Original Article

An analysis of the diagnosis, clinical characteristics, treatment, and survival outcomes of 36 extracranial malignant rhabdoid tumor patients

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Background: Extracranial malignant Rhabdoid tumors (eMRTs) are rare but aggressive lesions in young children. This work aimed to review and analyze the diagnosis, clinical characteristics, treatment, and survival of eMRTs so as to summarize experience for future therapy.

Methods: A total of 36 eMRT cases were treated between January 2008 and August 2019 according to Shanghai Children's Medical Center (SCMC) multimodal protocol of mixed surgery, radiation and chemotherapy involving vincristine, carboplatin, doxorubicin, etoposide, cyclophosphamide and ifosfamide. We collected information including: age at diagnosis, tumor location, disease stage, therapy, outcomes, etc. Overall survival (OS) and event free survival (EFS) were calculated and risk factors for survival were analyzed.

Results: The patients had a median age of 1.80 years at diagnosis (range, 1.4 m–13.42 years), and were followed up for 9.17 months in median (range, 4 d–11.14 y). A total of 16 patients achieved complete remission (CR), and 7 survived without reoccurrence till December 2019. The 3-year EFS was 17.4% (95% CI: 11.0–23.8%) with a 3-year OS of 23.4% (95% CI: 15.8–31.0%). Recurrence was found only in children younger than the median age (1.80 y). Localized staging (Log Rank P=0.039 for OS and P=0.021) and older age (Log Rank P=0.016 for OS and P=0.002 for EFS) were associated with improved outcome. Younger age (Cox regression, OS, OR =2.610, 95% CI: 1.147–5.937, P=0.022; EFS, OR =3.401, 95% CI: 1.495–7.752, P=0.004) were independent risk factors for death and recurrence.

Conclusions: Those eMRTs treated according to SCMC protocol turned out to have poor outcomes. Higher staging at diagnosis and reoccurrence in younger patients remain major threats to the prognosis.

Keywords: Pediatric extracranial malignant rhabdoid tumor (eMRT); survival; recurrence; chemotherapy

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Introduction

Malignant rhabdoid tumors (MRTs/RTs), rare but extremely aggressive tumors, tend to predominantly affect young individuals, especially those patients younger than 4 years old (1). It was first reported as a special subtype of Wilms tumor, featuring a poor prognosis, but it actually has no anatomic site preference (2). In most recent years, extracranial malignant rhabdoid tumors (eMRTs) have been often described as an entity. According to latest studies, about 25% of eMRTs occur in the kidney, and 75% in other soft tissues (head-and-neck, liver, chest, retroperitoneum, pelvis and heart) (1). Despite such a diversity, eMRTs are described as lethal malignance, featured rapid progression and poor prognosis. Society of Pediatric Oncology intermediate nephroblastoma (SIOP) reported OS at 9.09% in a 1996 series (3). In the first decade of the 20th century, National Wilms' Tumor Study (NWTS) series, and Surveillance Epidemiology and End Results (SEER) programme also confirmed the poor prognosis with OS, at 4 years at 23.3% and 33.0%, respectively, as no improvement in outcome with time over decades (4,5).

In China, due to the infrequency and high mortality of this tumor, treatment strategies vary from center to center, and even from patient to patient. Lack of specific or uniform therapeutic protocol makes it hard to evaluate the efficacy of treatment and to some extent contributes to the poor prognosis. In 2019, Cheng *et al.* from Beijing Children's Hospital reported their experience in eMRTs treatment The EFS rates of 1 year and 3 years for the entire cohort were 21.80% and 14.53%, respectively, while OS rates of 3 years and 5 years were 23.71% and 18.44%, respectively, which was even worse than the previous researches in Caucasian races (6).

In our center, eMRT patients were treated in uniform Shanghai Children's Medical Center (SCMC) multimodal protocol since 2008, which is a protocol widely referred to in south-east China. No study has ever reported the efficacy of this treatment approach. This research aims to analyze the diagnosis, clinical characteristics, treatment, and survival outcomes of this protocol. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-459).

Methods

Patients

The current study retrospectively reviewed all eMRT cases under 17 years old diagnosed at our center from January 2008 to August 2019 in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of SCMC (SCMCIRB-W2021018) and individual consent for this retrospective analysis was waived. The patients were pathologically confirmed based on IHC staining. Clinical information of patients was collected, including: age, sex, clinical symptoms, imaging examination, primary tumor sites and metastatic sites, treatment schedules, IHC staining of SMARCB1, and outcomes.

Image evaluation and staging

Multiple imaging approaches, namely ultrasound, either computed tomography (CT) or magnetic resonance imaging (MRI) of the primary site, CT scan chest, MRI/CT scan of brain, and in some occasion, bone scan was used to evaluate the volume, local lymph invasion and distal metastasis as well as the treatment responses. The tumors were staged as localized, regional, distant according to the Surveillance, Epidemiology, and End Results (SEER) staging system (5).

Treatments (SCMC multimodal protocol)

Up-front resection of the primary tumor was encouraged, but if the tumor was unresectable, patients would receive a biopsy first. Complete resection with microscopic negative margin was R0, with microscopic positive margin was R1, and macroscopic positive margin was R2 (1).

Following initial surgery or biopsy, patients were recommended for chemotherapy protocol according to their primary tumor location and stages. Malignant rhabdoid tumors of the kidney (MRTK) that received initial resections would follow WT (4) protocol (Carboplatin, Cyclophosphamide, Doxorubicin, Vincristine, and Etoposide) proposed by the Fifth National Wilms Tumor Study Group (NWTSG-5) for 27 weeks (7,8). For those MRTK patients received biopsy only, the WT (5) protocol was employed and then patients were reevaluated for radical surgery. Treatment of extrarenal extracranial rhabdoid tumor (EERT) would follow the RS-99 protocol according to the experience of the Intergroup Rhabdomyosarcoma Study Committee (IRS) (9,10). The overall treatment schedule and details of chemotherapy are shown in *Table 1*. If the tumor could not be removed at presentation, delayed surgery was arranged after course 6 when the tumor could reach complete or good gross resection.

Patients aged 3 years and above were considered for local radiation of all primary tumor sites and all sites of metastatic

Table 1 details of chemotherapy for eMRT

MRTK resectable				MRTK unresectable				EERT				
Week	Agents			Week	Agents			Week	Agents			
0	Surgery			0	Biopsy			0	Surgery/Biopsy			
1	C	E	Radiotherapy	1	I	E	V	1	D*	V*	Cy*	P
4	C	E		2			V	4	I	E*	V*	
7	Cy	D	V	3				7	D*	V*	Cy*	P
8			V	4	I	E	V	10	I	E*	V*	
9			V	5			V	13	D*	V*	Cy*	P
10	C	E		6	Evaluation	Surgery	Radiotherapy	16	I	E*	V*	
13	C	E						19	Radiotherapy			
16	Cy	D	V					22	Surgery			
17			V					23	V*	Cy*	P	
18			V					26	A	E	V*	
19	C	E						29	V*	Cy*	P	
22	C	E						32	A	E	V*	
25	Cy	D	V					35	V*	Cy*	P	
26			V					38	A	E	V*	
27			V									

C, Carboplatin 15 mg/kg/d (≤12 months), 450 mg/m^2/d (>12 months), d1–d2, iv; E, Etoposide 3.3 mg/kg/d (≤12 months), 100 mg/m^2/d (>12 months), d1–d3, iv; Cy, cyclophosphamide 14.7 mg/kg/d (≤12 months), 440 mg/m^2/d (>12 months), d1–d5, iv; D, Doxorubicin 1 .25 mg/kg/d (≤12 months), 37.5 mg/m^2/d (>12 months), d1, iv; V, vincristine 0.025 mg/kg/d (≤12 months), 0.05 mg/kg/d (1–3 years), 1.5 mg/m^2/d (>3 years), maximum to 2 mg, d1, iv; I, Ifosfamide 1.5 g/m^2/d (≥12 months), 75% dose for infants <12 months; 50% dose for infants<6 months, d1–d5, iv. D*, Doxorubicin 30 mg/m^2/d), 75% dose for infants <12 months, d1, d8, iv; V*, vincristine 1.5 mg/m^2/d, 75% dose for infants <12 months, maximum to 2 mg/dose, d1, d8, iv; Cy*, cyclophosphamide, 300 mg/m^2/d, 75% dose for infants <12 months, d1–d3, iv; P, Cisplatin 90 mg/m^2/d, 75% dose for infants <12 months, cumulative dose maximum to 540 mg/m^2, d1, iv; E*, Etoposide 100 mg/m^2/d, 75% dose for infants <12 months, d1–d5, iv; A, Actinomycin,12μg/kg/d, 75% dose for infants <12 months, maximum to 600 μg/d, d1–d5, iv. eMRT, extracranial malignant Rhabdoid tumors.

disease. Radiation therapy started within 10 days post-operation for MRTK patients whose primary tumors were resected, and was delivered after course 6 for EERT patients. The prescribed dose of radiation was accumulatively 4,500–5,500 cGy, divided to 200 cGy daily, 5 days a week. The detailed dose and fractionation varied among different sites, tumor volumes, and type of metastases.

Follow up

Complete remission (CR) was considered with no overt lesion detection by imaging for ≥1 month (11). Disease progression (DP) was considered with increased lesion size or detection of novel sites of malignancy by imaging (11). Recurrence was the reappearance of the tumor after clearance of both primary and metastatic malignancy (12). Overall survival (OS) was the time from diagnosis to death or final follow-up. Event free survival (EFS) was measured from diagnosis to disease progression, recurrence, or death due to any causes. The 3-year EFS and OS were reported along with their 95% confidence intervals (CIs). Patients got reassessed once every month after diagnosis, until CR or death; next, every 3 months until half a year after CR; and then, every 6 months until 1year; and every year until 3 years thereafter.

Statistical analysis

All statistical analyses were carried out using SPSS 22.0

Table 2 Clinical information of eMRT patients (originality: yes)

Variable	N (%)/Total (N=36)
Age, median (range), y	1.80 (0.12–13.42)
Sex	
Male	19 (52.78)
Female	17 (47.22)
Primary location	
MRTK	18 (50.00)
EERT	18 (50.00)
Head and neck	8 (22.22)
Limbs	6 (16.67)
Pelvis	1 (2.78)
Liver	1 (2.78)
Retroperitoneum	1 (2.78)
Sacrococcyx	1 (2.78)
SEER stage	
Localized	4 (11.11)
Regional	15 (41.67)
Distal metastasis	17 (47.22)
Lung	7 (19.44)
Bone	10 (27.78)
Peritoneum	3 (8.33)
Brain parenchyma	2 (5.56)
Liver	1 (2.78)
Tumor size, median (range) cm^3	114.07 (0.42–5,272.56)
Loss of histologic SMARCB1	
Entire	27 (75.00)
Partial	9 (25.00)
Surgery	
Upfront	15 (41.67)
Delayed	8 (22.22)
Margin (N=23)	
R0	7 (30.43)
R1	16 (69.57)
Chemotherapy	
Complete	25 (69.44)
Incomplete	11 (30.56)
Radiation (N=23)	
Complete	21 (91.30)
Incomplete	2 (8.70)

MRTK, malignant rhabdoid tumors of the kidney; EERT, extrarenal extracranial rhabdoid tumor.

(SPSS, USA). Continuous variables were presented in median and range, and compared by the Mann-Whitney U test. Categorical variables were presented in percentage, and investigated by the Chi-square test. The survival rate was analyzed by means of the Kaplan-Meier method and compared through the log-rank test between subgroups. To investigate the impact of the variables on EFS and OS, survival multivariable analysis was conducted using the Cox regression model. $P<0.05$ was considered as statistically significant.

Results

Patients

From January 2008 to August 2019, totally 36 patients (19 males and 17 females), with a median age at diagnosis of 1.80 years (range, 1.4 months to 13.42 y), were reviewed retrospectively, including 18 MRTKs and 18 EERTs. About half of EERT cases had primary site in head-and-neck (n=8). Twenty-seven patients had entire histologic loss of SMARCB1 and the other 9 had partial loss. Patient staging data, sites, and size of primary tumors are listed in *Table 2*. Seventeen patients had distant metastases. The most common site of metastasis was the lung (7 patients), followed by the bones (10).

Treatment

Fifteen patients (3 with metastases and 12 without) underwent surgical resection of primary tumors up front. 25 patients completed the protocol treatment in a median period of 8.4 months (minimum 6.5 maximum 13.0). Ten patients discontinued chemotherapy due to early progressive disease between 3 d and 10.9 months. One patient in metastatic stage after biopsy chose to participate in molecular targeted therapy trial with Anlotinib. 8 more patients received delayed radical resection after chemotherapy. Totally 7 patients had R0 resection margin, and 16 had R1. Among those 23 patients, only 21 patients received local therapeutic radiotherapy. The other 2 had progressive disease during first-line treatment prior to the planned radiotherapy. Details of the treatment process are described in *Figure 1*.

Outcome

Median follow-up for the whole cohort was 9.17 months

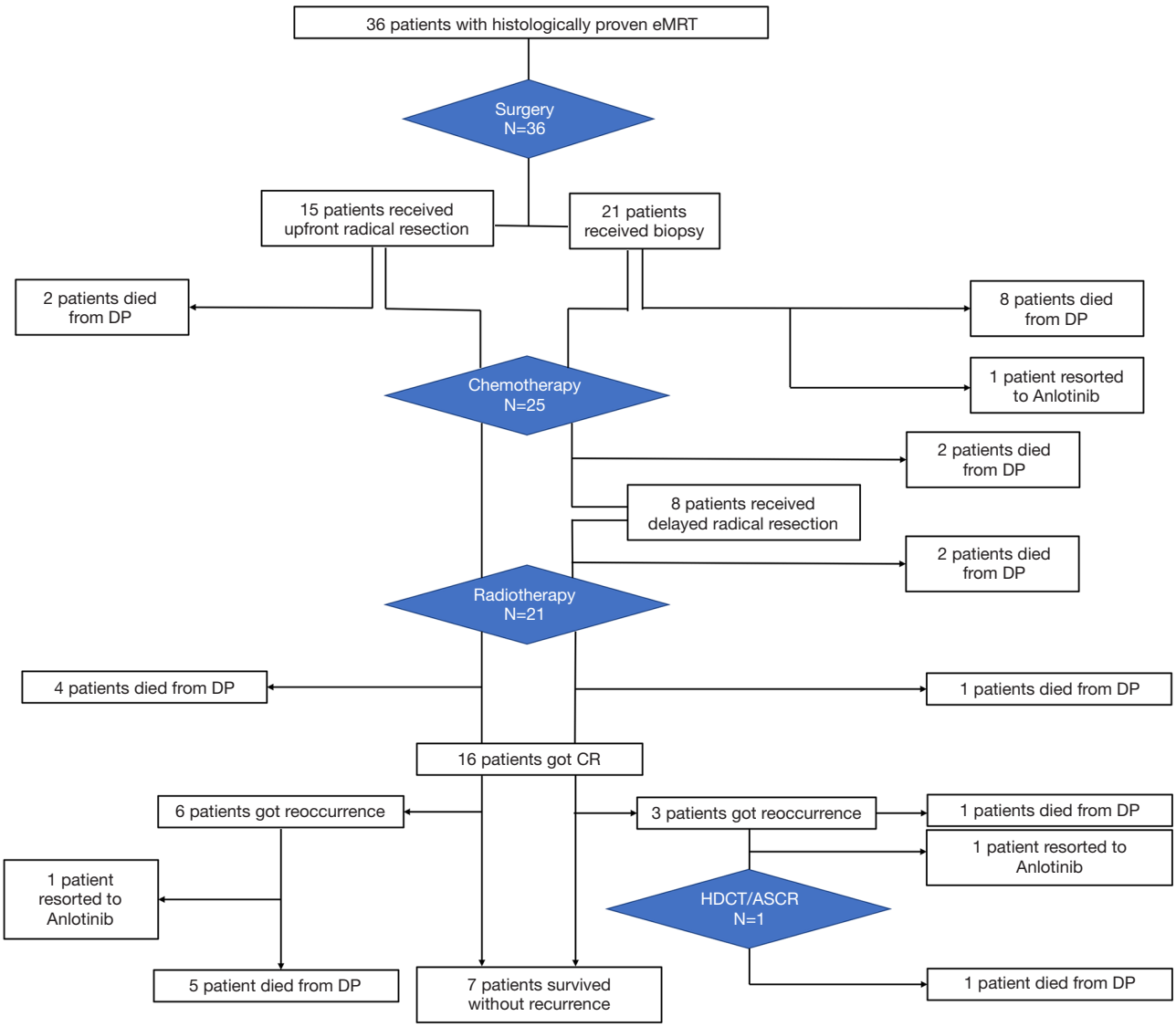

Figure 1 The recruiting and grouping process of the research.

(range, 4 d–11.14 years), for 10 alive patients was 20.07 months (range, 4.06–133.67 months), for localized patients was 17.33 months (range, 10.10–133.67 months), whereas for metastatic patients was 25.05 months (range, 4.06–89.00). Finally, 29 patients developed an event (15 in localized and 14 metastatic patients) and subsequently 26 died (13 in localized and 13 metastatic patients). 16 patients achieved CR. Nine patients got recurrence after achieving CR. Time to recurrence in median was 12.7 months (minimum 4.8 months, maximum 22.4 months). One patient resorted to high-dose chemotherapy and autologous stem cell rescue (HDCT/ASCR), and died from DP in 1 year. Two patients resorted to Anlotinib, and now in disease control. The other 7 patients died from DP in half a year.

For the whole cohort, the 3-year EFS was 17.4% (95% CI: 11.0–23.8%) with a 3-year OS of 23.4% [95% CI: 15.8–31.0%); *Figure 2A*,*B*]. The localized and regional diseases didn't differ in OS or recurrence pattern with the metastatic ones. For localized and regional diseases, the 3-year EFS was 21.1% (95% CI: 11.7–30.5%) with a 3-year OS of 25.3% (95% CI: 15.1–35.5%; *Figure 2C*,*D*). For distant metastatic disease, the 3-year EFS was 12.8% (95% CI: 4.3–21.3%) with a 3-year OS of 20.0% (95% CI: 8.6–31.4%). For localized disease, 3 patients achieved CR

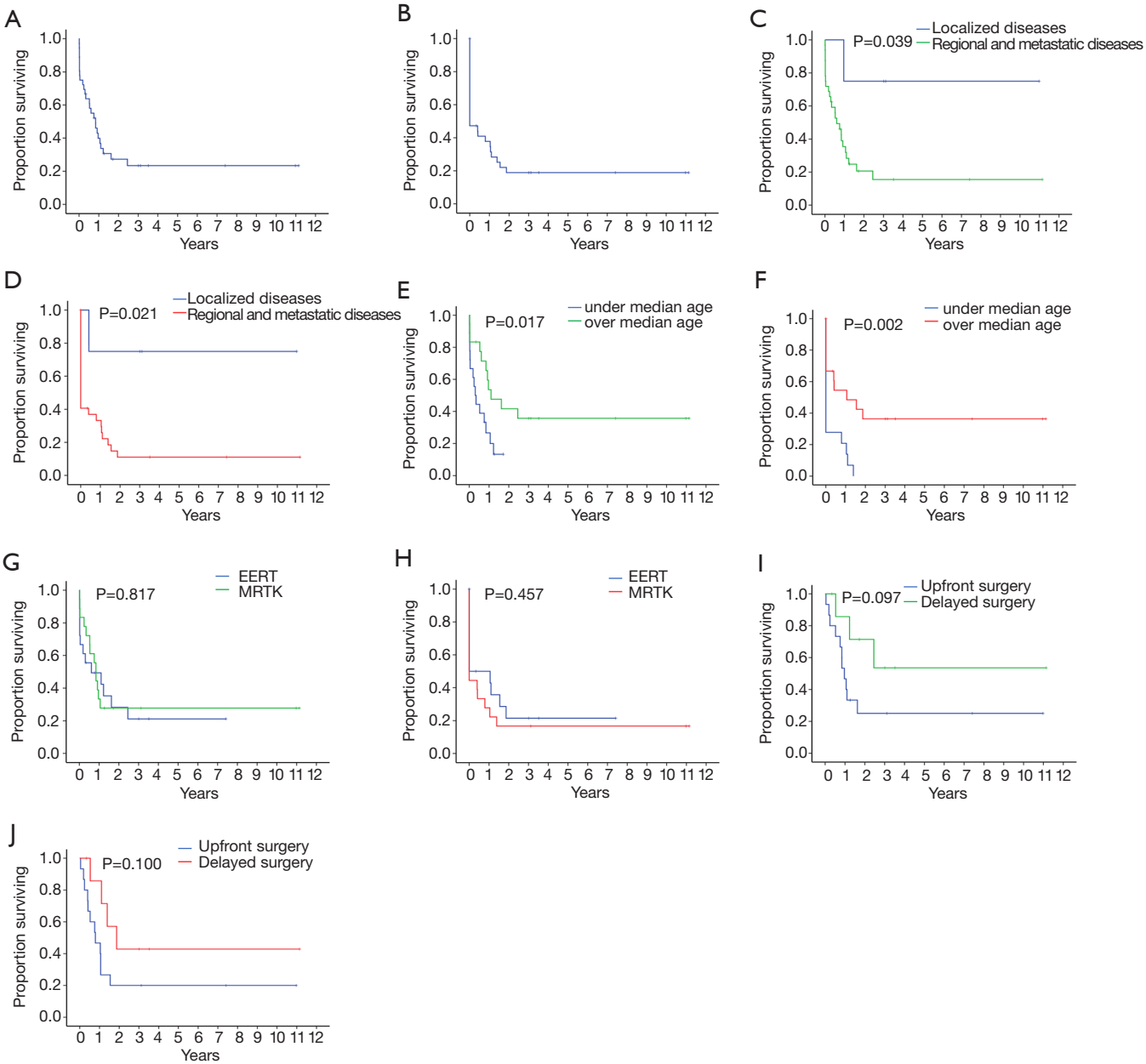

Figure 2 Kaplan–Meier survival analyses. (A) OS for the entire cohort. Dotted lines show the 95% confidence interval. (B) EFS for the entire cohort. Dotted lines show the 95% confidence interval. (C) OS stratified by age above or below the median age of 1.80 years (P=0.016). (D) EFS stratified by age above or below the median age of 1.80 years (P=0.002). (E) OS of localized diseases compared with other staging (P=0.039). (F) EFS of localized diseases compared with other staging (P=0.021). (G) OS comparison between MRTK and EERT (P=0.817). (H) EFS comparison between MRTK and EERT (P=0.457). (I) OS stratified by upfront surgery and delayed surgery (P=0.097). (J) EFS stratified by stratified by upfront surgery and delayed surgery (P=0.100).

and had no reoccurrence by the end of observation, with a statistically significant (P<0.0001) advantage in 3-year EFS and OS of 75% (95% CI: 53.3–96.7%) than those with higher staging (EFS: 9.90%, 95% CI: 4.5–15.3%, Log Rank, P=0.021; OS:15.5, 95% CI: 8.2–22.8%, Log Rank, P=0.039).

Table 3 Cox regression analysis of overall survival (OS) and Event-free survival (EFS) (originality: yes)

Variable	Comparison	OS Univariate		EFS Univariate	
		HR (95% CI)	P Value	HR (95% CI)	P Value
Age	<1.80 *vs.* >1.80 y	2.610 (1.147–5.937)	0.022*	3.401 (1.495–7.752)	0.004**
Sex	female *vs.* male	1.009 (0.457–2.229)	0.982	0.992 (0.477–2.064)	0.983
Primary location	MRTK *vs.* EERT	1.147 (0.519–2.534)	0.735	1.050 (0.505–2.188)	0.895
Metastasis	Metastatic *vs.* non-metastatic	0.836 (0.380–1.842)	0.657	0.932 (0.444–1.956)	0.851
	Non-localized *vs.* localized	1.158 (0.021–1.176)	0.072	0.144 (0.019–1.071)	0.058
Tumor size	<114.07 *vs.* >114.07 mL	0.697 (0.315–1.542)	0.373	0.746 (0.345–1.615)	0.458
Loss of histologic SMARCB1	Entire *vs.* partial	1.466 (0.542–3.965)	0.451	1.505 (0.561–4.034)	0.417
Surgery	Upfront *vs.* delayed	2.766 (0.755–10.129)	0.153	2.515 (0.802–7.883)	0.114
Resection status	R0 *vs.* R1	0.475 (0.129–1.743)	0.262	0.721 (0.249–2.089)	0.547
MRTK					
Age	<1.80 y *vs.* >1.80 y	3.355 (0.853–13.200)	0.083	4.053 (1.052–15.624)	0.042*
Sex	female *vs.* male	1.907 (0.587–6.198)	0.283	0.843 (0.291–2.440)	0.752
Metastasis	Metastatic *vs.* non-metastatic	0.836 (0.380–1.842)	0.657	0.970 (0.331–2.844)	0.956
	Non-localized *vs.* localized	1.742 (0.466–6.518)	0.409	0.803 (0.179–3.605)	0.774
Tumor size	<523.33 mL *vs.* >523.33 mL	1.514 (0.394–5.809)	0.546	1.241 (0.414–3.724)	0.700
Loss of histologic SMARCB1	entire *vs.* partial	1.299 (0.270–6.254)	0.744	0.839 (0.231–3.051)	0.790
Surgery	upfront *vs.* delayed	2.377 (0.508–11.119)	0.272	0.928 (0.232–3.722)	0.916
Resection status	R0 *vs.* R1	1.638 (0.484–5.547)	0.428	0.856 (0.179–4.089)	0.846
EERT					
Age	<1.80 *vs.* >1.80 y	2.010 (1.067–3.787)	0.031*	2.183 (1.178–4.147)	0.013*
Sex	Female *vs.* male	0.719 (0.405–1.277)	0.260	0.765 (0.441–1.327)	0.341
Metastasis	Metastatic *vs.* non-metastatic	1.318 (0.732–2.375)	0.358	1.116 (0.643–1.939)	0.696
	Non-localized *vs.* localized	0.390 (0.047–3.245)	0.384	0.039 (0.000–63.952)	0.391
Tumor Size	<73.00 *vs.* >73.00 mL	0.500 (0.157–1.597)	0.242	0.569 (0.188–1.721)	0.318
Loss of histologic SMARCB1	Entire *vs.* partial	0.906 (0.237–3.462)	0.451	0.295 (0.022–3.951)	0.357
Surgery	Upfront *vs.* delayed	0.139 (0.015–1.306)	0.084	3.202 (0.572–17.928)	0.185
Resection status	R0 *vs.* R1	0.408 (0.066–2.521)	0.334	0.852 (0.152–4.770)	0.856

*, P<0.05; **, P<0.01. MRTK, Malignant rhabdoid tumors of the kidney; EERT, extrarenal extracranial rhabdoid tumor.

Prognostic risk factors

The OS and EFS seemed to be improved in patients above the median age (1.80 years, Log Rank P=0.016 for OS and P=0.002 for EFS; *Figure 2E,F*) and with localized diseases (Log Rank P=0.039 for OS and P=0.021 for EFS; *Figure 2C,D*). On univariant Cox regression model, age was the only factor that significantly influenced the EFS and OS (Log Rank P=0.0036; OR=4.678, 95% CI: 1.693–12.925; *Table 3*). MRTK and EERT were compatible in clinical information and treatment administration (*Table 4*). The two groups had a similar pattern in OS (Log Rank P=0.016; *Figure 2G*) and EFS (Log Rank P=0.457; *Figure 2H*). Further hierarchical Cox analysis revealed that age was the only risk factor with EFS in both MRTK and EERT, it also affected OS

Table 4 Clinical information of MRTK and EERT (originality yes)

Variable	MRTK (N=18)	EERT (N=18)	P value
Age, median (range), y	1.60 (0.29–6.24)	2.33 (0.12–13.42)	U test, 0.650
Sex, n (%)			
Male	10 (55.56)	9 (50.00)	χ^2 test, 0.738
Female	8 (44.44)	9 (50.00)	
SEER stage, n (%)			
Localized	3 (16.67)	1 (5.56)	χ^2 test, 0.807
Regional	5 (27.78)	10 (55.56)	
Distal metastasis	10 (55.56)	7 (38.89)	
Tumor size, median (range), cm^3	523.33 (37.55–920.81)	73.00 (0.42–5,272.56)	U test, 0.013*
Loss of histologic SMARCB1, n (%)			
Entire	14 (77.78)	13 (72.22)	χ^2 test, 0.704
Partial	4 (22.22)	5 (17.78)	
Surgery, n (%)			
Upfront	10 (55.56)	5 (27.78)	χ^2 test, 0.135
Delayed	3 (16.67)	5 (27.78)	
Margin^, n (%)			
R0	4 (30.77)	3 (30.00)	χ^2 test, 0.969
R1	9 (69.23)	7 (70.00)	
Chemotherapy, n (%)			
Complete	15 (83.33)	10 (55.56)	χ^2 test, 0.074
Incomplete	3 (16.67)	8 (44.44)	
Radiation^, n (%)			
Complete	13 (100.00)	8 (80.00)	χ^2 test, 0.099
Incomplete	0 (0.00)	2 (20.00)	

*, P<0.05; **, P<0.01; ^, N=13 of MRTK and N=10 of EERT. MRTK, Malignant rhabdoid tumors of the kidney; EERT, extrarenal extracranial rhabdoid tumor.

in EERT but not in MRTK (*Table 3*). Up-front surgery and delayed surgery achieved similar OS and EFS in both MRTK and EERT (*Figure 2I,2J*; *Table 3*).

Discussion

In this study, we reported the clinical characteristics, treatment, and outcome of 36 consecutively diagnosed Chinese eMRT patients at SCMC. Despite the comparatively small sample, our research is compatible with peer studies in age range, staging level and treatment protocol. As a highly aggressive malignance, eMRT featured poor outcomes, especially in younger patients. In our research, recurrence and relapse were only observed in children under 1.80 y which is in accordance with the conclusion of previous researches that older age predicts better outcome (11,13). Such a difference may lie in less aggressive treatment protocol of chemotherapy and radiation therapy in younger children. Higher staging is the other risk factor for poor outcome, but no prognostic difference was found between MRTKs and ERRTs.

RTs could happen almost anywhere in the body,

which makes it hard to standardize the staging system or make specific treatment methodology. Generally, most MRTKs followed the protocol of NWTSG-5 strategy, while the protocol for ERRTs usually follows various therapeutic pathway of soft tissue sarcoma. Though, all those protocols involve multiple regimens combining surgical, radiotherapeutic and chemo agent like vincristine, carboplatin, doxorubicin, etoposide, cyclophosphamide and ifosfamide, etc., dosage between different researches varied a lot. In our research, MRTK patients received accumulative dose of 13.5 mg/m^2 for vincristine, 112.5 mg/m^2 for doxorubicin, 5,400 mg/m^2 for carboplatin, 6,600 mg/m^2 for cyclophosphamide and 1,800 mg/m^2 for etoposide separately in 27 weeks. For those cases who received delayed resections, another 6 mg/m^2 of vincristine, 15 mg/m^2 of ifosfamide and 600 mg/m^2 of etoposide were added during 6 weeks before radical or gross resection. As for ERRT patients, a total of 180 for doxorubicin, 36 mg/m^2 for vincristine, 5,400 mg/m^2 for cyclophosphamide, 540 mg/m^2 for cisplatin, 22.5 mg/m^2 for ifosfamide, 2,400 mg/m^2 for etoposide and 180 μg/kg for dactinomycin was given in 38 weeks. According to available data, medical centers that adopted similar NWTSG-3 or NWTSG-5 protocol achieved compatible outcomes in MRTKs, with a 4- year OS of 23.2% in NWTS report (4) and 25% in an Irish study (2). In 2014, Furtwängler *et al.* reported significantly improved responses of MRTKs to pre-operative treatment intensified with doxorubicin. After pre-operative treatment with 4 weeks of AV (actinomycin D and vincristine with a cumulative dose 180 mg/kg and 6 mg/m^2) or 6 weeks of AVD [actinomycin D (270 mg/kg), vincristine (9 mg/m^2), and doxorubicin (50 mg/m^2)], the 2-year OS reached 39% (14). The European Rhabdoid Registry recommended a standardized dosage of 220.5 μg/kg for cyclophosphamide, 200.4 μg/kg for carboplatin and 59.4 μg/kg for etoposide in 24 weeks known as protocol Rhabdoid 2007. Such protocol achieved a 5-year OS at 20.9% and pointed out that consensus protocol helped to improve the outcome (15). Children's Hospital Los Angeles concluded in an over 20 years study that HDCT benefitted the outcome with a long-term OS at 35.7%. In 2005, the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) conducted a 10-year multinational prospective study of registered cases of eMRTs to test an intensive multimodal approach of treatment named UH-1 for children involving 22.5 mg/m^2 for vincristine, 375 mg/m^2 for doxorubicin, 17,000 mg/m^2 for cyclophosphamide, 3,000 mg/m^2 for carboplatin and 2,500 mg/m^2 for etoposide in 28 weeks. Such a high-dose chemotherapy is much more aggressive than previous ones, and seemed to benefit survival. The 3-year EFS was at 32.3% (95% CI: 23.2–41.6%) and a 3-year OS of 38.4% (16). The advantage in lower stages seemed more obvious, with a 4-year OS at 68.6% for Stage I and 41.7% for Stage II. Brennan *et al.* demonstrate in their 10-year multicenter trial that: higher dose of cyclophosphamide may have contributed to the better outcome in their patients diagnosed after 2002 (17). However, in the recent Beijing study, researchers failed to find improvement of prognosis in 13 patients referred to the UH-1 protocol with 3-year OS at 23.07% (6). Anyway, higher doses and combined use of chemotherapeutics have reached a bottleneck, while such regimens show toxicity-associated mortality approximating at 5% (1,17,18). It was reported that radiotherapy has survival benefits (4,11). More than 50–60% of eMRT cases were suggested for systematic radiation. However, its contribution to prognosis, according to the above data in this research, remains obscure considering lack of appropriate controls.

In 2009, Koga *et al.* reported a 5-month-old male with stage II MRTK and a 24-month-old male with stage III MRTK treated with surgical resection of tumors and chemotherapy of alternating combination of ifosfamide, carboplatin, etoposide and vincristine, doxorubicin, cyclophosphamide, followed by HDCT using etoposide, carboplatin, and melphalan with ASCR. Two patients have been alive without any evidence of disease in 30 and 37 months after diagnosis, respectively (19). A Korean study also approved the active effect of HDCT/ASCR on patients with poor prognostic factors. The OS was 66.7% and EFS of 75.0% with a median follow-up duration of 23.8 months (20). However, another Japanese study pointed out that such advantage no longer existed after balancing selection bias (18). In our study, the only patient who received ASCR died 1 year after diagnosis. In fact, lack of legal access of melphalan is a potential limit for ASCR promotion in China. Due to the small number of present researches, the exact role of HDCT/ASCR rescue in eMRTs is still under controversy.

Since traditional resorts can't promise satisfactory outcomes of eMRTs, scientists turned to focus on more targeted compounds for future treatment. Histological SMARCB1 loss is considered a characteristic mutation in RT. About 95% of MRT cases present SMARCB1 loss histologically, and almost 30% of RT patients harbor a germ line or mutation in SMARCB1 (21,22). SMARCB1 is part of the chromatin remodeling complex SW1/SWF, pivotal in cell cycle control, and functions as a classic tumor suppressor gene. Mutations of other SWI/SNF associated proteins such as SMARCA4 was also reported

to participate in RT pathogenesis (23). Activation of cyclin D due to the loss of SMARCB1 has been illustrated as one of the pathogenetic mechanism behind eMRT. Targeted therapies of CDK inhibitors to cyclin D1 expression silence made disease control in some clinical trials (24). Other alternatives include the histone deacetylase (HDAC) inhibitors like EZH2 (25), a histone methyltransferase, regulating methylation or acetylation patterns of histones in rhabdoid tumors and the recruitment of SWI/SNF complexes target genes, aurora kinase A, as a downstream target of SMARCB1 (24,26-28).

A rich expression of VEGF in rhabdoid tumor gives rise to the rationale of treatment with VEGFR inhibitors. Several case reports have mentioned successful use of Anlotinib in refractory and metastatic sarcoma (29-31). Three patients who respond poorly to traditional treatment in our study are now under experimental treatment of Anlotinib. All of them had apparent shrinkage of tumor on imaging in 2 months. The long-term prognosis is still under observation. What's more, in 2017, Geoerger *et al.* have reported response of refractory eMRT to Pembrolizumab, a PD-L1 blocker. Those new attempt may shed light on further breakthrough in eMRT treatment.

Conclusions

In summary, this retrospective study reviewed the clinical characteristics and outcomes of eMRT cases in our center. Younger age, higher staging was shown to be unfavorable factors for prognosis. The response rate of our current protocol is inferior to peer studies, and recurrence in younger patients remains a major threat to survival. Though, more aggressive strategy in chemo and radiation therapy may help to elevate the outcomes, more specific molecular targets are critical for breakthrough in eMRT treatment.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of SCMC (SCMCIRB-W2021018) and individual consent for this retrospective analysis was waived.

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