ORIGINAL ARTICLE

Epidemiology Profile and Prognostic Factors of Childhood Rhabdomyosarcoma in Indonesia: A Five Year Single Institution Study

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ABSTRACT

Introduction: Rhabdomyosarcoma (RMS) is the major soft tissue sarcoma in childhood, correlated with high morbidity and mortality. We defined clinico-epidemiological profiles and prognoses on pediatric RMS patients in Indonesia. **Methods:** This study was conducted retrospectively by examining all medical records of pediatric RMS patients in Dr. Sardjito Hospital, Yogyakarta, Indonesia, for 5 years from 2011 until 2016. **Results:** There were 21 RMS patients in this study. The median age of our subjects was 6 years and predominantly under 10 years old (71.4%). There was a greater tendency for the disease in males, with a male to female ratio of 2:1. The head and neck region was the primary tumor site (52.4%). The most common histological subtype of tumor was embryonal RMS (85.7%). The most common measured diameter for tumor size was ≤ 5 cm (42.9%). Almost half of the patients received combination therapy, including surgery and chemotherapy (47,6%). Overall survival rate was 71.7%. **Conclusion:** We concluded that the epidemiological profile and prognostic factors of childhood RMS patients in our center are similar to the world reference data and were clinically associated with the mortality rate of our RMS patients, but the findings were not considered statistically significant.

Keywords: Children, Epidemiology, Prognostic factors, Rhabdomyosarcoma

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INTRODUCTION

Rhabdomyosarcoma (RMS) is the third most common extracranial pediatric solid tumor after neuroblastoma and Wilm's tumor (1). RMS is a primary soft tissue sarcoma in children which originates from immature mesenchymal cells that become various parts of the human body except bones (2). The incidence of RMS is 4.3 cases/ one million children, and about 350 new cases of RMS are diagnosed each year (3). Fifty percent of RMS patients were diagnosed before the age of five (3). Primarily, sites of RMS are in the head and neck region (25%), genitourinary tract (22%), and extremities (18%), where other possible sites of appearance include the thoracic wall, perianal/anal, abdominal part, retroperitoneal, and biliary tract (4).

Several prognostic factors are known to affect the 5-years survival in patients with RMS and they include among others: age, gender, histological type of tumor, primary site, staging tumor according to Inter-Rhabdomyosarcoma Study Group, recurrence time after first diagnosed, and the course of treatment (5). The data of those factors that affect the survival rate of patients with RMS in Indonesia are still limited, thus we conducted this research to investigate the epidemiological profiles and prognostic factors of pediatric RMS patients in a single institution in Yogyakarta, Indonesia.

MATERIALS AND METHODS

We performed a retrospective study by collecting secondary data from medical records of pediatric RMS patients at Dr. Sardjito Hospital, Yogyakarta, Indonesia from 2011 until 2016. The medical records were reviewed for clinical features and prognostic factors (gender, age of diagnostic, histopathology subtype, tumor size, primary site of tumor, and the type of therapy). The histopathology subtype was confirmed by pathologist

based on the histopathological tissue analysis. To analyze the combined effects of the prognostic factors and patient survival, we conducted cox proportional hazard regression. A p-value of < 0.05 was considered significant. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (Reference number KE/FK/1176/EC/2016).

RESULTS

From 2011 to 2016, a total of 60 patients were diagnosed as RMS in our medical record data. We excluded 12 patients which did not have histopathological examination results. From 48 patients, 32 patients were confirmed as RMS based on histopathological results. We excluded 11 of 32 patients with insufficient data from our analysis. Thus, we used 21 patients as a sample to analyze gender, age of diagnostic, histology type, tumor size, primary site of tumor group, and type of therapy in this study.

Our study showed that RMS patients were mainly diagnosed before 10 years old. They were predominantly males with male to female ratio of 2:1. In more than half of the patients, the major primary site of tumor was in the head and neck region (Table I).

Table I: Demographic characteristics of the patients and primary site of tumor

	N = 21	Percentage (%)
Gender		
Males	14	66,7
Females	7	33,3
Age of diagnostic		
< 1 years	3	14,3
1 - 9 years	12	57,1
> 9 years	6	28,6
Primary Site of Tumor		
Head and neck	11	52,4
Genitourinary	2	9,5
Extremities	6	28,6
n/a	2	9,5

The tumor size of the patients was mainly less than 5 cm. Embryonal RMS subtype was the most frequent histopathological finding of these patients, followed by pleomorphic and alveolar subtype. Most patients received a combination of therapies involving surgery and chemotherapy (Table II).

Prognostic factor analysis was used to examine the correlation between gender, age of diagnosis, histologic type, tumor size, primary site of tumor and therapy toward mortality rates of pediatric patients with rhabdomyosarcoma (Table III). We found no significant correlation between gender, age of diagnosis, histologic type, tumor size, primary site of tumor, type of therapy and survival rate of the pediatric RMS patients, probably due to our small sample population.

Table II: Tumor size, histopathological sub types, and type of therapy

	N = 21	Percentage (%)
Tumor Size		
≤ 5 cm	9	42,9
> 5 cm	4	19,0
n/a	8	38,1
Histopathological sub types		
Embryonal	18	85,7
Alveolar	1	4,8
Pleomorphic	2	9,5
Types of Therapy		
Surgery	3	14,3
Chemotherapy	3	14,3
Surgery + Chemotherapy	10	47,6
n/a	5	23,8

DISCUSSION

Three to four percent of malignancy cases in children are diagnosed to be RMS (3). In our review of the literature, it was found that age of diagnosis, tumor staging, tumor histologic type and primary site of the tumor were important as the main predictors of survival in children with RMS (6). The presence of these prognostic factors is important for the selection of the RMS therapy approach (7).

In this study, the percentage of male patients with RMS was higher by 66.7% (14 patients) than the female RMS patients 33.3% (7 patients). The male and female ratio was 2:1. These results are similar to the findings of Company and Rezaei at Shafa Hospital in Ahvaz City where 61.66% were male and 38.33% female (8). According to another study conducted at two hospitals in Jakarta, Cipto Mangunkusumo Hospital and Darmais Cancer Hospital, the ratio of male and female patients was 2:1 in the Cipto Mangunkusumo Hospital, which matched the results of this study. Different results were found in the second hospital study at Darmais Cancer Hospital where the ratio was 1:1.7 (9).

The most common age of our RMS patients was in the group of 1-9 years (57.1%), followed by age group > 9 years (28.6%), and the least in the <1 year age group (14.3%). The age distribution was similar to the findings of the study by Punyko et al., where the most common group was 1-4 years with 252 patients (30%), followed by the 5-9 years group with 224 patients (26%), then the group more than 15 years old with 174 patients (21%), and the group of 10-14 years were 142 patients (17%), and lastly the group of patients less than 1 year old with 56 patients (7%) (6). The differences in age distribution occur because the various types of RMS have their own characteristics with regard to age. For example, the embryonic type of RMS often affects patients with age range from birth to 15 years, then the type of alveolar RMS is common in patients aged 10-25 years, and RMS pleomorphic type usually occurs at age of more than 40 years (10).

Table III: Association between prognostic factors and survival status of the pediatric RMS patients

Variables	Lives		Dead		Total		P value	RR	CI 95%	
	N	%	N	%	N	%			Lower	Upper
Gender										
Females	6	85,7%	1	14,3%	7	100%	0,613	3,333	0,308	36,110
Males	9	64,3%	5	35,7%	14	100%				
Age										
> 9 years	5	83,3%	1	16,7%	6	100%		1,000	Reference	
1-9 years	8	66,7%	4	33,3%	12	100%	0,615	2,500	0,214	29,254
< 1 years	2	66,7%	1	33,3%	3	100%	1,000	2,500	0,100	62,605
Histologic type										
Alveolar	0	0,0%	1	100%	1	100%		1,000	Reference	
Embryonic	13	72,2%	5	27,8%	18	100%	0,222	0,167	0,012	2,368
Pleomorphic	2	100%	0	0,0%	2	100%	1,000	2,000	0,500	7,997
Size of tumor										
> 5 cm	4	100%	0	0,0%	4	100%	1,000	1,285	0,028	11,849
≤ 5 cm	7	77,8%	2	22,2%	9	100%				
Primary site										
Head and neck	9	81,9%	2	18,2%	11	100%		1,000	Reference	
Genitourinary	1	50,0%	1	50,0%	2	100%	0,316	4,500	0,190	106,823
Extremities	4	66,7%	2	33,3%	6	100%	1,000	2,250	0,229	22,140
Types of therapy										
Chemotherapy	1	33,3%	2	66,7%	3	100%		1,000	Reference	
Surgery	2	66,7%	1	33,3%	3	100%	1,000	4,000	0,134	119,230
Combination (Surgery and chemotherapy)	8	80%	2	20%	10	100%	1,000	0,500	0,029	8,706

(RR: Relative Risk; CI: Confidence Interval)

The most common primary sites of RMS in this study were head and neck region (52.4%), followed by extremities region (28.6%), then genitourinary region (9.5%) and others (9.5%) were unknown. In the study conducted at Cipto Mangunkusumo Hospital, the primary tumor site was found in the head and neck region with 13 patients (43.3%), in the genitourinary region of 8 patients (26.67%), the extremity with 4 patients (13.3%), and other locations as many as 5 patients (15.6%). Different results were shown in the study at Dharmais Cancer Hospital where the primary tumor location was in the head and neck region with 3 patients (27.2%), in the genitourinary region with 2 patients (18%), followed by extremities with 1 patient (9%) and at other sites with 5 patients (45.45%) (9). The relationship between histologic type, tumor predilection and age of diagnosis can explain the differences in primary site location of RMS, since the embryonic type of RMS often affects children with a predilection of head and neck regions, while alveolar and pleomorphic RMS often appear at an older age-old and have a major predilection in the extremities (11).

In this study, the highest size-frequency was in the group of diameter ≤ 5 cm (42.9%). Results of this study matched the findings of Ma et al.'s research which showed that patients with the size of tumors less than 5 cm had the highest frequency with 67 cases (41.6%), followed by the size tumor of 5-10 cm with 59 cases (36.6%) (12).

Based on the histopathological subtype in this study, the embryonic type RMS had the highest frequency (85.7%), followed by pleomorphic type (9.5%), and lastly the alveolar type (4.8%). These findings are similar to those found in Ma et al.'s research, which described the highest number of cases was the embryonic type with 130 cases (80.7%), followed by the alveolar type with 19 cases (11.8%), then the botryoid type, spindle cell, and others with 5 cases (3.1%), 4 cases (2.5%) and 3 cases (1.9%), respectively (12). The embryonic type of RMS often affects children in the age range of after birth up to 15 years and appears mainly in males. This type of RMS is closely related to the history of cancer in the family with P53 mutations (5). Besides, embryonic type RMS often occurs in children with some cancer-predisposing syndrome, for example, Li-Fraumeni Syndrome (LFS) (13). However, this type of tumor has a better prognosis than the alveolar and pleomorphic types (10).

Therapeutic groups that were most commonly used

in this study involved a combination of surgery and chemotherapy in 10 patients (47.6%). This finding is in contrast with the study conducted by Tri et al. where there were 18 RMS patients (40.9%) treated with chemotherapy, followed by the combination therapy (surgery and chemotherapy) with as many as 17 patients (38.6%), and finally 7 patients (15 9%) were treated with surgery (7). Choice of therapy is usually based on the patient's tumor stage or based on the clinical group system developed by the IRS (14).

Prognostic factors that affect 5-year survival in RMS patients are age, gender, histology type of the tumor, primary site of the tumor, staging according to the Intergroup Rhabdomyosarcoma Study Group, tumor size, time from initial diagnosis to recurrence, and treatment (8). Although not statistically significant, clinically the prognosis of RMS patients was less in female patients than male (3,3:1). This finding was in line with the results of the Pedram and Rezaei study that showed the 5-year survival on RMS patients was greater in male patients than female while not considered statistically significant (8). Another study also found that there was no statistically significant difference in survival between male and female patients (6).

The higher possibility of RMS patients to live was mainly in the age of more than 9 years when diagnosed, but it was not statistically significant. This result is different from a SEER Population-Based Study where the highest survival percentage was in the age 1-4 years group (5-year survival at 74%) and it was statistically significant (11). Another study results found that there was 96% RMS survival in the < 10 years age group at diagnosis (12). In adolescence, RMS patients appear more often with alveolar type, and predilection in the extremities that are usually already metastasized at the time of diagnosis, which is why prognosis in adolescence is worse than other ages (15).

Clinically in this study, patients with the embryonic type had the highest possibility to live, followed with alveolar type and the worse was pleomorphic type. This is in accordance with the results of other studies where the embryonic type has the highest survival rate (12).
Even though not statistically significant the group with tumor size ≤ 5 cm has a higher prognosis than patients with tumor size > 5 cm. This result is in line with the research of Perez et al. which found that 5-year survival was higher in RMS patients with tumor size < 5 cm (13). The IRS IV study reported that tumor size (> 5 cm) was a factor that could worsen a patient's prognosis (16).

The genitourinary region as a primary site of tumor had the worst prognosis while the head and neck region has the best which was clinically significant in this study. This finding is in accordance with other studies that found the location of primary tumors in the head and neck region has a higher 5-year survival than the non-head and neck region (6). However, the study of Rafsanjani et al. found different results in which the genitourinary region had the highest 5-year survival rate (100%) compared to other regions (17). Differences in the results might be due to the differences in the sample size used in each study.

In this study, the combination of therapy (surgery and chemotherapy) gave the best prognostic outcome and survival, followed by chemotherapy, and surgery. This finding is different from the study by Stepan et al. that found the best clinical response was in embryonal RMS treated with surgical therapy followed by radiochemotherapy (18). Interestingly, another study found the survival rate of RMS patients treated with complete surgical methods was higher than patients treated with radiotherapy (19).

CONCLUSION

We concluded that the epidemiological profile of childhood RMS patients in our institution is similar to the world reference data. Thus, prognosis factors (age, primary site, histological type, tumor size, and therapy) were clinically significant in determining the outcome of patients with rhabdomyosarcoma, but the findings were not considered statistically significant probably due to the small sample population.

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