

RESEARCH ARTICLE

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# Inferior Clinical Outcomes of Pediatric Rhabdomyosarcoma in Thailand: A 16-Year Experience in a Single Tertiary Institution

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## Abstract

**Introduction:** There is limited data available on the treatment outcomes of pediatric rhabdomyosarcoma (RMS) in Asian populations. Therefore, we aimed to review the baseline characteristics, clinical outcomes, and prognostic factors in children with RMS from Thailand. **Methods:** The data of children under 15 years of age diagnosed with RMS between 2003 and 2019 from a large tertiary hospital in Southern Thailand were retrospectively reviewed. Descriptive statistics were utilized to describe the clinical characteristics. The Kaplan–Meier method was utilized to estimate survival. Cox proportional hazards regression analysis was utilized to determine prognostic factors that affect survival. **Results:** A total of 42 children RMS were included in this study. The median age at diagnosis was 6.4 years (IQR, 2.4–10.2). Among these patients, 11 (26%) were older than 10 years, and 13 (31%) presented with metastatic disease at diagnosis. The 5-year overall survival (OS) rate was 39% for all children. Age greater than 10 years (hazard ratio (HR): 3.3, 95% CI: 1.2–9.2) and metastatic disease at diagnosis (hazard ratio (HR): 2.8, 95% CI: 1.1–7.5) were independently associated with poorer survival. The 3-year OS for children with metastatic disease (stage IV) was 15% (95% CI: 4.3–55). **Conclusion:** The percentage of metastatic disease in our cohort was higher than that in previous reports and may have contributed to a poorer outcome. Age greater than 10 years and metastatic disease at diagnosis were noted as adverse prognostic factors.

**Keywords:** Childhood cancer- rhabdomyosarcoma- survival outcome- prognostic factors- Asians

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## Introduction

Rhabdomyosarcoma (RMS) is the most prevalent soft tissue sarcoma, accounting for 3% of all pediatric cancers (Meyer and Spunt, 2004; Amer et al., 2019). The age-standardized incidence rate (ASR) is 4.4 per million children (Perez et al., 2011). In Asian countries, the incidence of RMS is less frequent than that in western countries, with the ASR ranging from 1.8–3.0 per million children (Wiangnon et al., 2011; Liu et al., 2015). The reported prognostic factors associated with survival include: age at diagnosis, pre-treatment TNM staging, primary site, histology subtype, and operable status (Dasgupta et al., 2016). In Western studies, the 5-year overall survival (OS) for RMS ranges from 30 to 90% (Meza et al., 2006; Amer et al., 2019). In Asian countries, the survival outcome varies from 10 to 80% (Bhurgrri et al., 2004; Salman et al., 2012).

While 80% of childhood cancer patients reside in low-and middle-income countries (LMIC), there is limited

data available on the treatment outcomes reported from Southeast Asian countries (Rodriguez-Galindo et al., 2015). Disparities in cancer treatment among LMIC and western countries have existed for decades (Bhatia, 2011). In Thailand, a previous population-based registry analysis showed that the 5-year OS for children with RMS ranged from 28 to 50%, which was much lower than the reported outcome from an international study (Wiangnon et al., 2011; Wiangnon et al., 2014; Bidwell et al., 2019).

Our study aimed to describe the baseline characteristics and clinical outcomes as well as to determine the prognostic factors of children diagnosed with RMS at the Songklanagarind hospital in Thailand, a middle-income country, and to compare these results with those from other Asian countries.

## Materials and Methods

We retrospectively reviewed the medical documents of all children aged under 15 years who were diagnosed

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with RMS at Songklanagarind hospital, the biggest tertiary hospital in Southern Thailand, between November 2003 and September 2019. The diagnosis of RMS was confirmed based on the pathological report. The data collected included demographics, clinical characteristics, histology, staging, clinical group, risk group classification, and treatment outcomes. The pre-treatment staging of RMS was defined as stage I-IV based on primary site, tumor size, regional node involvement, and metastatic disease (TNM staging) (Lawrence et al., 1997). The clinical group classification was defined as group I-IV, contingent on the magnitude of residual disease after surgery. In brief, group I-II included children who postoperatively achieved grossly total resection of tumor (GTR). Group III included children with localized grossly residual tumor, and group IV represented those with distant metastasis at diagnosis (Sangkhatat, 2015; Rhee et al., 2020). Risk stratification into low risk, intermediate risk, and high risk, was based on pre-treatment TNM staging system, histology, and clinical group as described by the Intergroup Rhabdomyosarcoma Study Group (IRSG) (Hayes-Jordan and Andrassy, 2009; Malempati and Hawkins, 2012). The treatment plan was dependent on the period of diagnosis. Prior to 2015, all children in our cohort received the standard VAC regimen comprising of vincristine, actinomycin-D and cyclophosphamide 2.2 g/m<sup>2</sup>/cycle, based on IRS-IV study (Crist et al., 2001; Arndt et al., 2009). In 2015, the Thai Pediatric Oncology Group (Thai-POG) proposed a national protocol defined by prognostic risk group stratification, in which low-risk patients received VAC (with cyclophosphamide 1.2 g/m<sup>2</sup>/cycle) for four cycles followed by VA for four cycles (Walterhouse et al., 2014), while intermediate-risk patients received the standard VAC regimen. The Thai-POG protocol for high-risk patients comprised an alternating intensive 6-drug combination, including ifosfamide, vincristine, etoposide, carboplatin, actinomycin-D, and cyclophosphamide (IVA/CbE/IVE/VAC) (Thai Pediatric Oncology Group, 2014).

*Statistical analysis*

Descriptive statistics were utilized to present clinical characteristics. For continuous variables, median and interquartile range (IQR) were used, and for categorical variables, frequency with percentage. The overall survival curve was depicted by the Kaplan–Meier method. Prognostic factors associated with clinical outcomes were evaluated using the Cox proportional hazards model in univariate and multivariate analysis. From the univariate analysis, prognostic factors having a p value less than 0.2 were included in the multivariate logistic regression model for the assessment of independent prognostic factors. Statistical significance was defined as a p value of less than 0.05. All analyses were performed in R program version 4.1.0 (The R foundation for Statistical Computing, Vienna, Austria).

**Results**

There were 45 children diagnosed with RMS during the 16-year study period. We excluded three children who had incomplete data; two children had received treatment

at other centers; one child presented with advanced stage disease and eventually died prior to treatment. A total of 42 children were included in the analysis with a median follow-up time of 23.6 months (range, 11.6 – 60.9). Demographic data, clinical characteristics and clinical outcomes are presented in Table 1. The median age at diagnosis was 6.4 years (IQR 2.4–10.2). Of the 42 children, 31 (74%) were younger than 10 years of age. The male to female ratio was 2.3:1. Embryonal RMS was the most frequent histologic subtype (40%). The primary tumor site was unfavorable site in 33 (79%) children. The tumor size at diagnosis was larger than 5 cm in 29 (69%) children. Fourteen (33%) children had regional lymph node involvement at diagnosis, and 13 (31%) presented with metastatic disease at diagnosis. The distant metastatic sites included lungs (n=9), bone (n=6), bone marrow (n=2), and brain (n=1). Of these, six patients had two concurrent metastatic sites. All children with metastatic disease had a tumor size larger than 5 cm. The TNM pre-treatment staging were stage I, II, III, and

Table 1. Clinical Characteristics and Outcomes of 42 Children with Rhabdomyosarcoma

Characteristics	n	(%)	5-year OS (95%CI)	P value
Median age at diagnosis (years) [IQR]	6.4	(2.4–10.2)		
Age <10 years	31	(74)	51 (36–72)	0.011
Age ≥10 years	11	(26)	-- ( --, --)	
Sex				
Male	29	(69)	38 (23–62)	0.9
Female	13	(31)	46 (26–83)	
Histology				
Embryonal	17	(40)	39 (21–73)	0.9
Alveolar	11	(26)	32 (13–80)	
Undetermined	14	(34)	42 (22–79)	
Primary tumor site				
Favorable	9	(21)	52 (27–100)	0.3
Unfavorable	33	(79)	37(23–59)	
Tumor size (cm)				
≤5	13	(31)	60 (38–95)	0.069
>5	29	(69)	31 (17–56)	
Regional nodes				
N0	28	(67)	37 (22–61)	0.5
N1	14	(33)	48 (27–85)	
Extent of disease				
Localized	29	(69)	53 (37–76)	0.007
Distant metastasis	13	(31)	-- ( --, --)	
Post-operative group				
I-II	12	(29)	71 (48–100)	0.006
III	17	(40)	40 (22–72)	
IV	13	(31)	-- ( --, --)	
Prognostic risk group				
Low risk	13	(31)	83 (64–100)	0.001
Intermediate risk	16	(38)	29 (13–64)	
High risk	13	(31)	-- ( --, --)	

IQR, interquartile range; OS, overall survival rate

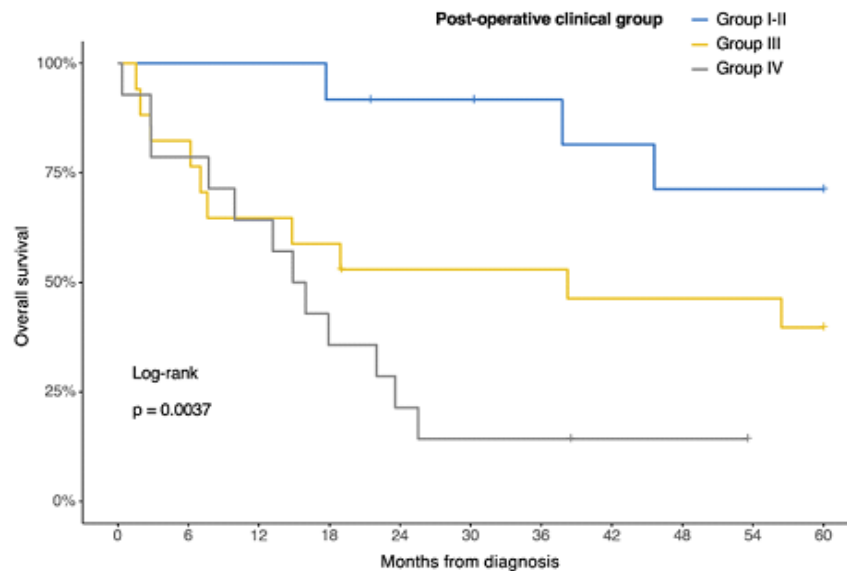


Figure 1. The Overall Survival of Children with RMS, According to Post-Operative Clinical Group

IV in 8 (19%), 4 (10%), 17 (40%), and 13 (31%) children, respectively.

The post-operative clinical group were evaluated after surgery; 12 (29%) were classified as post-operative group I-II (achieved GTR) 17 (40%) as group III, and 13 (31%) as group IV. According to prognostic risk group stratification, 13 (31%) were determined as low risk, 16 (38%) as intermediate risk and 13 (31%) as high risk. All

children in our cohort received chemotherapy; 36 (86%) children received standard VAC regimen. Four children in the high-risk group received the IVA/CbE/IVE/VAC regimen, whereas two children in the low-risk group received VAC for four cycles and additional VA for four cycles. Thirty-eight (90%) children received radiotherapy.

The 5-year OS and EFS rates for all children with RMS were 39% (95% CI; 27–58) and 38% (95% CI; 26–56), respectively. The 5-year OS for children less than 10 years of age was 51% (95% CI; 36–72) vs 0% for those more than 10 years of age, p value = 0.011). The median survival time for the latter was 14.8 months (range, 1.5–56.4). Thirteen children with metastatic disease showed a dismal outcome with 3-year OS rate of 15% (95% CI; 4.3–55). Of these, 11 children eventually died from disease progression.

Children in clinical groups I–II, wherein the tumor could be totally resected, had better survival outcomes than those who underwent only biopsy or incomplete resection (clinical group III), with a 5-year OS rate of 71% vs. 40% (p value = 0.004) (Figure 1). We then stratified children with non-metastatic disease according

Table 2. Univariate Analysis of Prognostic Factors Associated with RMS Outcomes

Prognostic factors	Overall survival	
	Hazard ratio	P value
Age at diagnosis		
<10 years	Ref	0.015
≥10 years	2.9 (1.2–6.8)	
Tumor size		
≤5 cm	Ref	0.078
>5 cm	2.4 (0.9–6.5)	
Regional node involvement		
Negative	Ref	0.46
Positive	0.7 (0.3–1.7)	
Extent of disease		
Localized	Ref	0.01
Distant metastasis	3.0 (1.3–7.0)	
Gross total resection		
Post-operative clinical group I-II	Ref	0.015
Post-operative clinical group III-IV	4.6 (1.4–15.0)	
Radiotherapy		
Yes	Ref	0.037
No	3.8 (1.1–13.4)	
Prognostic risk group		
Low	Ref	0.008
Intermediate	7.3 (1.6–33.0)	
High	11.0 (2.5–53.0)	

Ref, reference; RMS, rhabdomyosarcoma

Table 3. Multivariate Analysis of Prognostic Factors Associated with RMS Outcomes

Prognostic factors	Overall survival	
	Hazard ratio	P value
Age at diagnosis		
<10 years	Ref	0.021
≥10 years	3.3 (1.2–9.2)	
Tumor size		
≤5 cm	Ref	0.508
>5 cm	1.5 (0.4–4.9)	
Extent of disease		
Localized	Ref	0.032
Distant metastasis	2.8 (1.1–7.5)	

Ref, reference; RMS, rhabdomyosarcoma

Table 4. Survival Outcomes of Childhood Rhabdomyosarcoma in Asian Countries

Country	First Author /Year	N	Study period	Metastasis at diagnosis (%)	5-year OS	5-year OS (%) by prognostic risk group		
						LR	IR	HR
China	Ma 2015	161	2001–2014	37.3	65.3†	100†	88.6†	23.1†
	Xu 2019	213	2006–2018	25.8	64	100	74	48
Hongkong	Yuan 2008	19	1989–2005	31.6	42	66		17
Iran	Company 2011	60	1996–2002	40	47.9	71 (IRS-II)	60 (IRS-III)	22 (IRS-IV)
India	Bansal 2017	77	1990–2012	11	43.6‡		NA	
	Swaminathan 2008	42	1990–2001	NA	36.4		NA	
Japan	Hosoi 2007	331	1991–2002	23.2	60.7	94	62.7	38.1
Korea	Park 2008	77	1986–2005	24.7	77	100 (IRS I-II)	80 (IRS-III)	43 (IRS-IV)
	Lee 2018	51	2001–2015	45.1	63.8	ERMS 5-year OS = 75.1% ARMS 5-year OS = 33.6%		
Lebanon	Salman 2012	23	2002–2010	4.4	83		NA	
Pakistan	Bhurgri 2004	100	1998–2002	NA	10		NA	
Singapore	Aung 2014	50	1993–2010	24	80.3	81.3‡	61.4‡	25.0‡
Taiwan	Chou 2019	37	1995–2016	32.4	54.7	83.3	47.4	33.3
Turkey	Akyüz 2012	409	1973–2003	11	34	50-71 (IRS-II)	34 (IRS-III)	16 (IRS-IV)
	Sezgin 2015	24	2000–2011	NA	40.1-68.2		NA	
Thailand	Wiangnon 2011	178	1990–2011	NA	28.5		NA	
	Bidwell 2019	137	2003–2005	NA	50.1	NA		
IRS-IV study	Crist 2001, Raney 2001	883	1991–1997	16	71	80-99	59-83	30
Current study		42	2003–2019	30.9	39	83	29	0

Abbreviations: ARMS, alveolar rhabdomyosarcoma; ERMS; embryonal rhabdomyosarcoma; IRS, International Rhabdomyosarcoma Study; LR, low risk; IR, intermediate risk; HR, high risk; NA, data not available; OS, overall survival rate; † Data are presented as the 10-year overall survival rate; ‡ Data are presented as the 5-year event-free survival rate.

to their prognostic risk group. The 5-year OS of children in the low-risk group was 83% while that of children in the intermediate risk group was 29% (p value < 0.001). (Figure 2)

The 5-year EFS for children diagnosed before 2015 (n = 30) was 29% compared to 64% in those diagnosed after 2015 (n = 12) (p value = 0.035). The percentage of metastatic disease was not different between the two eras, but children who received treatment after 2015 seemed to have a higher rate of surgical management (75% vs. 60%, p value = 0.485) although not statistically significant.

In univariate analysis, five prognostic factors that were statistically associated with overall survival outcome included: age greater than 10 years, presence of metastatic disease at diagnosis, gross total resection, radiotherapy, and prognostic risk group, as shown in Table 2. Children who failed to achieve GTR (HR 4.6, 95% CI: 1.4–15.0) or had metastatic disease (HR 3.0, 95% CI: 1.3–7.0) were correlated with worsened outcomes. Children who had not received radiotherapy also had lower OS rates (HR 3.8, 95% CI: 1.1–13.4) while chemotherapy regimen did not affect the survival in our study. Prognostic risk

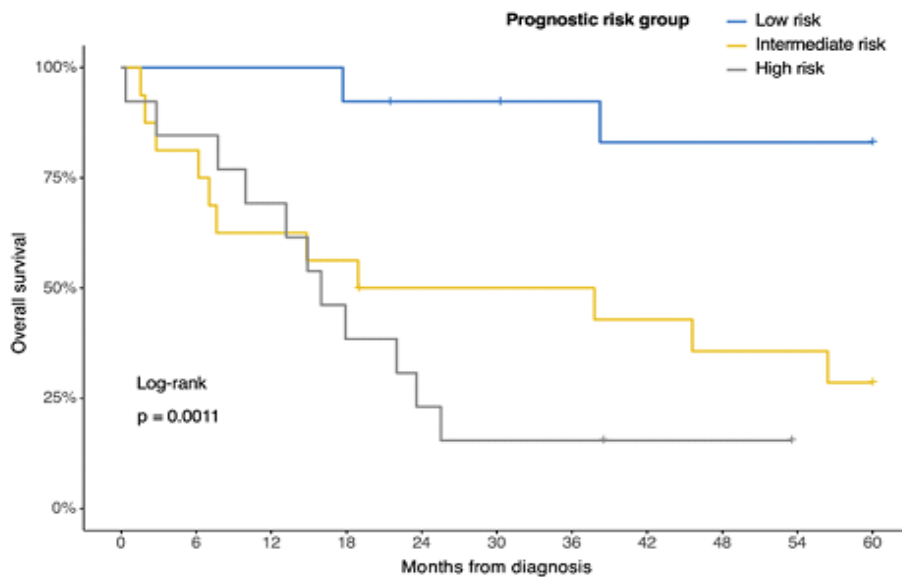


Figure 2. The Overall Survival of Children with RMS, According to Prognostic Risk Stratification

group was strongly associated with the survival outcome ( $p$  value = 0.008).

In multivariate analysis, the independent prognostic factors associated with end outcome are shown in Table 3. The two prognostic factors associated with a poor outcome were age greater than 10 years (HR: 3.3, 95% CI: 1.2–9.2) and metastatic disease at diagnosis (HR: 2.8, 95% CI: 1.1–7.5).

## Discussion

Our study was a descriptive analysis of clinical characteristics, survival outcome, and adverse prognostic factors in children with RMS from Southern Thailand. The majority of our children (74%) were aged below 10 years, similar to those in international studies (Perez et al., 2011; Weiss et al., 2013; Amer et al., 2019). In our study, the 5-year OS rate of children with RMS was 39% (95% CI: 27–58). In western countries, data from IRS-IV studies reported a 5-year OS rate of 71% (Crist et al., 2001). Overall, the 5-year OS rate for children with RMS in Asian countries was lower than that in children in studies from western countries, except those from Lebanon and Singapore, where the 5-year OS rate was comparable to that of western studies (Salmon et al., 2012; Aung et al., 2014). In Thailand, previous reports on RMS were solely from population-based studies focusing on the incidence and crude survival rate of childhood cancer (Wiangnon et al., 2011; Wiangnon et al., 2014; Bidwell et al., 2019).

Despite the rarity of the disease, RMS usually appears insidiously among children. In our study, 31% of the affected children ( $n=13$ ) showed distant metastasis at diagnosis, which is two times higher than the rates from western studies (16%) (Weiss et al., 2013). This might be explained by the fact that our hospital is the only university hospital and one of two pediatric cancer referral centers in Southern Thailand. Therefore, most patients in our cohort visited the local municipality for investigation and were further referred to us for diagnosis and treatment. Badr (2012) found that 44% of children with RMS in Egypt presented with metastatic disease at diagnosis, which mainly was explained by lack of recognition of presenting symptoms by the primary health care providers and unavailability of facilities for early diagnosis (Abd El-Aal et al., 2006). This finding was similar to previous reports from China, Hongkong, Iran, Japan, Korea, Taiwan, and Singapore, wherein metastasis on diagnosis ranged from 23–45% as shown in Table 4 (Hosoi et al., 2007; Park et al., 2008; Yuan et al., 2008; Company et al., 2011; Ma et al., 2015; Lee et al., 2018; Xu et al., 2019). In South Asia, South East Asia or the Middle East, descriptive data regarding of clinical characteristics of childhood RMS and its local outcomes were scarce (Wiangnon et al., 2011; Bansal et al., 2017; Bidwell et al., 2019).

About 69% of children in our cohort had tumors larger than 5 cm. The median time from symptom presentation to diagnosis was 8 weeks (range, 4–28). Therefore, the delayed diagnosis from the lack of awareness of parents and primary care physicians about early signs of cancer was the contributing factor to the higher metastatic disease in this study. The advanced stage of disease was

attributed to the inferior outcomes. Thus, education for general practitioners and public awareness raising are needed to build the expertise for early cancer diagnosis. The comprehensive referral network might also shorten the duration of diagnosis and investigation.

In our cohort, the histology subtype was not associated with final outcome while previous reports showed a strong correlation between histology subtype and pattern of distant metastasis on end outcome (Meza et al., 2006; Weiss et al., 2013). This might be explained by the limited sample size and retrospective nature of our study, wherein the histologic subtype was undetermined in 32% of the affected children.

The outcome of RMS appears dependent on many factors, which formed the prognostic risk group (Malempati and Hawkins, 2012). From the IRS-III-IV study, the 5-year OS rates were 95–98% for low risk, 59–83% for intermediate-risk and 30% for high-risk RMS (Raney et al., 2001)(Table 4). In our cohort, the 5-year OS of children in the low risk group was 83%, which was comparable to the that in the IRS study and our neighboring countries, like Singapore (5-year EFS 81.3%) (Aung et al., 2014) or Taiwan (Chou et al., 2019). However, the survival for children in the intermediate risk group was much lower than that reported in other Asian countries and the IRS study. The 5-year OS rate for this group was 29%, in contrast to 59–83% from the IRS studies (Crist et al., 2001; Raney et al., 2001). This finding might be explained by a low GTR rate (28%) in our cohort and even lower in the intermediate risk group (19%).

Our study identified two adverse prognostic factors from the multivariate analysis using the Cox regression model to predict inferior overall survival, including age older than 10 years and the presence of distant metastases at diagnosis. This finding conformed to previous studies; Joshi (2004) reported that the 5-year EFS for children aged 1–9 years (72%) was significantly better than that in infants (53%) and children age above 10 years old (51%) ( $p < 0.001$ ). The particularly poor outcome for children older than 10 years old in our cohort was mainly explained by the advanced stage at diagnosis. In this group, 4 of 11 children (36%) presented with metastatic disease at diagnosis and 10 of 11 children (91%) had tumor sizes larger than 5 cm at diagnosis. Total resection was achievable in only 3 of 11 children (27%) in this group, which then resulted in a poor outcome. This finding concurred with the previous report by Badr (2012), which found that the 5-year OS for children aged > 10 years was only 25%.

The 3-year OS for metastatic RMS in our study was 15%, which lower than previous report from Bailey (2020) that stated a 3-year OS for metastatic RMS of 34% and that those with bone marrow metastasis showed the worst prognosis, with a 3-year OS of 14% (Rudzinski et al., 2017). Oberlin (2008) reported a strong correlation of four adverse factors and worse prognosis: age above 10 years, unfavorable primary tumor site, bone or bone marrow involvement, and presence of three or more metastatic sites. All children who had metastatic disease in our cohort were aged above 10 years; 93% had unfavorable primary site tumor, and two children had an Oberlin score of 3.

In our cohort, the treatment outcome improved over time from a 5-year EFS at 29% in the earlier period to 64% in the later five years. The improvement of treatment outcomes during the last 5 years (2015–2020) was mainly explained by the increasing trend of surgical management. This was in concordance with the result of the IRSG studies wherein the 5-year OS rate continuously improved from 55% in IRS-I study to approximately 71% in the IRS-III and IRS-IV studies (Raney et al., 2001).

Our study had some limitations. First, the retrospective design of this study might be associated with potential bias. Further, some clinical characteristics such as histologic subtype were unavailable. Second, the small sample size was insufficient for comparison between different chemotherapy protocols. Lastly, genetic abnormalities or PAX-FOXO1 fusion status, which strongly adversely affects outcome and had been recently included in risk stratification, was not screened in this study (Rudzinski et al., 2017; Hibbitts et al., 2019; Heske et al., 2021).

In conclusion, survival outcomes for pediatric RMS from one institution in Thailand were inferior to those in developed countries but were comparable to those in other developing countries in Asia. After stratification according prognostic risk group, children in the low-risk group showed outcomes comparable to those in international studies; however, the survival outcome in both intermediate and high-risk groups were far below those from international studies. A high percentage of metastatic disease at diagnosis in developing countries may adversely influence the outcome. This reflects a need for effective strategies, such as early diagnosis, increased attempts for GTR, and comprehensive multidisciplinary care, to enhance the clinical outcome for children with RMS in developing countries.

### Author Contribution Statement

All authors contributed significantly to both the research and the composition of the work, and they all reviewed and approved the final version.

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#### Ethics statement

This study was granted ethical approval by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.

#### Data availability statement

The data supporting the study results is obtainable upon request from the corresponding author. Due to

privacy and ethical concerns, the data is not publicly accessible.

#### Conflict of Interest

The authors declare that they have no conflict of interest.

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