Pediatric Rhabdomyosarcoma : A 7-Year Experience at King Hussein Medical Center

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ABSTRACT

Objective: To evaluate the clinical characteristics and treatment outcomes of children with rhabdomyosarcoma diagnosed and treated at King Hussein Medical Center.

Methods: This retrospective descriptive study was conducted by the hematology-oncology unit of pediatric department at Queen Rania Al Abdullah Hospital for Children at King Hussein Medical Center. The medical records of children with rhabdomyosarcoma were reviewed over a period of 7 years, between April 2005 end of March 2012. The age of children included in the study was less or equal to 14 years at the time diagnosis.

The charts of 52 patients were reviewed regarding: patient demographics, tumor characteristics, risk stratification, treatment outcomes. Descriptive analysis using frequencies was used to describe the study variables.

Results: There were 27males and 25 females with M: F ratio of 1.08:1. The median age at diagnosis was 5 years (range 0.25-13.75 years) with 80.8% below the age of 10 years . Head and neck was the most common primary site of tumor (46.2%) , followed by the extremities (21.2%).

Pathologically, embryonal rhabdomyosarcoma was the most frequent subtype (90.4%). The stage frequencies were as follows: stage I (25.0 %) , stage II (9.6 %) , stage III (36.5 %) and stage IV (28.8 %) . Regarding postsurgical grouping classification, group III and IV were the most prevalent, constituting 42.3% and 28.8% respectively.

The 3- year event - free survival rate for patients was 55.8 % , and the 3- year overall survival rate was 61.5 % .

Conclusion: Advanced stages (stage III and IV) and postsurgical groups (group III and IV) were the most commonly encountered in pediatric patients, which showed a negative effect on event free survival and overall survival rates. Epidemiological features other than gender distribution were close to the previously reported data

Key words: Rhabdomyosarcoma, embryonal, overall survival, stage, group.

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Introduction

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma, accounting for about 40%[1,2] Its annual incidence is 4.3 cases per million people younger than 20 years.[3,4] Among solid tumors of childhood, RMS is the fourth most

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common neoplasm. [5] It originates from undifferentiated mesenchymal cells that can arise at any site in the body except in the bone and resembles morphology of developing skeletal muscle. [6,7] Overall survival (OS) rates for children with RMS have risen significantly due to the use of combined modality therapy trials including surgery, radiotherapy, and chemotherapy conducted by large international cooperative groups, such as the Intergroup Rhabdomyosarcoma Study Group IRSG(now known as the Soft Tissue Sarcoma Committee of the Children's Oncology Group). [8,9] Histologically , embryonal and alveolar RMS are the two major subtypes, accounting for over 90 percent of cases in children under the age of five.[10] Other, minor, histologic variants include spindle cell, botryoid, and not otherwise specified(NOS). [11-14] Risk stratification for RMS used by the Children's Oncology Group (COG) is based on pre-treatment TNM staging system based on tumor size, invasiveness, nodal status, primary site of primary tumor, and distant metastases. [15] Surgical/pathologic clinical group, and tumor histology are also independently associated with outcome. [16,17] The combination of stage, group, and histology stratify patients into three distinct RMS risk groups .[2,13,18] Our study was conducted to describe and analyze the epidemiological features and treatment outcomes among pediatric RMS cases treated at King Hussein Medical Center according to COG protocol .

Methods

This retrospective study was approved by the Ethics Committee of Jordanian Royal Medical Services. Medical records and pathology databases review of children with RMS who were younger than 14 years at the time diagnosis was conducted at King Hussein Medical Center in Amman-Jordan during the period between April 2005 and end of March 2012. The charts of 52 RMS cases followed up at the hematology-oncology unit of pediatric department were reviewed for Patients' age , gender, primary site of the tumor, histopathologic type of the tumor , Tumor size , Regional lymph node involvement , presence or absence of distant metastasis ,tumor stage, clinical group, risk stratification and treatment outcomes . Over the study period, the patients were treated with the same chemotherapy protocol.

Classification of tumor into four groups and four stages was determined using both post surgical grouping classification developed by the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG) and Intergroup Rhabdomyosarcoma Study Group (IRSG) pretreatment Clinical staging System (modified from a tumor-node-metastasis system).Patients were stratified into three risk groups as follows:

1. Low risk(LR): localized embryonal (i.e., embryonal histology ,stage I, group I, II, or III; or embryonal histology, stage I or II, group I or II).
2. Intermediate risk(IR) : localized alveolar histology tumors (i.e., stage I, II, or III, group I, II, or III) or an unresected embryonal histology at unfavorable sites (i.e., stage II or III, group III).
3.High risk (HR) : metastatic tumors (i.e., stage IV, group IV).

Overall survival(OS) was calculated from the date of diagnosis to death or to the date of follow-up loss .Event Free Survival (EFS) was calculated from the date of diagnosis to an event (relapse or death) .

Descriptive analysis using frequencies was used to describe the study variables.

Results

The total number of RMS patients diagnosed during the period from April 2005 to March 2012was 52. Their ages ranged between 0.25-13.75 years .The median age of our patients at diagnosis was 5 years .Forty two patients(80.8%) were below the age of 10 years. The male to female ratio was 1.08 : 1. The demographic characteristics of the patients are summarized in Table I. Embryonal RMS was the most frequent histopathologic subtype (n =

47, 90.4%), while the alveolar histology was encountered in only 2 patients (3.8%).Regarding the primary site of RMS , it was found to be highest in the head and neck (46.2%) followed by extremities (21.2%) .

Table I: Patient demographic characteristics .

	n = 52	%
Age (years)		
Median	5	80.8
Range	0.25-13.75	19.2
<10	42	
≥10	10	
Gender		
Male	27	51.9
Female	25	48.1

The size of the tumor was found to be >5cm in 30 cases (57.7%) and ≤5 cm in 22 cases (42.3%) and Fifteen (28.8%) patients had distant metastases at the time of diagnosis.
Concerning IRS stage distribution , Stage III was the most frequent stage encountered (36.5%), followed by stage IV (28.8%), stage I (25.0%),and stage II which constituted (9.6%). Regarding postsurgical group classification , group III was the most commonly encountered group (42.3%), followed by group IV (28.8%), group II (21.2%) and group I (7.7%) . Tumor characteristics , various stages and clinical groups were illustrated in Table II and III. The 3- year event - free survival rate and the 3- year overall survival rate for patients according to the three risk groups was illustrated in Table IV.

Table II: Tumor characteristics.

	n = 52	%
Primary site		46.2
Head and neck	24	
Orbit	6	15.4
Parameningeal	15	
Nonparameningeal	3	21.2
Genitourinary	8	17.3
Bladder/prostate	4	
Nonbladder/prostate	4	
Extremities	11	
Others	9	
Histopathology		
Embryonal	47	90.4
Alveolar	2	3.8
Others	3	5.8
Tumor size (cm)		
<5	22	42.3
>5	30	57.7
Lymph node Involvement		
Yes	5	9.6
No	47	90.4
Distant metastases		
Yes	15	28.8
No	37	71.2

Table III: Stages and clinical groups and Risk Stratification .

	n=52	%
Stage		
1	13	25.0
2	5	9.6
3	19	36.5
4	15	28.8
Post surgical group		
I	4	7.7
II	11	21.2
III	22	42.3
IV	15	28.8
Risk group		
Low	13	25.0
Intermediate	24	46.2
High	15	28.8

Table IV: Outcome of RMS in relation to Risk group

Risk group	No. (%)	3-year EFS No. (%)	3-year OS No. (%)
Low	13(25.0)	11 (84.6)	11 (84.6)
Intermediate	24(46.2)	17 (70.8)	19 (79.1)
High	15(28.8)	1 (6.7)	2 (13.3)
total	52	29 (55.8)	32 (61.5)

Discussion

At our institution at King Hussein Medical Center ,Children with Rhabdomyosarcoma are managed according to Children's Oncology Group (COG) protocol by a multidisciplinary team of pediatric cancer specialists with experience of treating pediatric cancers. As illustrated in Table I, the median age of the entire patient population in our study was 5 years , with 80.8% of patients below the age of 10 years. This result was closely comparable to an an Egyptian Multicenter study which was conducted over a 5 - year period between 2004 and 2009 , and showed that the median age of patients was 6 years with 80.4% below 10 years .[19] This is similar to a recent study done in the central region of Tunisia by Missaoui N et al. in 2010 who reported that almost two third of patients with RMS were diagnosed before 7 years of age. [20] This also agrees with data from the IRS IV which reported that the median age of patients with RMS was 5-year, with 72% of patients below the age of 10 years.[21] Our current study showed that RMS was slightly more predominant in males (51.9%) ,with male to female ratio 1.08 : 1. This ratio was lower than an earlier Jordanian study which was conducted over a 5 - year period between Jan 2004 and Dec 2008 , and showed that out of 45 patients , 31(69%) were males and 14(31%) were females. [22] Compared to our results , IRS IV also reported higher male to female ratio (1.6 : 1) . [21] The male to female ratio was even higher in three african studies from central region of Tunisia, Morocco and Egypt where it reached up to 2.7 , 2 and 1.75 respectively. [3,20,23] Company F, *et al*. from Iran also addressed the relation between RMS and gender, and found that males constituted 61. 66% (37 cases) while females constituted 38.33% (23 cases),with male to female ratio 1.6:1. [2] Our study showed that Embryonal RMS was the most frequent pathologic subtype, accounting for 90.4% as showed in Table II. This is comparable to Abd El-Aal H, et al. study who found that embryonal subtype represents 87.3% while alveolar subtype represents 12.7% of patients .[3] Similarly,

Hessissen *et al*. Found that embryonal and alveolar subtypes represent 73% and 13% of patients, respectively. [23] This is supported by a five-year study from East Egypt conducted between 2004 and 2009, which showed that the embryonal RMS was the most commont histopathologic subtype (61.9%), followed by alveolar (28.6%) and lastly the botryoid and spindle subtypes in 4.7% for each. [19] This is not similar to a study conducted in the Japan by Suita S, *et al*. in 2005 ,who reported that the alveolar type accounted for 36. 8% of RMS cases, while 35. 8% were of embryonal type. [24]The IRS IV reported that the embryonal subtype represents 70% including the botryoid and spindle cell variants, which is comparable to our results as the most frequent pathologic type . [21] The present study showed that head and neck was the most common primary site of RMS (46.2%) followed by the extremities(21.2%). Our results were similar to that observed in Egypt,Tunisia,Morocco, Turkey ,Iran and Europe which showed that head and neck was the most frequent site of involvement by RMS. [2,3,19,20,23,25-27] . This is supported by the IRS IV , who reported that head and neck was the most commonly affected primary site of tumor (41%).[21] On contrary to our results, regarding the second frequent primary site of tumor , an Egyptian study in 2006, Tunisian study in 2010 and IRS IV reported that the genitourinary is the second most common affected site constituting 23.6% , 23.3% and 31% respectively. [3,20,21] On the other hand ,similar to our results, a more recent study from Egypt in 2012 found that the extremities ranks second after head and neck regarding the primary site of tumor. [19] These differences may be explained by the variable number of patients included in these studies. The present study described the stages of RMS in pediatric age group, as seen in Table III. In which, the more advanced stages(stage III and IV) were unfortunately the predominant accounting for 36.5% and 28.8% respectively ,while the less advanced stages (stage I and II) constituted 9.6% and 25.0% respectively. These results slightly differ from an earlier Jordanian 5 - year retrospective study of 45 children with RMS , which revealed that stage III was the most frequent stage (n= 22), followed by stage I (n=8), then stage II (n=8), and lastly stage IV (n=7).[22] Badr M et al. from Egypt found that stage IV was the most frequent stage (43.9%) followed by stage III (29.3%). [19] In our study, the relative frequencies of RMS groups showed that the majority of patients, were classified as post surgical group III and IV, constituting 42.3% and 28.8% respectively, as illustrated in Table III. [22] Regarding the surrounding countries, a different order of frequency of post surgical groups was reported in Egypt and Morocco. [19,23,25]. The high percentage of advanced stage and group of our patients at presentation may indicate the lack of awareness of families and primary health care physicians of the need for early medical advice of specialized centers for diagnosis and treatment . This can be also explained by the wide presenting symptoms and signs of this highly malignant and heterogeneous soft tissue tumor. This may indicate the need for health education for the general population to create awareness , and building up trained health professionals at all levels to promote early diagnosis.

In the present study , the 3- year EFS (55.8 %) and OS (61.5 %) rates were slightly lower than the 4-year progression-free survival (61% ± 7.5%) and OS (72% ± 6.9%) rates reported by Al-Jumaily U *et al* from Jordan .[22]This can be explained by the higher percentage of stage IV ,post surgical group IV and high risk group (28.8 %) in our study compared to 15.6% in the earlier Jordanian study. several studies from Egypt and Japan showed EFS and OS rates close to our results.[19,28] The IRS IV reported 3-year FFS and OS OF 77% and 86%, respectively. [21] Moreover, in this study ,the 3-year FFS and OS was significantly lower in patients with high risk group (6.7% , 13.3% respectively) compared to low and intermediate risk groups as showed in Table IV, which is consistent with results reported previously about RMS.

[21,29,30] the European experience showed by the International Society of Paediatric Oncology (SIOP) is illustrated in the MMT(Malignant Mesenchymal Tumor) 89 study, which included 503 patients and revealed that the Five-year overall survival (OS) and event-free survival (EFS) rates were 71and 57, respectively. [31] There are some limitations of this study, which included the retrospective nature of the present work and being an experience of a single institution .Moreover, it included a relatively small number of subjects Future multi-institutional prospective clinical studies have to be carried out to study the epidemiology and clinical characteristics of this tumor at the level of the country.

Conclusion

Childhood Rhabdomyosarcoma in patients treated at KHMC showed unfortunately high frequencies of advanced stages(stage III and IV) , advanced postsurgical groups (group III and IV) and then high risk groups , which significantly affected the clinical outcome and survival. Data describing the epidemiological features other than the gender distribution were close to the previously reported worldwide data.

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