Second Malignant Neoplasms in Patients with Rhabdomyosarcoma: A US Population-Based Analysis

HONGNAN ZHEN

PUMCH: Peking Union Medical College Hospital <https://orcid.org/0000-0002-3924-9183>

ZHIKAI LIU

PUMCH: Peking Union Medical College Hospital

HUI GUAN

PUMCH: Peking Union Medical College Hospital

JIABIN MA

PUMCH: Peking Union Medical College Hospital

WENHUI WANG

PUMCH: Peking Union Medical College Hospital

JING SHEN

PUMCH: Peking Union Medical College Hospital

ZHENG MIAO

PUMCH: Peking Union Medical College Hospital

FUQUAN ZHANG (✉ zhangfuquan3@126.com)

PUMCH: Peking Union Medical College Hospital

Research

Keywords: Rhabdomyosarcoma, second malignant neoplasm, radiation therapy, chemotherapy.

Posted Date: June 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-639505/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objective

Rhabdomyosarcoma (RMS) is a rare malignant tumor. The main treatment modality is comprehensive with chemotherapy, radiation therapy, and surgery. With the advancement in recent decades, patient survival has been prolonged, and long-term complications are attracting increasing attention among both physicians and patients. This study aimed to present the survival of patients with RMS and analyze the risk factors for the development of a second malignant neoplasm (SMN).

Methods

The Surveillance, Epidemiology, and End Results (SEER) Program 18 registry database from 1973 to 2015 of the National Cancer Institute of the United States was used for the survival analyses, and the SEER 9 for the SMN analysis.

Results

The 5-, 10-, and 20-year overall survival rates of the patients with RMS were 45%, 43%, and 33%, respectively. The risk of SMN was significantly higher in patients with RMS compared to the general population (SIR = 1.95, 95% CI: 1.44–2.57, $p < 0.001$). The risk of developing SMN was increased in multiple locations, including the bones and joint (SIR = 35.25) and soft tissues including the heart (SIR = 22.5), breasts (SIR = 2.10), male genital organs (SIR = 118.14), urinary system (SIR = 2.36), brain (SIR = 9.21), and brain and other nervous system organs (SIR = 8.59). The multivariate analysis indicated that RMS in the limbs and earlier diagnosis time were independent risk factors for the development of SMN. Patients with head and neck (OR = 0.546, 95% CI: 0.313–0.952, $p = 0.033$) and trunk RMS (OR = 0.322, 95% CI: 0.184–0.564, $p < 0.001$) and a later diagnosis time were less likely to develop SMN (OR = 0.496, 95% CI: 0.421–0.585, $p < 0.001$).

Conclusion

This study describes the risk factors associated with the development of SMN in patients with RMS, which is helpful for the personalized screening of high-risk patients with RMS.

1. Introduction

Rhabdomyosarcoma (RMS), although rare, is a common childhood cancer and is the most common soft tissue sarcoma among children. The overall incidence among those aged < 20 years is 4.5 cases per million people^[1]. In the United States, approximately 350 new cases are recorded each year. According to

the data of the Surveillance Epidemiology and End Results (SEER) program, the incidence of RMS varies depending on age and histopathology [2].

Significant advances have been made over the past four decades in the treatment of RMS. The majority of children with the early-stage disease will essentially be cured. Because of the collaborative effort dedicated to clinical trials, the current 3-year overall survival rate of patients with high-risk RMS is approximately 80% and treatment failure is largely attributed to local relapse. Therefore, increasing the local control rate remains challenging in the treatment of RMS [1].

Increasing the dosage of cytotoxic drugs may lead to prognostic improvement but is accompanied by increased side effects, including long-term ones such as Second malignant neoplasm (SMNs), which have particularly drawn the attention of both physicians and RMS survivors [1]. There is a need to assess the risk of SMN in patients with RMS. However, it is difficult to do so in a single-center cohort with a long-term follow-up due to the limited incidence. Therefore, this study aimed to assess the risk of SMN development in patients with RMS through this population-based study using clinical data from the SEER database.

2. Material And Methods

Data of patients with RMS, including treatment information between 1973 and 2015 was collected from the SEER 18 database using the SEER*Stat software (version 8.3.6). The inclusion criteria were patients with all types of RMS (pleomorphic, mixed-type, embryonal, spindle cell, alveolar, with ganglionic differentiation, and Not otherwise specified(NOS)) according to the following codes: ICD-O-3Hist/behavior="8900/3: rhabdomyosarcoma, NOS ", "8901/3:pleomorphic rhabdomyosarcoma, adult-type", "8902/3:mixed type rhabdomyosarcoma", "8910/3:Embryonal rhabdomyosarcoma,NOS", "8912/3:spindle cell rhabdomyosarcoma", "8920/3:alveolar rhabdomyosarcoma", "8921/3:rhabdomyosarcoma with ganglionic differentiation". Moreover, patients with clear pathologic types and classifications, as well as those with complete follow-up information were included. The exclusion criteria were cases diagnosed by autopsy and those with incomplete follow-up information.

The survival time used in this study was Overall survival(OS). SMNs were defined as other malignant tumors that were present at least 2 months after the diagnosis of RMS. Information at diagnosis, including age, sex, race, pathologic type and differentiation level, year of diagnosis, major location, radiation therapy, chemotherapy, survival time, and survival condition was collected. Authorization was obtained from the SEER website to collect the data from the database and no additional ethical approval was required.

2.1 Statistical analysis

Categorical data was presented as frequencies and percentages. The Kaplan-Meier method was used for survival analysis. Univariate analyses were performed using the log-rank test, and multivariate using the

Cox regression model. Independent risk factors for the development of SMNs were determined using logistic regression analysis. The Standardized incidence ratio(SIR)was calculated using SEER*Stat and was analyzed and presented with 95% Confidence interval[CI]. All statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL). A *p-value* of ≤ 0.05 was used to indicate statistical significance.

3. Results

3.1 Demographic and clinical characteristics of study patients

A total of 4,787 pathologically diagnosed patients with RMS were included in this study. The demographic and clinical characteristics of all patients with RMS and those with SMNs are shown in Table 1. The trunk was the most common primary site (50.6%, n = 2,420), followed by the head and neck (36.1%, n = 1,728) and the limbs (12.2%, n = 586). In terms of pathologic types, embryonal was the most common (41.0%, n = 1,964), followed by NOS (36.5%, n = 1,746) and alveolar type (22.5%, n = 1,077). The risk of primary SMNs was 34.1% in the head and neck and 32.9% in both the limbs and the pelvis. Patients with SMN were most likely to have NOS (54.7%) and embryonal (36.0%) as opposed to alveolar type.

Table 1
Demographic and clinical characteristics of patients with rhabdomyosarcoma

		Cohort (%)	
Variables	Categories	All RMS patients (n = 4,787)	SMN (n = 86)
Sex	Male	2,678 (55.9)	48 (55.8)
	Female	2,109 (44.1)	38 (44.2)
Age at RMS diagnosis (years)	0–19	2,646 (55.3)	39 (45.3)
	20–39	639 (13.3)	11 (12.8)
	40–59	568 (11.9)	15 (17.4)
	≥ 60	934 (19.5)	21 (24.4)
Year of diagnosis	1973–1979	435 (9.1)	30 (34.9)
	1980–1989	479 (10.0)	17 (19.8)
	1990–1999	686 (14.3)	22 (25.6)
	2000–2009	1,926 (40.2)	12 (14.0)
	2010–2015	1,261 (26.3)	5 (5.8)
Primary site	Head and Neck	1,728 (36.1)	29 (34.1)
	Trunk	2,420 (50.6)	28 (32.9)
	Limbs	586 (12.2)	28 (32.9)
Pathologic type	NOS	1,746 (36.5)	47 (54.7)
	Embryonal	1,964 (41.0)	31 (36.0)
	Alveolar	1,077 (22.5)	8 (9.3)
Race	White	3,694 (77.2)	68 (78.2)
	Black	715 (14.9)	11 (12.6)
	Other	353 (7.4)	8 (9.2)
Radiation therapy	Yes	2,556 (53.4)	48 (55.8)
	No/Unknown	2,231 (46.6)	38 (44.2)
Chemotherapy	Yes	3,633 (75.9)	54 (62.8)

Abbreviations: SEER 18, Surveillance, Epidemiology, and End Results Program 18; RMS, rhabdomyosarcoma; SMN, second malignant neoplasm; NOS, not otherwise specified.

Cohort (%)		
No/Unknown	1,154 (24.1)	32 (37.2)
Abbreviations: SEER 18, Surveillance, Epidemiology, and End Results Program 18; RMS, rhabdomyosarcoma; SMN, second malignant neoplasm; NOS, not otherwise specified.		

3.2 OS of patients with RMS

The 5-, 10-, and 20-year OS rates for the entire RMS cohort were 45%, 43%, and 33%, respectively. The survival data of the different variables are presented in Fig. 1. Univariate analysis of the independent risk factors for mortality was initially conducted, and those with $p < 0.1$ were included in the multivariate analysis. The statistically significant predictors of survival were sex ($p = 0.007$), age ($p < 0.001$) and year of diagnosis ($p < 0.001$), primary site ($p < 0.001$), RMS type ($p < 0.001$), radiation therapy ($p < 0.001$), chemotherapy ($p < 0.001$), and degree of differentiation ($p < 0.001$), and SMN ($p = 0.013$). After adjusting for other factors, the multivariate analysis indicated that SMN (Hazard Ratio(HR)= 2.43, 95% CI: 1.369–4.312, $p = 0.002$) was independently associated with decreased survival.

3.3 Risk of SMN in patients with RMS

Overall, 86 patients developed SMNs with an SIR of 1.95 (95% CI: 1.44–2.57, $p < 0.001$) and the SIR of solid tumors was 1.95 (95% CI: 1.54–2.44 and $p < 0.05$). Bones and joints (SIR = 35.25, 95% CI: 14.17–72.63, $p < 0.001$), soft tissues including the heart (SIR = 22.5, 95% CI: 10.29–42.7, $p < 0.05$), breasts (SIR = 2.10, 95% CI: 1.05–3.75, $p < 0.05$), male genital organs (SIR = 118.14, 95% CI: 14.31–426.78, $p < 0.05$), the urinary system (SIR = 2.36, 95% CI: 1.02–4.66, $p < 0.05$), the brain (SIR = 9.21, 95% CI: 3.98–18.16, $p < 0.05$), and the brain and other nervous system organs (SIR = 8.59, 95% CI: 3.71–16.93, $p < 0.05$) all had an increased risk of SMN. The most common hematological SMNs were non-lymphocytic leukemia (SIR = 5.24, 95% CI: 1.43–13.42, $p < 0.05$), and myeloid and monocytic leukemia (SIR = 5.90, 95% CI: 1.61–15.1, $p < 0.05$).

3.4 Analysis of SMN risk factors

The univariate analysis showed that the year of diagnosis ($p < 0.001$), primary site ($p < 0.001$), and chemotherapy ($p = 0.006$) were associated with SMN, whereas radiation therapy was not ($p = 0.58$). The multivariate analysis indicated that RMS in the limbs and earlier diagnosis time were independent risk factors for the development of SMN. Patients with head and neck (OR = 0.546, 95% CI: 0.313–0.952, $p = 0.033$), trunk RMS (OR = 0.322, 95% CI: 0.184–0.564, $p < 0.001$), and a later diagnosis time were less likely to develop SMN (OR = 0.496, 95% CI: 0.421–0.585, $p < 0.001$).

4. Discussion

In this study, we found that the development of SMNs, primary site, pathologic type, age, radiation therapy, and the degree of differentiation were independent risk factors affecting the prognosis of patients with RMS. Compared to the general population, patients with RMS had a significantly increased

risk of developing SMNs, and risk factors found to be associated with their development included primary site and the time of diagnosis.

In recent decades, survival has significantly improved among patients with RMS. This has been mainly due to the multidisciplinary treatment approach, which includes optimal cytotoxic drug combinations, and advances in radiation therapy. The greater number of RMS survivors leads to an increased risk of late complications, such as SMNs. The results of our study suggested that the year of diagnosis was a risk factor affecting the incidence of SMN, and the incidence of SMN was increased with the prolongation of survival time. Heyn et al. found that the incidence rate of SMN increased significantly with increased time since diagnosis^[3]. Studies conducted on childhood tumors have also reached similar conclusions of the prolonged time of several years, and sometimes even decades of follow-up to observe the occurrence of SMN. These studies showed that the 10-year cumulative incidence rate of SMN in patients with childhood tumors was approximately 1.2–1.7%, the 20-year cumulative incidence rate was 3.3–4.3%, and the 25-year cumulative incidence rate was 3.7–12.1%^[3–10]. The above studies indicate that the incidence of SMN will gradually increase as the survival period of childhood tumor survivors increases. We believe that there are two possible reasons. One is that the SMN (such as leukemia, radiation carcinogenesis, etc.) caused by therapeutic factors usually takes years to decades to manifest. The other is that survivors are getting older, and the incidence of SMN is increased due to non-therapeutic factors represented by heredity. The above two factors work together to cause the diagnosis time to become a factor that affects the occurrence of SMN. Moreover, we found that patients with RMS of the limbs were more likely to develop SMNs. There have not been relevant research studies that verify this conclusion, and the effects of different primary sites of RMS on SMN have not been explored. Because RMS of the extremities is correlated with a higher rate of treatment failure, we suppose that the higher risk of SMN of the extremities could be related to the cumulative dose of cytotoxic drugs and the intensity of radiation therapy.

Whether radiotherapy and chemotherapy will increase the incidence of SMN is still controversial. The results of our study did not show that radiation therapy and chemotherapy were independent risk factors for the development of SMNs, similar to other studies that found that the SIR of SMN for patients who received radiation therapy was not significantly different to that of patients who did not^[5]. In addition, for most types of radiation therapy, the SMN sites were located outside the field of irradiation. Therefore, it was speculated that radiation therapy did not directly lead to an increase in the incidence of SMN^[5]. But the mainstream view is that radiotherapy is a risk factor for SMN^[11–14]. They found that the radiation therapy doses may be correlated with the risk of SMN. Moreover, radiation is carcinogenic and the mechanism is unclear. It is difficult to exclude the influence of it on SMN. Whether chemotherapy affects independent risk factors for SMN is also controversial, and mainstream views also believe that chemotherapy can cause SMN. Cytotoxic drugs, such as cyclophosphamide and etoposide, have been reported to significantly increase the risk of secondary malignant leukemia in patients with RMS^[15]. The incidence of SMNs was even lower in patients who used actinomycin for treatment, suggesting that this drug may have some protective effects^[15]. Our results showed that chemotherapy was a risk factor for

SMN in a univariate analysis ($p = 0.006$), but it was not statistically significant in multivariate analysis ($p > 0.05$).

Consistent with Scaradavou et al. [5], our study found that the pathologic type was not a risk factor of SMN. One possible reason is that patients with embryonal RMS are prone to cancer syndromes, such as Li-Fraumeni, which is a correlation that many studies have confirmed [6,8–10]. Li-Fraumeni syndrome is a chromosomal dominant disease that has been closely associated with RMS and with mutations in the tumor suppressor *TP53* gene. Common SMNs in patients with RMS include breast cancer, osteosarcoma, brain tumors, leukemia, and adrenocortical malignancy, which are very similar to the clinical characteristics of Li-Fraumeni syndrome. Other studies have also reached similar conclusions [3, 5, 7]. Since Li-Fraumeni syndrome has a clear family history, the probability that high-risk family members will develop invasive malignant tumors before the age of 30 years is as high as 50%. Therefore, an understanding of the patients' family history is important in order to establish which ones require more frequent and detailed screenings and helps determine the etiology of SMN. Time since diagnosis was found to be another risk factor for the development of SMN. Some studies have suggested that the main factors associated with the development of SMN were internal, such as cancer susceptibility (including a family history of Li-Fraumeni syndrome) rather than external such as radiation therapy and chemotherapy. Another important issue is whether the incidence of SMNs affects both solid tumors and hematological malignancies. It has been believed that the increase in the incidence of SMNs is significant in both types, yet the findings of our study indicate that the SIR for SMNs in all solid tumors was 1.95 (95% CI: 1.54–2.44, $p < 0.05$), but it was not statistically significant in hematological malignancies. In addition, there was an increased risk of some specific types of hematological malignancies, such as non-lymphocytic leukemia. Heyn et al. showed that the rates of solid SMNs (represented by osteosarcomas) and hematological malignancies (represented by acute non-lymphocytic leukemia) were significantly increased in RMS patients [3], whereas Archer et al. found that the increased risk of SMNs was only significant in solid tumors [16]. This could be related to the sample size of the different studies, duration of the follow-up as well as the evolvement of systemic treatment.

This study has several limitations. Firstly, there are biases inherent to the retrospective design. Moreover, detailed treatment information, such as the exposure range of radiation therapy target areas, as well as the chemotherapy regimen and dose could not be acquired from the SEER database. Lastly, information on the tumor size, in addition to the sequence of radiation therapy and chemotherapy was not available.

5. Conclusion

This study is a population cohort-based study that objectively describes the occurrence of SMN and its risk factors in patients with rhabdomyosarcoma. We found that the pathologic type and time since diagnosis were independent risk factors for the development of SMNs in patients with RMS. The results of this study can help with individualized screening approaches and follow-up timelines of RMS

survivors. In the future, we will focus on the survival of RMS cohort and the occurrence of SMN through longer follow-up.

Abbreviations

RMS
Rhabdomyosarcoma
SEER
Surveillance Epidemiology and End Results
SMN
Second malignant neoplasm
SIR
Standardized incidence ratio
CI
Confidence interval
HR
Hazard Ratio
SIR
Standardized incidence ratio

Declarations

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval and Consent to participate

Authorization was obtained from the SEER website to collect the data from the database and no additional ethical approval was required.

Consent for publication

Informed consent for publication was collected from all the patients.

Availability of supporting data

The data used and analysed during the current study are available from the SEER program.

Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Funding

This work was supported by the National Key Research and Development Plan, the Ministry of Science and Technology of the People's Republic of China [grant number 2016YFC0105207].

Authors' contributions

Author statement: HNZ and FQZ conceptualized and designed the study. ZKL and HG reviewed the literature. JS and JBM collected data and performed statistical analysis. WHW and ZM drafted the manuscript. All authors revised the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

Thanks for Shiyu Jiang and Xiaoyin Bai for their encouragement.

References

1. A.M.Linabery, J.A.Ross, Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975–1999, *Cancer*. 113(2008)2575–2596. <https://doi.org/10.1002/cncr.23866>.
2. E.A.Perez, N.Kassira, M.C. Cheung, L.G. Koniaris, H.L. Neville, J.E. Sola, Rhabdomyosarcoma in children: a SEER population based study, *J. Surg. Res.* 170(2011)243–251. <https://doi.org/10.1016/j.jss.2011.03.001>.
3. R.Heyn, V.Haeberlen, W.A. Newton, A.H. Ragab, R.B. Raney, M. Tefft, M. Wharam, L.G. Ensign, H.M. Maurer, Second malignant neoplasms in children treated for rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee, *J. Clin. Oncol.* 11(1993)262–270. <https://doi.org/10.1200/JCO.1993.11.2.262>.
4. Mike V, Meadows AT, D'Angio GJ. Incidence of second malignant neoplasms in children: results of an international study, *Lancet*. 2 (1982) 1326–31. [https://doi.org/10.1016/s0140-6736\(82\)91524-0](https://doi.org/10.1016/s0140-6736(82)91524-0).
5. A. Scaradavou, G. Heller, C.A. Sklar, L. Ren, F. Ghavimi, Second malignant neoplasms in long-term survivors of childhood rhabdomyosarcoma, *Cancer*. 76 (1995) 1860–1867. [https://doi.org/10.1002/1097-0142\(19951115\)76:10<1860::aid-cncr2820761027>3.0.co;2-i](https://doi.org/10.1002/1097-0142(19951115)76:10<1860::aid-cncr2820761027>3.0.co;2-i).
6. Yang P, Grufferman S, Khoury MJ, Schwartz AG, Kowalski J, Ruymann FB, Maurer HM. Association of childhood rhabdomyosarcoma with neurofibromatosis type I and birth defects, *Genet Epidemiol* 12 (1995) 467–74. <https://doi.org/10.1002/gepi.1370120504>.
7. Rich DC, Corpron CA, Smith MB, Black CT, Lally KP, Andrassy RJ. Second malignant neoplasms in children after treatment of soft tissue sarcoma. *J Pediatr Surg*. 1997;32:369–72. [https://doi.org/10.1016/s0022-3468\(97\)90213-x](https://doi.org/10.1016/s0022-3468(97)90213-x).
8. Estep AL, Tidyman WE, Teitell MA, Cotter PD, Rauen KA. HRAS mutations in Costello syndrome: detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. *Am J Med Genet A*. 2006;140:8–16. <https://doi.org/10.1002/ajmg.a.31078>.

9. Kratz CP, Rapisuwon S, Reed H, Hasle H, Rosenberg PS. Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes, *Am. J Med Genet C Semin Med Genet.* 2011;157C:83–9. <https://doi.org/10.1002/ajmg.c.30300>.
10. S. Ognjanovic, M. Olivier, T.L. Bergemann, P. Hainaut, Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database, *Cancer.* 118 (2012) 1387–1396. <https://doi.org/10.1002/cncr.26390>.
11. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RD, Marsden B, Nesbit M, Newton W, Oberlin O, Sallan SG. Second malignant neoplasms in children: an update from the Late Effects Study Group. *J Clin Oncol.* 1985;3:532–8. <https://doi.org/10.1200/JCO.1985.3.4.532>.
12. Hawkins MM, Draper GJ, Kingston JE. Incidence of second primary tumours among childhood cancer survivors. *Br J Cancer.* 1987;56:339–47. <https://doi.org/10.1038/bjc.1987.200>.
13. de Vathaire F, François P, Hill C, Schweisguth O, Rodary C, Sarrazin D, Oberlin O, Beurtheret C, Dutreix A, Flamant R. Role of radiation therapy and chemotherapy in the risk of second malignant neoplasms after cancer in childhood. *Br J Cancer.* 1989;59:792–6. <https://doi.org/10.1038/bjc.1989.165>.
14. Pui CH, Hancock ML, Raimondi SC, Head DR, Thompson E, Wilimas J, Kun LE, Bowman LC, Crist WM, Pratt CB. Myeloid neoplasia in children treated for solid tumours. *Lancet.* 1990;336:417–21. [https://doi.org/10.1016/0140-6736\(90\)91956-b](https://doi.org/10.1016/0140-6736(90)91956-b).
15. R. Heyn, F. Khan, L.G. Ensign, S.S. Donaldson, F. Ruymann, M.A. Smith, T. Vietti, H.M. Maurer, Acute myeloid leukemia in patients treated for rhabdomyosarcoma with cyclophosphamide and low-dose etoposide on Intergroup Rhabdomyosarcoma Study III: an interim report, *Med. Pediatr. Oncol.* 23 (1994) 99–106. <https://doi.org/10.1002/mpo.2950230206>.
16. Archer NM, Amorim RP, Naves R, Hettmer S, Diller LR, Ribeiro KB. C. Rodriguez-Galindo. An increased risk of second malignant neoplasms after rhabdomyosarcoma: Population-based evidence for a cancer predisposition syndrome? *Pediatr. Blood Cancer.* 2016;63:196–201. <https://doi.org/10.1002/pbc.25678>.

Figures

Figure 1

Figure 1

Kaplan-Meier curves of overall survival stratified by age at diagnosis (A); year of diagnosis (B); pathologic type (C); radiation therapy (D); primary site (E); and SMN (F). Abbreviations: H&N, head, and neck; SMN, second malignant neoplasm; NOS, not otherwise specified.