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Impact of Rhabdomyosarcoma (RMS) Characteristics on Prognosis of Pediatric RMS: A SEER Database Large Population Study

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Abstract: To provide a better insight into the epidemiology, characteristics, therapeutics, and outcomes of pediatric RMS. Data of 1,623 pediatric RMS were acquired from the Surveillance, Epidemiology and End Results (SEER) database. Detailed information on demographics, primary site, size, subtype, stage, surgery, and survival had been recorded during 1975-2016. The most common subtype was embryonal RMS (64.9%) followed by alveolar RMS (29.9%). Additionally, the majority of RMS size was larger than 5 cm. Multivariable analysis exhibited that the age over 10, unfavorable primary site, distant metastasis was respectively correlated with the poor OS, whereas surgery could improve the outcomes of pediatric RMS. In conclusion, our large population-based analysis described that age, subtype, primary tumor sites, stage and surgery are all independent prognosis factors for RMS.

Keywords: Rhabdomyosarcoma; Prognosis; Subtype; Survival; Surgery; SEER

Introduction

Rhabdomyosarcoma (RMS), mainly derived from certain mesenchymal cells that undergo an aberrant differentiation process in the embryonal development, is the most common malignant soft-tissue neoplasm of children. Identification the impact of biological characteristics and treatments on RMS survival is of significance for the patients, especially for the pediatric patients. To better optimize the RMS treatment procedures, it is critical to explore and identify sensitive prognosis factors, especially comparing the risk factors within tumor-related biological characteristics. In this study, we performed a comprehensive analysis of the RMS cases that were registered in the Surveillance, Epidemiology and End Results (SEER) database to investigate the clinical characteristics and outcomes of pediatric RMS.

1. Materials and methods

1.1 SEER database

SEER serves as a public database provided by the National Cancer Institute (NCI), which includes information from population-based cancer registries of 20 geographic areas, and covers approximately 34.6% of the United States population. Data of the pediatric patients with RMS from 1975 to 2016 in this study were extracted from the SEER database.

1.2 Identification of RMS cases

All of the pediatric RMS patients were diagnosed by the histological confirmation according to biopsy or surgical pathology. Total 1,103 in 2,726 cases were excluded because of unknowns in the pediatric age, gender, race, tumor size, vital status, survival months, primary site, subtype or stage.

1.3 Statistical analysis

For analysis, “age” was converted from a continuous variant to a categorical variant as “< 10” and “≥ 10”. The “race” was classified as white or non-white, and “stage” was used to define the RMS neoplasm development including “localized”, “regional”, and “distant”. “Localized” was identified as an invasive tumor confined entirely to the origin organ; “regional” was identified as an extended neoplasm, which invades 1) beyond the limitations of origin organs and directly to surrounding organs; 2) to the regional lymph nodes; 3) with extension and to regional lymph nodes; “distant” was identified as metastasis. The “subtype” was categorized into three sections: the “alveolar”, “embryonal” as well as “others” which contains pleomorphic, spindle cell, mixed type and ganglionic differentiation.

IBM SPSS Statistics (version 25.0) was used for analyzing the statistical significance. A nomogram and calibration plots were formed according to the results of multivariate analysis via the package rms26 in R program language (version i386 3.6.0). Results were considered statistically significant at $P < 0.05$.

2. Results

2.1 A prognosis nomogram for OS of pediatric RMS patients

A nomogram was used to analyze the potential prognosis factors in pediatric patients with RMS. Results showed a 0.742 index of concordance (C-index) for OS prediction (95% CI, 0.7234 - 0.7606), indicating that this nomogram is useful for the OS forecast of pediatric RMS patients (Fig. 1A). The calibration plot of survival probabilities at 3- and 5-year also presented a similar result in the RMS prediction via a nomogram and clinical observations (Fig. 1B and 1C).

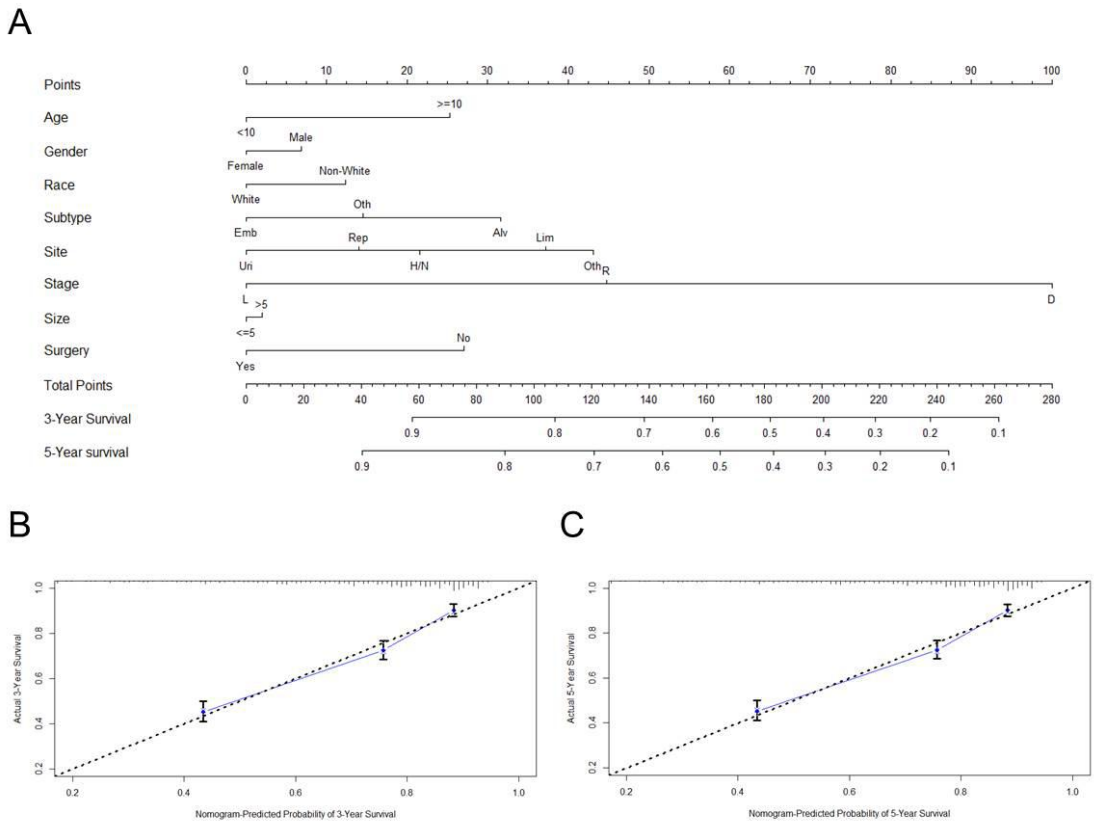

Fig 1. (A) A nomogram for pediatric RMS.

An individual child’s value was located on each variable axis, and a solid line was drawn upward to define the number of points received for each variable value. The sum of above numbers was located on the total point axis, and a solid line was drawn to the survival axes to define the likelihood of 3- or 5-year survival. (B-C) Two calibration curves were used for

predicting the 3-year OS (B) and 5-year OS (C) of pediatric RMS patients, respectively. X-axis refers to nomogram-predictied survival probability; y-axis refers to actual OS.

Abbreviations: Alv, Alveolar; Emb, Embryonal; Uri, urinary system; H/N, head/neck; Lim, limbs; Oth, other sites; L, localized; R, regional; D, distant.

2.2 Independent prognosis factors for pediatric RMS

As shown in Table 1, children older than 10 years old exhibited a higher risk of death (HR, 1.4673; 95% CI, 1.2218 - 1.7620; $P < 0.001$) compared with those of control. Then, the mortality was different according to each primary site. Compared with the reproductive system, HR for RMS in other sites rather than urinary system, head/neck and limbs was 1.5521 (95% CI, 1.1365 - 2.1199; $P < 0.001$). In addition, pediatric RMS patients in regional and distant stage presented a significantly higher mortality rate. HR was notably higher in patients with a regional stage (1.9683; 95% CI 1.5069 - 2.5710; $P < 0.001$) or a distant metastasis (4.5493; 95% CI, 3.4944 - 5.9225; $P < 0.001$). Taken together, these data show that age, primary site, and stage were all poor prognosis factors for outcomes of pediatric RMS.

We also found that the embryonal subtype and surgery could increase the OS of pediatric RMS. Embryonal RMS presented a higher survival rate (HR, 0.6196; 95% CI, 0.5019 - 0.7648; $P < 0.001$) compared with other subtypes. Surgery could also help to improve the survival rate of pediatric RMS (HR, 0.6638; 95% CI, 0.5467 - 0.8058; $P < 0.001$).

Table 1 Multivariable analysis of factors associated with overall survival in the pediatric RMS patients

Variables		HR[1]	95% CI[2]	*P*
Age (year)	< 10	1	Reference	
	≥ 10	1.4673	1.2218-1.7620	**0.00004 < 0.01**
Gender	Female	1	Reference	
	Male	1.1096	0.9254-1.3304	0.26173
Race	White	1	Reference	
	Non-white	1.2051	0.9892-1.4680	0.06399
Subtype	Alveolar	1	Reference	
	Embryonal	0.6196	0.5019-0.7648	**0.000008 < 0.01**
	Other	0.7716	0.4997-1.1915	0.24213
Primary site	Reproductive system	1	Reference	
	Urinary system	0.8084	0.4289-1.5235	0.51065
	Head/neck	1.1212	0.8053-1.5609	0.49810
	Limbs	1.4199	0.9966-2.0288	0.05221
	Other	1.5521	1.1365-2.1199	**0.00571 < 0.01**
Tumorsize (cm)	≤ 5	1	Reference	
	> 5	1.0308	0.8605-1.2351	0.74273
Stage	Localized	1	Reference	
	Regional	1.9683	1.5069-2.5710	**0.0000006 < 0.01**
	Distant	4.5493	3.4944-5.9225	**0.0000002 < 0.01**
Surgery	No	1	Reference	
	Yes	0.6638	0.5467-0.8058	**0.00003 < 0.01**

2.3 Independent prognosis factors for pediatric-alveolar/embryonal RMS

Table 2 displayed that in the pediatric alveolar RMS, the primary site was no longer a prognosis factor for OS. However, the death risk was increased to 1.89 times (HR, 1.8915; 95% CI, 1.0693 - 3.3459; $P < 0.05$) in the embryonal RMS located in limbs. This observation highlights that oncologists should thoroughly consider the impact of primary sites on outcomes of pediatric RMS according to different RMS subtypes.

Table 2 Multivariable analysis of factors associated with overall survival in the pediatric RMS patients according to the subtype

Variables	Alveolar (N = 485)			Embryonal (N = 1,053)		
Age (year)	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
< 10	1	Reference		1	Reference	
≥ 10	1.5803	1.21323-2.0584	**0.000691 < 0.01**	1.3490	1.0281-1.7701	**0.03080 < 0.05**
Gender						
Female	1	Reference		1	Reference	
Male	1.2792	0.98170-1.6669	0.068266	0.9797	0.7489-1.2818	0.88136
Race						
White	1	Reference		1	Reference	
Non-white	1.1932	0.90176-1.5789	0.216322	1.1354	0.8380-1.5382	0.41252
Primary site						
Reproductive system	1	Reference		1	Reference	
Urinary system	0.4880	0.06105-3.9012	0.498779	0.7898	0.3990-1.5635	0.49821
Head/neck	1.0087	0.49130-2.0711	0.981090	1.0472	0.6953-1.5772	0.82546
Limbs	1.1848	0.59281-2.3680	0.631220	1.8915	1.0693-3.3459	**0.02851 < 0.05**
Other	1.4826	0.73067-3.0084	0.275357	1.4117	0.9719-2.0506	0.07028
Stage						
Localized	1	Reference		1	Reference	
Regional	1.4768	0.97352-2.2403	0.066694	2.2201	1.5541-3.1715	**0.00001 < 0.01**
Distant	3.4562	2.29728-5.1998	**0.000002 < 0.01**	5.0804	3.5716-7.2266	**0.0000001 < 0.01**
Tumor size (cm)						
≤ 5	1	Reference		1	Reference	
> 5	0.8702	0.66835-1.1330	0.301729	1.2412	0.9532-1.6161	0.10865
Surgery						
No	1	Reference		1	Reference	
Yes	0.7343	0.55174-0.9772	**0.034187 < 0.05**	0.6347	0.4822-0.8356	**0.00119 < 0.01**

2.4 Independent prognosis factors for metastasis or non-metastasis RMS

Table 3 was shown that age, subtype, and surgery were independent factors related to the survival rate of pediatric RMS patients regardless of metastasis. To our surprise, primary site was a negative prognosis factor in non-metastasis RMS, while this phenomenon could not be observed in metastasis RMS. According to the observation in the non-metastasis group, pediatric RMS located in both head/neck and limbs displayed a significantly higher mortality with an estimated HR 1.6325 (95% CI, 1.0195 - 1.2.6141; $P < 0.05$) in head/neck group and 1.7147 (95% CI, 1.0067 - 2.9206; $P < 0.05$) in limbs group, respectively.

Table 3 Multivariable analysis of factors associated with overall survival in the pediatric RMS patients with or without metastasis

Variables	No metastasis (N = 1,175)			Metastasis (N = 448)		
Age (year)	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
< 10	1	Reference		1	Reference	
≥ 10	1.4870	1.1482-1.9257	**0.002637 < 0.01**	1.4492	1.1100-1.8919	**0.00638 < 0.01**
Gender						
Female	1	Reference		1	Reference	
Male	1.0661	0.8258-1.3763	0.623187	1.1337	0.8733-1.4719	0.34594
Race						
White	1	Reference		1	Reference	
Non-white	1.0942	0.8236-1.4535	0.534620	1.2412	0.9380-1.6425	0.13054
Subtype						
Alveolar	1	Reference		1	Reference	
Embryonal	0.4836	0.3608-0.6481	**0.000001 < 0.01**	0.7121	0.5279-0.9605	**0.02617 < 0.05**
Other	0.4863	0.2434-0.9716	**0.041208 < 0.05**	1.1441	0.6462-2.0258	0.64414
Primary site						
Reproductive system	1	Reference		1	Reference	
Urinary system	1.0841	0.3722-3.1579	0.882279	0.6602	0.2989-1.4582	0.30446
Head/neck	1.6325	1.0195-2.6141	**0.041300 < 0.05**	0.7771	0.4796-1.2592	0.30575
Limbs	1.7147	1.0067-2.9206	**0.047215 < 0.05**	1.0552	0.6540-1.7025	0.82586
Other	2.4004	1.5165-3.7994	**0.000186 < 0.05**	1.0320	0.6766-1.5742	0.88368
Tumorsize (cm)						
≤ 5	1	Reference		1	Reference	
> 5	1.0772	0.8273-1.4026	0.580707	0.9607	0.7455-1.2380	0.75669
Surgery						
No	1	Reference		1	Reference	
Yes	0.5691	0.4322-0.7495	**0.00005 < 0.01**	0.6818	0.5199-0.8940	**0.00560 < 0.01**

3. Discussion

In our study, the RMS embryonal and alveolar subtypes were both frequent in pediatric patients, and embryonal subtype accounted for 64.9% of all the subtypes. And embryonal subtype was a positive prognosis factor for the OS of pediatric RMS ($P = 0.000008 < 0.01$). We moved on to compare the risk factors in these two subtypes. Notably, compared with the alveolar subtype, the OS for embryonal RMS located in limbs was in a higher mortality rate (HR, 1.8915; 95% CI, 1.0693 - 3.3459; $P < 0.05$). In summary, these observations not only highlight that the embryonal subtype is the prognosis factor of RMS, but also indicates that the outcomes of embryonal RMS is strongly correlated with the tumor location.

Genitourinary and head/neck are the frequently original sites of pediatric RMS, even though RMS can be found in any anatomy area of human body. Bradley et al. showed that the most common primary site of RMS was reproductive system (40%), followed by para-meningeal (14%) and limbs (11%) [1]. However, the outcomes of RMS with different primary sites are controversial. Kirsch et al. confirmed that the survival rates were of no difference in multiple primary sites in female pediatric RMS patients in the period of 1973-2006 [3], while a lower 5-year survival rate of RMS was also reported with primary sites in extremities (25%), and other sites (28.9%) rather than orbit (57.2%), head/neck (51.3%), para-meningeal (41.2%), and genitourinary (79.8%) [2]. In fact, our study confirms this observation and suggests that the mortality was higher in the pediatric RMS located in other primary sites ($P = 0.00571 < 0.01$) rather than reproductive system, urinary system, head/neck, and limbs.

For the RMS stage, the majority is localized and less than 30% of the RMS neoplasms are with metastasis. In fact, distant metastasis is a poor prognosis factor for pediatric RMS. Kirsch et al. mentioned that 38.8% (N = 26) of, 16.2% (N = 11) of and 28.4% (N = 15) of RMSs were in the stage of localized, regional and distant, respectively [3]. Notably, tumor stage is a key biological characteristic in the diagnosis and treatment of pediatric RMS. Some prior studies on pediatric RMS had mentioned that a distant metastasis was correlated with a poor prognosis [4, 5]. Meanwhile, several studies also concluded that localized stage is the most favorable prognosis factor of RMS [6, 9]. Our multivariate analysis results identified the regional (HR, 1.9683; 95%, 1.5069 - 2.5710; $P < 0.001$) and distant (HR, 4.5493; 95%, 3.4944 - 5.9225; $P < 0.001$) stage as two independent predictors for mortality of pediatric RMS. In summary, these data display evidences that distant metastasis is a poor prognosis factor of pediatric RMS.

In conclusion, we studied a large population-based cohort of RMS and suggested that the biological characteristics, such as age, subtype, primary site, stage and no surgery are correlated with a poor outcome of pediatric RMS patients. Therefore, differences of the prognostic factors among populations with various characteristics should be thoroughly considered, and further investigations are needed to identify long-term poor prognosis impact from each RMS characteristics.

Disclosure of potential conflict of interest

No potential conflicts of interest were disclosed.

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