Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Retrospective analysis of rhabdomyosarcoma (RMS) in children in a single center

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Keywords
Children; prognosis; rhabdomyosarcoma; therapeutic efficacy.

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Received: 26 June 2018;
Accepted: 1 July 2018.

doi: 10.1111/1759-7714.12823

Thoracic Cancer **9** (2018) 1180–1184

Abstract

Background: This study was conducted to explore the influence of clinical features of rhabdomyosarcoma (RMS) and a refined therapeutic protocol on the therapeutic efficacy and prognosis in children in the past five years.

Methods: Forty children diagnosed with RMS were retrospectively studied, using a version of the therapeutic protocol refined by Shanghai Children's Medical Center (version 2009.9.1). The patients' demographic characteristics, clinical manifestations, pathological features, therapeutic efficacy, and prognosis were analyzed.

Results: Of the 40 children, 17 abandoned treatment. Of the remaining 23 cases, two children were rated as low risk, 12 as medium risk, and nine as high risk, and all received treatment. Patients in the low and medium-risk groups had better prognosis than those in the high-risk group, and treated patients had higher survival rates and longer survival than untreated patients.

Conclusion: Children with RMS should be treated positively. Combined treatment shows better therapeutic efficacy and prognosis. The refined therapeutic protocol seems more effective than the standard treatment, with a significant impact on long-term RMS prognosis.

Introduction

Rhabdomyosarcoma (RMS) is the most common malignant soft-tissue sarcoma in children, originating from immature mesenchymal cells that will differentiate into striated muscle, belonging to the skeletal muscle lineage.[1] The disease tends to appear insidiously and occurs in children aged under 15 years. The sarcoma often exhibits very early metastasization, followed by a high recurrence rate and poor prognosis.

Between February 2010 and December 2015, 40 children diagnosed with RMS were admitted to the Qilu Hospital of Shandong University. We retrospectively analyzed their demographic characteristics, clinical manifestations, pathological features, therapeutic efficacy, and prognosis using an approach that sheds new light on this refractory disease.

Methods

Patients

Forty children with RMS admitted to the Qilu Hospital of Shandong University between February 2010 and December 2015 were enrolled in this study. All demographic characteristics and clinical manifestations, including primary onset site, lymphatic or distal metastasis, pathological features, therapeutic efficacy, and prognosis were reviewed, and all children were followed up after discharge. Of the 40 children, 22 were boys and 18 were girls (ratio 1.2:1 boys to girls). They ranged in age from three to 204 months, with a median age of 61.5 months (37 months for boys and 96 months for girls) and an average age of 88.05 months (74.13 months for boys and 105.06 months for girls) (Table 1).

Table 1 Age and gender information of children with RMS

Age (months)	Total	Boys	Girls
≤ 12	5 (12.5%)	3 (7.5%)	2 (5%)
13–36	9 (22.5%)	7 (17.5%)	2 (5%)
37–60	8 (20%)	3 (7.5%)	5 (12.5%)
61–120	7 (17.5%)	4 (10%)	3 (7.5)
121–204	13 (32.5%)	5 (12.5%)	8 (20%)
Average	*88.05*	*74.13*	*105.06*
Total	40 (100%)	22 (55%)	18 (45%)

RMS, rhabdomyosarcoma.

Diagnosis and staging

All children received a definite pathological examination result and were staged according to Union for International Cancer Control (UICC) Tumor Node Metastasis (TNM) staging defined by the International Association of Pediatric Oncology. The children were categorized into low-risk (stage I RMS, except outer acinar RMS); medium-risk (stage I RMS acinar, stage II RMS, and stage III RMS, except outer acinar RMS); and high-risk (stage III RMS acinar, stage IV RMS) groups. Patients were grouped by TNM staging accordingly.

Treatment

Seventeen patients abandoned treatment after diagnosis. The remaining 23 children underwent the routine treatment protocol for RMS refined by Shanghai Children's Medical Center (version 2009.9.1). Most patients first underwent tumorectomy of the primary onset site. Patients in the low-risk group received circulatory chemotherapy under the vincristine, cyclophosphamide, prednisone (VCP) + ifosfamide, etoposide, vincristine (IEV) regimen for 15 weeks. The medium and high-risk groups were treated for 55 weeks, comprising: adriamycin, vincristine, cyclophosphamide, prednisone (AVCP) + IEV chemotherapy for the first 15 weeks; radiotherapy combined with chemotherapy for 18 weeks; followed by VCP + dactinomycin, etoposide, vincristine (DEV) regimen chemotherapy until the 55th week. Reoperation was performed during the second period of treatment.

Follow-up

Patients were followed up for at least two years, including telephone calls and visits, and inpatient and outpatient recording to evaluate therapeutic efficacy according to solid tumor evaluation criteria. The follow-up sessions recorded patients' complete remission, partial remission, non-remission, or disease progression, as well as the duration of disease-free and long-term survival of deceased children.

Results

Clinical information

Of the 40 children, two cases were at stage I, nine at stage II, six at stage III, and 23 at stage IV. Two cases were in the low-risk group, 15 in the medium-risk, and 23 in the high-risk group (Table 2). The primary occurrence sites were intracranial in two cases, head and neck in 10 cases, mediastinum in three cases, abdominal cavity in six cases, urinary and reproductive tract in 10 cases, and limbs in nine cases (Table 3). The pathological results showed that 34 cases were embryonal RMS and six cases were acinar RMS in which the sarcoma was found with distal metastasis when the diagnosis was made.

Therapeutic efficacy

Of the 40 patients, 17 were not treated and died within a short time; three of these patients were medium-risk with maximum expected survival of 13 months, and 14 were high-risk with maximum expected survival of seven months.

Of the remaining 23 cases administered treatment, two patients were low-risk and underwent tumorectomy only. No tumor recurrence was found during follow-up (maximum follow-up 42 months).

In the medium-risk group consisting of 12 patients, only five patients underwent tumorectomy. To date their follow-up sessions (the longest being 30 months) have revealed no recurrence in three cases. Two patients relapsed within eight months of surgery, one of whom received chemotherapy after the second surgery with no observed tumor recurrence in 31 months of follow-up; the other patient underwent a third surgery because of relapse within six months of the second surgery, with no observed tumor recurrence in the following 10 months of follow-up. Another six medium-risk patients were administered chemotherapy after complete surgical resection. One died of recurrence 36 months after tumorectomy, while the other five cases had not relapsed at the 52-month follow-up

Table 2 Stages and risk groups of children with RMS

Stage	Boys	Girls	Total
I	0 (0%)	2 (5%)	2 (5%)
II	8 (20%)	1 (2.5%)	9 (22.5%)
III	4 (10%)	2 (5%)	6 (15%)
IV	10 (20%)	13 (32.5%)	23 (57.5%)
Group	Boys	Girls	Total
Low-risk	0 (0%)	2 (5%)	2 (5%)
Medium-risk	12 (30%)	3 (7.5%)	15 (37.5%)
High-risk	10 (25%)	13 (32.5)	23 (57.5)

RMS, rhabdomyosarcoma.

Table 3 Primary tumor occurrence sites in children with RMS

Gender	Total	Intracranial	Head and neck	Mediastinum	Urinary/reproductive system	Limb	Abdominal cavity
Boys	22 (55%)	1 (2.5%)	5 (12.5%)	2 (5%)	7 (17.5%)	4 (10%)	3 (7.5%)
Girls	18 (45%)	1 (2.5%)	5 (12.5%)	1 (2.5%)	3 (7.5%)	5 (12.5%)	3 (7.5%)
Total	40 (100%)	2 (5%)	10 (25%)	3 (7.5%)	10 (25%)	9 (22.5%)	6 (15%)

RMS, rhabdomyosarcoma.

point. One of the 12 medium-risk patients only had chemotherapy without tumorectomy and was partially relieved at the 36-month follow-up point. Except for the patient that died 36 months after diagnosis, all other patients survived during the follow-up period (maximum 52 months).

Of the nine patients in the high-risk group, three cases were only treated by surgery, but resection was incomplete and all died within six months of the tumorectomy. Two patients underwent complete resection combined with chemotherapy and achieved complete remission at the 16-month follow-up point. Three patients were treated with chemotherapy after incomplete resection: two died of disease progression, with maximum survival of 30 months; and one has been followed-up for seven months and has achieved partial remission. One patient who received radiotherapy combined with chemotherapy achieved partial remission eight months after onset (Fig 1).

Adverse reactions

Of the 23 children admitted to the hospital who received therapy, none suffered any abnormality in perception or hearing, 13 had obvious hair loss, and all gained weight consistent with the weight growth curve of healthy peers. During the chemotherapy process, the children showed various degrees of myelosuppression. Two patients suffered from severe infection but recovered after symptomatic treatment, and no death from myelosuppression or infection occurred following chemotherapy. No abnormalities were observed in the patients' cardiac enzymes, biochemistry, electrocardiogram, or echocardiography. Four children experienced liver dysfunction during chemotherapy, but no irreversible damage was found after symptomatic treatment.

Discussion

Rhabdomyosarcoma, which occurs mainly in children aged between one and five years, and particularly in boys, is the most common malignant soft-tissue sarcoma in children. It originates from striated muscle cells, or immature intercalated cells inclined to differentiate into striated muscle, belonging to the skeletal muscle lineage. According to its pathological features, RMS is categorized into embryonal RMS (ERMS), alveolar RMS (ARMS), pleomorphic RMS (PRMS), and fusiform/sclerosing RMS according to the Intergroup Rhabdomyosarcoma Study group.[2] Among these, ERMS is the most common type in children, accounting for 65% to 80% of all children with RMS.[3] ERMS may arise in any part of a child's body and is closely correlated with prognosis.[4] Based on clinical analysis of patients with RMS in Beijing over the past 10 years, previous studies have found that the genitourinary system is the most common onset site for RMS, followed by the head and neck, and the retroperitoneal space and limbs; no cases have been located in the mediastinum.[5,6] However, in our study, the primary onset sites in nine patients were the limbs and in three patients the mediastinum, accounting for 22.5% and 7.5%, respectively, indicating that RMS may occur in any part of the body with striated muscle cell-like tissues. The average age of the girls in this study was

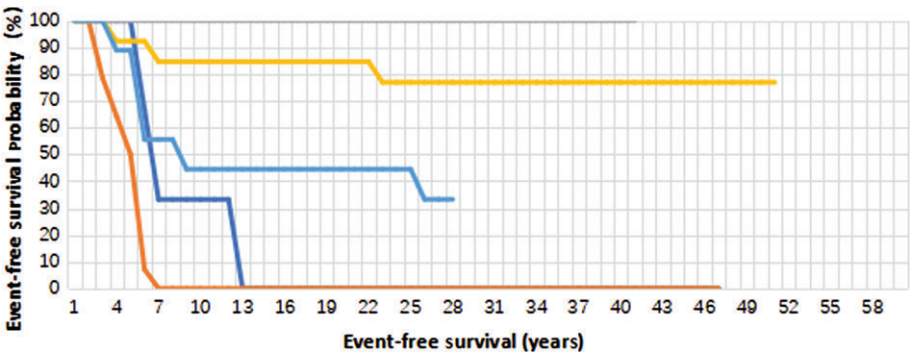

Figure 1 Survival curve for children with rhabdomyosarcoma. (——) Medium-risk (untreated), (——) High-risk (untreated), (——) Low-risk, (——) Medium-risk, and (——) High-risk.

markedly older than that of the boys, and boys appeared to be more likely to fall into the low-risk group.

Rhabdomyosarcoma often attacks very young children and manifests as local painless lumps and lump-related oppression. Tumor metastasis has often already occurred at diagnosis, therefore the overall prognosis under the previous chemotherapeutic protocol was poor. Although tumorectomy combined with chemotherapy is the preferred choice, many patients abandon treatment because of the poor prognosis. Children in the low-risk group in this study all received surgery and showed good prognoses, suggesting that surgical treatment alone at an early stage of RMS may have a satisfactory effect.

Most medium-risk patients in this study had relatively good prognoses. Patients who underwent tumorectomy followed by chemotherapy showed a significantly higher survival rate than those who only underwent surgery, suggesting that surgical resection plus chemotherapy in the medium-risk group has better therapeutic efficacy and is more effective than indicated in previous reports.[7]

In the high-risk group, in addition to tumorectomy, chemotherapy is an important subsequent treatment that can markedly improve survival rates. One child in the high-risk group who received radiotherapy and chemotherapy after surgery showed a good therapeutic effect, indicating that radiotherapy may partially replace surgery; however, the role of radiotherapy in the prevention of tumor recurrence remains controversial.[8,9] More clinical samples are needed to verify the effect.

Previous studies have shown that the prognosis of this disease has a relatively obvious correlation with the primary onset location, size, pathological type of tumor, occurrence of lymphatic or distal metastasis, age, and whether the tumor is completely or incompletely resected.[10–13] A good prognosis is generally expected in patients with tumors in the head, neck, or genitourinary area, but a poor prognosis in patients with tumors in the limbs, trunk, or retroperitoneal area. Older children show poorer prognosis than younger ones, which is consistent with our observations. In our study, RMS in the mediastinum resulted in poorer outcomes, whether the child was treated or not. However, a larger patient sample is required to draw a credible conclusion.

Tolerance and adverse reactions to drugs also have some effect on prognosis. The incidence of tumor recurrence increases and the long-term survival rate decreases in children whose chemotherapy dose must be reduced as a result of various intolerances.[14]

Rhabdomyosarcoma is the most common malignant soft-tissue sarcoma occurring in children, and the effects of treatment and prognosis relate to many factors. RMS without metastasization in the early stage has a significantly better prognosis than when lymphatic or distal metastasis occurs. A tumorectomy combined with chemotherapy may have a better therapeutic effect, particularly using treatment protocol refined by the Shanghai Children's Medical Center. Therefore, early detection and standard treatment are key to improving survival rates. In the high-risk group of children, although higher survival rates were observed than for those in the untreated high-risk group, further research of radiotherapy and other new treatment approaches, such as biotherapy, is required.

In conclusion, children with RMS should be treated positively. Combined treatment shows better therapeutic efficacy and prognosis. Our therapeutic protocol seems more effective as a standard treatment and has a significant effect on long-term RMS prognosis.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (30801258), the China Postdoctoral Science Foundation (2013T6675,2012M511 036), the Natural Science Foundation of Shandong Province (ZR2014HM093, ZR2014HM060), and the Star of Jinan Youth Science and Technology Project (2013021).

Disclosure

No authors report any conflict of interest.

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