION

Although RMS is the most frequent soft tissue sarcoma encountered in children, its overall incidence is low, accounting for 4.71 per million children and adolescents under 20 years of age in the United States (9). Racial differences in the clinicodemographic characteristics of this tumor have an area of debate (10, 11). This study evaluated the clinicodemographic features of pediatric RMS in Iraqi patients, providing information about patients' outcomes.

We observed an evident male predominance with a ratio of 3.21:1, which is higher than the figure reported previously in Iraq—2:1 (12) and the neighboring country Turkey—1.8:1 (13). It is also higher than what was reported in other countries—e.g., United States—1.5:1 (14) and Guatemala—1.3:1 (15). However, an Egyptian study reported higher male predominance with a ratio of 6.5:1 (16). Gender disparity has been previously reported in several studies. Research demonstrated that the prevalence of RMS in African-American girls is approximately half that of Caucasian girls, while the prevalence in males is comparable between the two racial groups (4).

The median age in the current study was 3.5 years, with a range of 1 to 12 years. This is comparable to the median age of 3.4 years in the Kadhem study from Iraq (12), but it is lower than the median age of 6 years in the Anitelon study from Guatemala (15) and the median age of 4.5 years in the Karkas study from Turkey (13). It is also higher than the median age of 3 years in the Al Sherbiny study from Egypt. (16). This may be contingent upon the age limit of each center and the quantity of the sample that was collected.

The average duration from the onset of symptoms to the diagnosis of RMS was 3.8 months, with a range of two weeks to two years. This duration exceeds the average duration of one month reported in the study conducted by other researchers (13). These findings suggest a delay in the diagnosis and referral of RMS cases. The most frequent clinical presentation in the current investigation was urine retention, which accounted for 25.4% of cases. Eye proptosis was present in 23.7% of cases, while Kadhim's study from Iraq demonstrated that ocular proptosis was the most common clinical manifestation (12). Consistent with the literature where the head and neck were reported as the most frequent site accounting for 40% of pediatric RMS (14), 39% of patients in our study had tumors in the head and neck. Similar findings were documented in other Iraqi studies (12, 17), while the Turkish study reported only 31.4%, and another wester study reported this involvement in 20% of cases (13, 18).

The dominant histological type of RMS in the current study was embryonal accounting for 71.3% of all cases. This is similar to a previous local study which reported 79% of embryonal histological type (17), which is higher than in other studies in which embryonal histological type accounted for 46% (15, 19) only. By contrast, a Turkish study reported a higher rate of embryonal RMS up to 80% (13).

We found that 23 (39%) patients were in stage III of the disease. In the literature, the rate of stage III disease ranged between 17–76% (12, 13, 16, 18). Delays in diagnosis and referral for reasons related to doctors and patients may explain this relatively high rate of advanced-stage disease. Additionally, lung metastasis seems to be underestimated in the current study (16.9%), which is likely to be due to a shortage of imaging facilities.

The UKCCSG treatment protocol was implemented in all 49 patients in the current study. Eighteen (36.7%) patients achieved complete remission, which is lower than the rate reported by other studies (45%) (15), (58.8%) (13). The mortality rate in the current study was 40.8%, which is comparable to that reported by other studies (41.2%) (13). The recurrence rate in our study was 14.2%, with a mean time of 21.3 months. Other studies reported a higher rate of recurrence reaching up to 52, which was related to patients' reluctance to complete treatment.

CONCLUSION

The pediatric RMS in Iraq is primarily prevalent in males. There is a significant delay in disease diagnosis from the onset of symptoms. A high rate of advanced-stage disease may relate to patients reluctant to discontinue treatment. A low disease-free survival rate is due to impediments that hinder the effectiveness of therapy, which is similar to reports of developing nations.

Conflict of interest

No conflict of interest.

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Rabdomiosarkom kod dece praćen u petogodišnjem periodu u Onkološkoj jedinici Pedijatrijske nastavne bolnice

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SAŽETAK

Uvod/Cilj. Rabdomiosarkom (engl. *rhabdomyosarcoma* – RMS) predstavlja najćešći sarkom mekih tkiva u pedijatrijskoj populaciji i kod adolescenata. Dostupni su ograničeni podaci o karakteristikama RMS-a u pedijatrijskoj populaciji Iraka. Cilj ove studije bio je da se ispitaju klinički i histološki aspekti RMS-a kod dece u Iraku, sa posebnim osvrtom na odgovor na terapiju, prognozu i stopu preživljavanja.
Metode. Sprovedena je retrospektivna kohortna studija u Onkološkoj jedinici Pedijatrijske nastavne bolnice pri Medicinskom centru u Bagdadu u Iraku. U studiju su uključeni bolesnici sa novodijagnostikovanim RMS-om koji su primali terapiju u periodu od 1. januara 2015. do 31. decembra 2019. godine. Bolesnici su praćeni od trenutka uspostavljanja dijagnoze do 1. oktobra 2020. godine.
Rezultati. U studiju je uključeno ukupno 59 bolesnika prosečne starosti 3,5 godina (raspon od jedna godine do 12 godina); odnos muškog i ženskog pola bio je 3,2 : 1. Najćešća klinička manifestacija RMS-a bila je urinarna retencija, koja se javila kod 15 (25,4%) bolesnika, a potom proptoza koja se javila kod 14 (23,7%) bolesnika. Najčešće zahvaćene regije bile su regije glave i vrata, kod 23 (39%) bolesnika, potom regija trupa utvrđena kod 17 (28,8%) bolesnika, dok je zahvaćenost urogenitalnog trakta bila utvrđena kod 15 (25,4%) bolesnika. Alveolarni tip RMS-a dijagnostikovan je kod 11 (18,7%) bolesnika, dok je embrionalni tip bio prisutan kod 42 (71,3%) bolesnika. Ostale histološke varijante zabeležene su kod 6 (9,7%) bolesnika. Od 49 bolesnika uključenih u procenu prognoze, kod 18 (36,7%) bolesnika zabeležen je kompletan odgovor na terapiju, dok je 20 (40,8%) preminulo, a 11 bolesnika prekinulo terapiju. Prosečno vreme do recidiva bolesti iznosilo je 21,3 meseca uz stopu recidiva od 7%. Ukupna stopa preživljavanja iznosila je 36,7%, sa prosečnim preživljenjem od 14,1 meseca.
Zaključak. Rabdomiosarkom kod dece u Iraku prvenstveno se javlja kod muške dece. Uočeno je značajno kašnjenje u dijagnostici bolesti od trenutka pojave simptoma. Visoka stopa uznapredovalih stadijuma bolesti može se dovesti u vezu sa odustajanjem bolesnika od terapije. Niska stopa preživljavanja osoba bez simptoma bolesti rezultat je faktora koji su ometali efikasnost terapije.

Ključne reči: **rabdomiosarkom, praćenje, pedijatrija, Irak**