

# Case Analysis of 14 Children with Malignant Rhabdoid Tumor of the Kidney

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**Objective:** This study aims to summarize the clinical features and prognoses of the malignant rhabdoid tumor of the kidney (MRTK) in children. It further aims to analyze the high-risk factors affecting MRTK prognosis.

**Methods:** Clinical data from 14 children with MRTK treated in Paediatrics of Beijing Tongren Hospital from January 2010 to December 2019, along with the high-risk factors affecting prognosis, were retrospectively analyzed.

**Results:** There were 14 children with MRTK included in the study, with a median onset age of 13 (3–46) months. Thirteen patients had distant metastases, the most common site for metastases being inside the lung. A comprehensive treatment protocol combined with chemotherapy was mainly applied during the surgery. A surgical resection of primary tumors was performed on 13 (13/14) patients, and all 14 children received chemotherapy with ifosfamide + carboplatin + etoposide, ifosfamide + etoposide, and vincristine + pirarubicin + cyclophosphamide regimens, alternately. Three patients received radiotherapy and two received oral targeted drugs after partial response. The median follow-up was after 16.5 months (3–53 months) and the four-year overall survival (OS) was 41.8%. In children aged  $\leq 24$  months and children aged  $> 24$  months, the two-year OS was 67.2% and 100% ( $\chi^2 = 108.998$ ,  $P < 0.05$ ), respectively. In children with Ki 67  $> 70\%$  and children with Ki 67  $< 70\%$ , the two-year OS was 52.6% and 86.9% ( $\chi^2 = 8.544$ ,  $P = 0.003$ ), respectively. In children with distant metastases and children without distant metastasis, the two-year OS was 70% and 100% ( $\chi^2 = 14.239$ ,  $P < 0.05$ ), respectively.

**Conclusion:** The most common MRTK distant metastasis site is the lung. Risk factors for poor MRTK prognoses include an age of  $< 24$  months, Ki 67  $> 70\%$ , and distant metastases.

**Keywords:** children, malignant rhabdoid tumor of the kidney, MRTK, treatment, prognosis

## Introduction

The malignant rhabdoid tumor (MRT) is a class of highly invasive tumors<sup>1</sup> mainly occurring in children. It is relatively rare in clinical practice. Most commonly, the MRT occurs in kidneys and accounts for 1.5%–4% of renal malignancies.<sup>2,3</sup> It was formerly considered a<sup>4</sup> special subtype of the renal Wilms tumor; however, in 1981, Haas et al<sup>5</sup> clarified that the tumor is a type of malignant renal tumor occurring in children and is completely independent of nephroblastoma. It was given the name MRTK. Due to the new understanding of the disease, other MRTs<sup>6–9</sup> in children with different primary sites, such as the central nervous system, liver, abdomen, retroperitoneum, or other soft tissues, have been reported. According to its different anatomical sites, the tumor can be divided into MRTK, atypical teratoid/rhabdoid tumor (AT/RT), extra-renal noncerebral rhabdoid tumor.<sup>10</sup> The MRT is a highly

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invasive tumor commonly occurring in children. It was first described<sup>14</sup> in children with renal tumors in 1978 and named “MRTK” by Haas et al in 1981.<sup>5</sup> With the development of research, it has been found that the MRT can occur in many tissues and organs of the whole body, of which the MRTK is the most common, accounting for 0.9%–2%<sup>15</sup> of renal tumors in children. The MRTK’s main pathological features are rhabdoid cells, and the deletion or mutation of SMARCB1 (also known as INI1) expression in immunohistochemical staining is a sensitive and specific diagnostic marker.<sup>20</sup> In most cases, skeletal muscle markers, such as desmin and myogenin, have detectable expression, while CK, EMA, and Vimentin have positive expression. Generally, the Ki67 proliferation index score is >50%. The expression of S-100 protein, NSE, and myoglobin varies. The immunohistochemical characteristics of this study are consistent with the literature reports in terms of INI1, desmin, and myogenin having detectable expression and the Vimentin and EMA having positive expression. A recent study shows that the Ki67 score is a good prognostic factor<sup>21</sup> in adult soft tissue sarcoma.

This study aims to improve the clinical understanding of MRTK by summarizing its clinical and biological characteristics as well as the prognoses in children with MRTK who have been diagnosed and treated in our hospital in the past 10 years.

## Methods

### Subjects

A total of 14 children were enrolled in this study. All of them were admitted to Beijing Tongren Hospital from January 1, 2010–December 31, 2019 and clearly diagnosed with MRTK by surgical resection or biopsy pathology, ie, the postoperative pathology or biopsy pathology was MRTK. Imaging findings in the children, including B ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography–computed tomography, were retrospectively collected and analyzed in order to evaluate the progression of primary tumors, distant metastases and their recurrence, etc. This study was approved by the Ethical Review Committee of Beijing Tongren Hospital, Capital Medical University. This study was conducted in accordance with the Declaration of Helsinki. All of the children’s guardians provided a signed informed consent form.

## Study Methods

### Diagnostic Criteria and Staging

All patients underwent either surgical resection or biopsy and were diagnosed with MRTK after two or more pathological consultations. Complete genome sequencing, which required the parents to confirm whether the patients had any mutated genes or not, was performed on the children.

Tumor staging (I, II, III, IV, and V)<sup>11</sup> was carried out with all patients according to the staging criteria of the National Wilms Tumor Study (NWTS).

### Treatment Protocols

The chemotherapy regimens consisted of the ifosfamide + carboplatin + etoposide (ICE), ifosfamide + etoposide (IE), or vincristine + pirarubicin + cyclophosphamide (VDC) regimen. Treatment was replaced by the adriamycin + vincristine + cisplatin + cyclophosphamide (AVCP) chemotherapy regimen or the European<sup>12</sup> Ewing’s sarcoma first-line vincristine + pirarubicin + ifosfamide + etoposide (VIDE) regimen in children who were insensitive to the above-stated chemotherapy. These treatments were also applied in the RS-99 ultra-high-risk group at Shanghai Children’s Medical Center.<sup>13</sup> Details of chemotherapy: VDC (vincristine 1.5mg/m<sup>2</sup> + doxorubicin (pirubicin 25 mg/m<sup>2</sup> × 3) + cyclophosphamide 600 mg/m<sup>2</sup> × 3) and ICE (carboplatin 450 mg/m<sup>2</sup> + etoposide 100 mg/m<sup>2</sup> × 4 + cyclophosphamide 1.5mg/m<sup>2</sup>) × 5) or IE (1.8mg/m<sup>2</sup> × 5 + etoposide 100mg/m<sup>2</sup> × 5) alternatively. 8 cases (8/14) had poor response to the above chemotherapy regimen. Shanghai Children’s Medical Center RS-99 super high risk group was replaced with AVCP regimen (pirubicin 25 mg/m<sup>2</sup> × 2 + vincristine 1.5 mg/m<sup>2</sup> × 2 + cisplatin 90 mg/m<sup>2</sup> + cyclophosphamide 300 mg/m<sup>2</sup> × 3) and Vide regimen (vincristine 1.5 mg/m<sup>2</sup>) + isocyclophosphamide 3mg/m<sup>2</sup> × 3 + pirubicin 25 mg/m<sup>2</sup> × 2 + etoposide 150mg/m<sup>2</sup> × 3). Due to the positioning and radiotherapy in the specialized radiotherapy department, and the small number of radiotherapy patients, the effect of radiotherapy for this disease was not exact, so we did not further analyze the correlation of radiotherapy. We are following up the children who have received radiotherapy and those who are receiving radiotherapy, to further compare the influence of radiotherapy or not on the survival rate.

### Evaluation Criteria for Tumor Lesions

Complete response (CR): All lesions have disappeared and have been completely gone for over four weeks.

Partial response (PR): The primary tumor shrank by  $\geq 64\%$  and the metastatic tumor shrank by  $\geq 30\%$ . There were no new lesions.

Progressive disease (PD): The primary tumor increased by  $\geq 40\%$  after the first visit and the metastatic tumor either increased by  $\geq 20\%$  or there was a new lesion.

### Evaluation Criteria for Overall Efficacy

CR: Both primary and metastatic tumors had CR, with no new lesions.

PR: The primary tumor had CR and the metastatic tumor either had CR, PR, or stable disease (SD), or there was a new lesion.

SD: The primary tumor had SD, the metastatic tumor either had CR, PR, or SD, or there was no new lesion.

PD: No primary and metastatic tumors had PD.

### Follow-Up Analysis

Outpatient or telephone follow-ups: Regular follow-ups of primary sites were conducted by ultrasound, CT or MRI, as well as by lung CT, abdominal ultrasound, cranial MRI, etc. Metastatic foci were monitored simultaneously in children with distant metastases. The follow-ups ended on June 30, 2020 or at the patient's time of death.

### Statistical Method

The SPSS 21.0 software was used to calculate the enumeration data, which were expressed with a percentage or rate. The rate was obtained through the  $\chi^2$  test and the survival analysis was conducted using the Kaplan–Meier Method in order to calculate the survival time and draw the survival curve.  $P < 0.05$  was considered a statistically significant difference.

## Results

### Clinical Characteristics

Among the 14 children with MRTK observed in this study, there were nine boys and five girls, with a median onset age of 13 (3–46) months. In six patients, the lesion was located in the left kidney and in eight patients it was located in the right kidney. The tumors were rather large. Of the patients, 13 had a tumor with the largest known diameter ( $>5$  cm). The first symptoms included abdominal pain in two patients, abdominal mass in six patients and gross hematuria in six patients (one patient had gross post-traumatic hematuria). Lung metastases at the beginning of the disease occurred in 12 patients, of whom two had liver

metastases, and four had lymph node metastases. During the treatment, liver metastases only occurred in one patient. Tumor embolus was found in 9/13 patients (Table 1).

### Immunohistochemical and Genetic Characteristics

Immunohistochemical results concerning 14 primary tumors showed a INI1 detectable expression present in 11 patients (11/14), desmin detectable expression in eight patients (8/10), myogenin detectable expression in seven patients (7/7), S-100 detectable expression in eight patients (8/10), EMA positive expression in seven patients (7/10), CD99 positive expression in six patients (6/7), and vimentin positive expression in eight patients (8/8). The Ki 67 proliferation index was high (30%–90%). The complete genome sequencing of tumor tissue was performed in four patients, two of whom showed SMARCB1 gene abnormalities. Namely, one patient had nonsense mutation and one had gene deletion. Furthermore, one patient showed a presence of SOX2 mutations and one patient showed an absence of tumor-related genotype changes (Table 2).

**Table 1** The Clinical Characteristics of Malignant Rhabdoid Tumor of the Kidney

Clinical Characteristics	N(%)
Gender	
Male	9(64. 3%)
Female	5(35. 7%)
Age	
$\geq 24$ months	4(28. 6%)
$< 24$ months	10(71. 4%)
Lesion location	
Left kidney	6(42. 9%)
Right Kidney	8(57. 1%)
First symptoms	
Abdominal mass	6(42. 9%)
Gross hematuria	6(42. 9%)
Abdominal pain	2(14. 2%)
Distant metastasis	
Lung	12(85. 7%)
Lymph node	4(28. 6%)
Liver	3(21. 4%)

**Table 2** Immunohistochemical Characteristics of 14 Children with Renal Rhabdomyoidoma

n	INI1	Desmin	Myogenin	S-100	EMA	Vimentin	CD99	Ki 67 (%)
1	+	-	-	+	+	+	+	70
2	-	-	Unmeasured	Unmeasured	Unmeasured	Unmeasured	Unmeasured	75
3	-	+	Unmeasured	-	+	+	+	70
4	-	Unmeasured	-	Unmeasured	Unmeasured	+	Unmeasured	25
5	-	Unmeasured	Unmeasured	Unmeasured	Unmeasured	Unmeasured	Unmeasured	50
6	-	Unmeasured	Unmeasured	-	+	Unmeasured	+	40
7	-	-	-	-	+	Unmeasured	Unmeasured	30
8	-	-	-	-	+	Unmeasured	+	85
9		-	Unmeasured	Unmeasured	+	Unmeasured	Unmeasured	90
10	+	+	-	-	-	+	+	70
11	-	-	-	-	-	+	Unmeasured	60
12	-	Unmeasured	Unmeasured	-	+	+	Unmeasured	40
13	+	-	Unmeasured	-	Unmeasured	+	+	90
14	-		-	+	-	+	-	30

**Notes:** "-" indicates negative expression, "+" indicates positive expression.

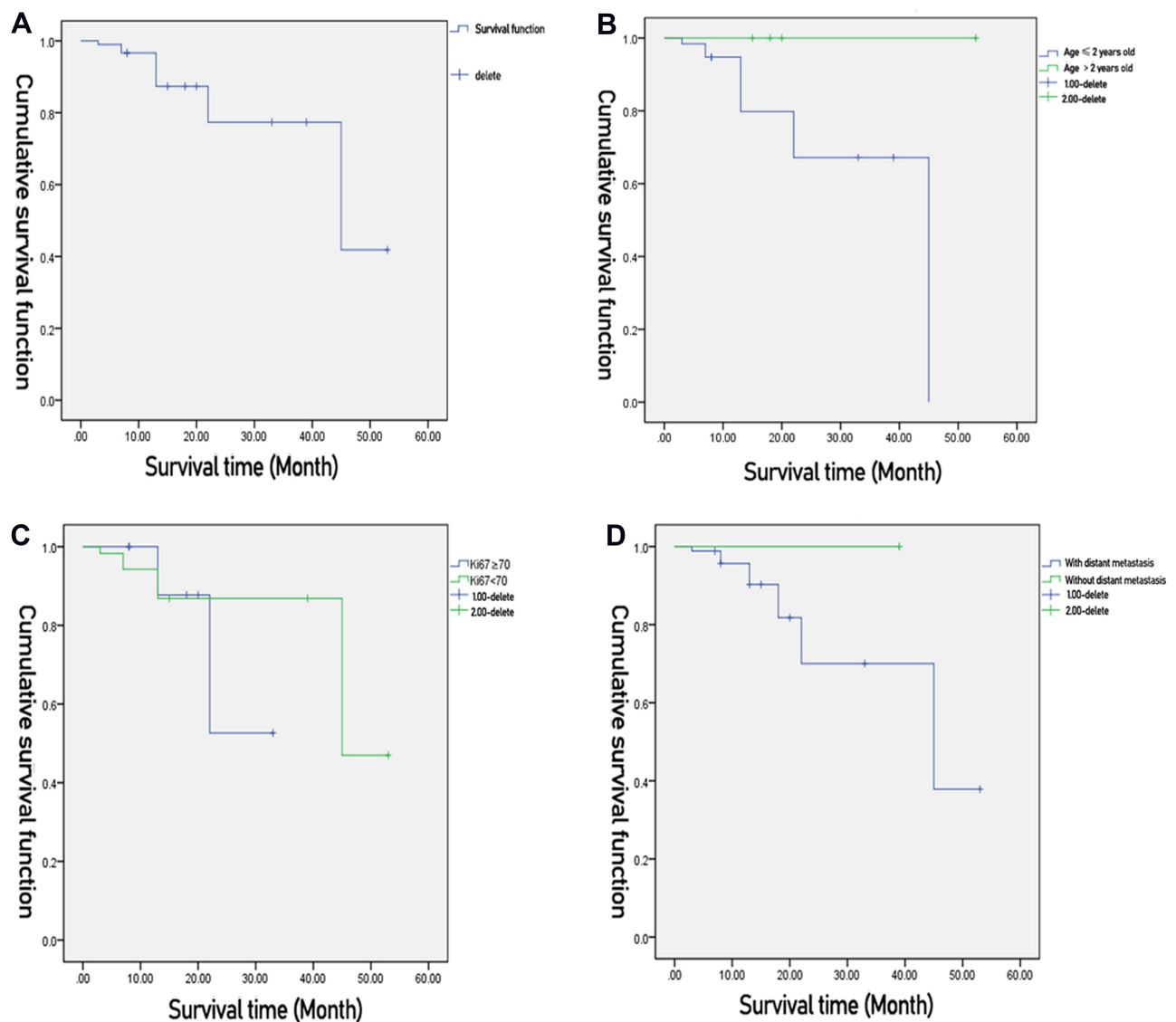
## Treatment and Prognosis

After the follow-up ending on June 30, 2020, the median follow-up time was 19 months (3–53 months). Complete primary resection was performed on 13 patients (13/14), of whom eight underwent direct excision and five received preoperative neoadjuvant chemotherapy after being confirmed to have MRTK by biopsy and undergoing surgical resection after partial regression. One patient (1/14) underwent neoadjuvant chemotherapy after being confirmed to have MRTK by biopsy. The tumor continued to progress until death. All 14 children received postoperative chemotherapy and six of them died. One patient died of tumor progression during the preoperative neoadjuvant chemotherapy, three patients died of tumor progression during postoperative chemotherapy, and two patients recurred after the CR after initial treatment. However, the re-treatment had a poor effect and the patients died after ceasing treatment. Two patients had CR. Both received surgery and achieved CR after chemotherapy. One case of PD was a patient with CR after surgery, chemotherapy, and radiotherapy, who recurred in situ after three months and was still in the progressive phase of the disease after re-chemotherapy and surgery. Among the patients, there were five cases of PR, two of which occurred after the

patients received surgery and chemotherapy. At present, one patient is taking sorafenib orally, and one patient is taking anlotinib orally. Two of the remaining three children have received local and primary radiotherapy and continued to maintain chemotherapy. Currently, all patients are in the maintenance stage of chemotherapy. The four-year OS was 41.8% (Figure 1A). In children aged <24 months and children aged >24 months, the two-year OS was 67.2% and 100%, respectively. The difference was statistically significant ( $\chi^2 = 108.998$ ,  $P < 0.05$ ) (Figure 1B). In children with Ki67  $\geq 70\%$  and children with Ki67 < 70%, the two-year OS was 52.6% and 86.9%, respectively. The difference was statistically significant ( $\chi^2 = 8.544$ ,  $P = 0.003$ ) (Figure 1C). In children with distant metastasis or children without distant metastasis, the two-year OS was 70% and 100%, respectively. The difference was statistically significant ( $\chi^2 = 14.239$ ,  $P < 0.05$ ) (Figure 1D).

## Discussion

The median onset age of susceptible MRTK infants and younger children is 18 months, and the male–female ratio is 1.5:1.0.<sup>11</sup> The median onset age is 13 (3–46) months, and the male–female ratio is 9:5. Tomlinson et al<sup>16</sup> find



**Figure 1** Clinical characteristics of malignant renal rhabdomyoid tumor in children.

that the onset age is an independent MRTK prognostic factor. In this study, the two-year OS is 67.2% and 100% in children with MRTK older than 24 months and children with MRTK younger than 24 months, respectively. The difference is statistically significant ( $\chi^2 = 108.998$ ,  $P < 0.05$ ). It is suggested that age may be a bad factor affecting prognosis. At the onset of the disease, the common clinical manifestations are gross hematuria, abdominal pain, abdominal distension, fever, etc.<sup>15</sup> The first symptoms of this group mainly include the gross hematuria ( $n = 6$ ) and abdominal mass ( $n = 6$ ).

The MRTKT staging is adopted from the staging criteria of the American Nephroblastoma Research Collaboration Group. Previous studies have shown that

more than 2/3 of children with MRTK are at the progressive stage of the disease (with distant metastasis in the lungs and/or brain)<sup>15</sup> when diagnosed. Among 12 patients (12/14) in this study, the lung metastasis occurs when the disease attacks. During this treatment, two patients (2/12) had liver metastasis, four patients (4/12) had lymph node metastasis, and one patient (1/14) had liver metastasis. This confirms that the MRTK has an extremely high level of malignancy. In patients with a presence of distant metastases and patients with an absence of distant metastases, the two-year OS is 70% and 100%, respectively. The difference is statistically significant ( $\chi^2 = 14.239$ ,  $P < 0.05$ ). The prognosis of distant metastases is suggested to be poor. It has also been reported that the MRTK may invade

the renal veins or inferior vena cava and transfer to the central nervous system.<sup>17</sup> In 1989, Weeks et al<sup>18</sup> summarized 111 patients with MRTK and found that approximately 10%–15% of children with MRTK also had intracranial tumors, most of them being AT/RT. Follow-up studies also report that MRTK is associated with secondary intracranial tumors, such as medulloblastoma and primitive neuroectodermal tumors.<sup>19</sup> However, no intracranial metastases were found in the children observed in this study during the initial diagnosis and treatment. The follow-up time should be prolonged and the head imaging closely monitored.

The MRTK Ki67 score is generally high. In this study's group, the Ki67 score is 30%–90%. The difference in the two-year survival rates of the >70% group and the <70% group is statistically significant ( $\chi^2 = 8.544$ ,  $P = 0.003$ ), indicating that the higher the Ki67 score, the worse the prognosis.

It is currently believed that the inactivation of the INI1 gene is located in the chromosome 22q11.2, leading to the deletion of INI1 protein expression, which is related to the occurrence of many malignant tumors.<sup>22</sup> Studies show that two genes are inactivated in malignant rhabdoid tumors,<sup>23</sup> namely, SMARCB1 or SMARCA4. When the SMARCB1 or SMARCA4 is abnormal, it can lead to the failure of the SWI/SNF complex to play an important role in the process of gene transcription and affect the normal expression of subsequent genes, thereby, resulting in the occurrence of an MRT.<sup>24</sup> In this study, the entire tumor tissue genome sequencing was conducted in four patients, including two patients (2/4) with abnormal SMARCB1 (one patient with nonsense mutations and one with SMARCB1 gene deletion), one patient with SOX2 mutations, and one patient with a reported unknown tumor-related genotype alteration. SOX2 amplification or activation of mutations may promote cancer stem-like behavior, namely, cell renewal. SOX2 overexpression has been reported as a driving event in several cancer types, especially squamous cell carcinoma. Many preclinical studies have also involved SOX2-mediated self-renewal, invasion, and tumorigenesis in non-small cell lung cancer. However, there are no relevant reports on SOX2 and MRT.<sup>25–27</sup>

Tomlinson et al<sup>16</sup> have found that the prognoses of children with MRTK who have SMARCB1 and SMARCA4 gene mutations are very poor. However, it is not possible to infer whether or not the children with tumor-related mutant genes have poor prognoses due to the short follow-up time and non-detected deaths.

Current studies show that radical surgery, supplemented by chemotherapy and radiotherapy, is an important basis for MRTK treatment. The previous chemotherapy protocols of nephroblastoma used in MRTK treatment have a poor therapeutic effect as the prognosis.<sup>16</sup> NWT5-5 recommends a chemotherapy regimen that includes carboplatin, etoposide, and cyclophosphamide. Subsequent case reports show that the ICE and IE, or, alternately, the VDC, regimens may be effective in MRTK treatment.<sup>28</sup> Post-retreatment with carboplatin and thiotepa is also recommended for hematopoietic stem cell transplantation,<sup>29</sup> however, there has been no observed significant improvement in the MRTK prognosis, which is still 20%–25%.<sup>16</sup> Moreover, the post-retreatment may increase the mortality of chemotherapy-related adverse reactions.<sup>30,31</sup> In the group observed in this study, 13 patients underwent complete resection of primary lesions and one patient was confirmed by biopsy. However, the chemotherapy had a poor effect and the tumor died rapidly. All 14 children received chemotherapy. The chemotherapy regimens mainly consist of VDC, ICE, or IE regimens. Eight (8/14) children did not respond well to the above-mentioned chemotherapy regimens. Their treatment was replaced with AVCP and VIDE chemotherapy regimens, alternately, in the RS-99 ultra-high-risk group of Shanghai Children's Medical Center. Four (4/8) patients were still insensitive to the chemotherapy regimen, had tumor progression and died. Four (4/8) patients experienced tumor reduction after a change in the regimen. Two patients had a poor outcome in re-chemotherapy after recurrence with tumor progression and died. Only three patients received radiotherapy for the primary foci and metastases in this study. However, one patient recurred again three months after CR and two patients are still in the maintenance stage of chemotherapy. This study suggests that radiotherapy may be beneficial to patients aged >3 years with have AT/RT limitations. Nevertheless, for all patients with MRT, the role of adjuvant radiotherapy still requires further clinical studies and validation.<sup>32</sup> For these conditions that have an uncertain effect of radiotherapy, the ability to find an effective chemotherapy regimen directly affects the survival rate.

Because of the poor prognosis of traditional treatment, the MRT also has obvious characteristics of epigenetics and gene expression heterogeneity. The targeted therapy has become a new study protocol. However, there are currently no FDA-approved anti-tumor drugs targeting SMARCB1. Tazemetostat, a histone methylation inhibitor [enhancer of zeste homolog (EZH) 2 inhibitor], is used to

treat the SMARCB1-expressed negative epithelioid sarcoma (NCT02601950) in the Phase II clinical trial, which has a total of 31 patients. The results show that four patients have PR and six patients have been stable for more than 32 weeks.<sup>33</sup> In a different Phase I clinical trial (NCT01897571) of Tazemetostat for treating SMARCB1 or SMARCA4-expressed epithelioid sarcoma, eight patients have a negative SMARCB1 expression. Among them, one patient suffering from MRT with negative SMARCB1 expression has CR and has lasted 65 weeks and two patients with SMARCB1-expressed negative epithelioid sarcoma are showing a stable condition, lasting 25 and 24 weeks, respectively. Although no gene detection was carried out in two of the study's patients, the disease is partially alleviated after oral administration of targeted drugs. Due to the small sample size, it should not be concluded that such targeted drugs are effective for MRTK treatment. This research data are very limited by the retrospective single-center research character, especially by the erroneous presentation of the data and results and unfortunately also by the tiny patient cohort.

To sum up, with the gradual understanding and research regarding the MRTK, the disease has always been considered rare, highly invasive and fatal. Age <24 months, Ki67 ≥ 70%, and the presence of distant metastases may be poor prognosis risk factors. There are still many unknown areas to explore, from pathogenesis to treatment options. Large sample size data may be obtained by clinical centers working together closely in order to comprehensively analyze the treatment and prognosis of this disease. Targeted therapy based on pathogenesis is becoming a hot spot in MRTK therapy and is expected to be a breakthrough in improving disease prognosis.

## Conclusion

The most common MRTK distant metastasis site is the lung. Risk factors for poor MRTK prognoses include an age of <24 months, Ki 67 > 70%, and distant metastases.

## Disclosure

Jing Li and Weiling Zhang are co-first authors for this study. The authors report no conflicts of interest in this work.

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