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Prognostic Factors and Survival in Non-Central Nervous System Rhabdoid Tumors

Benjamin A. Farber, MD[1], **Neerav Shukla, MD**[2], **Irene Isabel P. Lim, MD**[1], **Jennifer M. Murphy, MD**[1], and **Michael P. La Quaglia, MD**[1]

[1]Pediatric Surgical Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065

[2]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, 12 75 York Avenue, New York, NY 10065

Abstract

Introduction—Non-central nervous system (non-CNS) rhabdoid tumors tend to present at a young age and have an extremely aggressive course, with dismal overall survival rates. Inactivation of the tumor suppressor gene *SMARCB1* has been shown in rhabdoid tumors regardless of anatomic location, suggesting a common genetic basis. We retrospectively analyzed our institutional experience with non-CNS rhabdoid tumors to determine overall survival and prognostic variables.

Methods—We reviewed records of pediatric patients (age <22y) with non-CNS rhabdoid tumor at our institution between 1980 and 2014. Variables evaluated for correlation with survival included: age > or <1.5 years (median) at diagnosis, M1 status, and radiation therapy. The log-rank test was used to compare Kaplan-Meier probability distributions with P values adjusted for multiple testing using the false discovery rate approach.

Results—Nineteen consecutive patients (10 female) with histologically verified rhabdoid tumor were identified. Mean age at diagnosis was 3.2 years (median 1.5y, range 1.3mo–21.8y). Primary tumors were located in the kidney (n=10), head and neck (n=5), and in the liver, thigh, mediastinum and retroperitoneum (n=1 each). SMARCB1 expression was absent in all 10 patients tested. Eight patients had distant metastases at diagnosis. Median overall survival was 1.2 years. Age greater than the median and radiation therapy were associated with better outcome, with a median overall survival of 2.7 years (P=0.049 and P=0.003, respectively).

Conclusion—Survival rates for rhabdoid tumor remain poor, but prognosis is better in older children, regardless of primary tumor location. Because of its rarity, clinical trials with present

Corresponding author: Michael P. La Quaglia, MD, FACS, FRCS (Ed Hon), FAAP, Pediatric Surgical Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone: 212-639-7002/Fax: 212-717-3373, laquaglm@mskcc.org.

agents are difficult to conduct. Further progress will require a focus on therapies targeted at tumor biology rather than anatomic location for non-CNS rhabdoid tumors.

Keywords

Rhabdoid tumor; *SMARCB1*; pediatric cancer

1. Introduction

Malignant rhabdoid tumors (MRTs) are a rare and highly aggressive group of pediatric tumors, accounting for about 2% of renal tumors in childhood [1]. During the first National Wilms' Tumor Study (NWTS), these tumors were identified in the kidney as a rhabdomyosarcomatoid variant of Wilms' tumor [2]; however, since 1981 these tumors have been recognized as a distinct pathologic entity [3]. Between 10–15% of patients with MRTs present with primary CNS disease known as atypical teratoid/rhabdoid tumors (AT/RT) [4, 5]. Although MRTs were initially described as arising from the kidney and have been well described in the CNS, other cases have been identified in various locations, including the liver, lung, and soft tissues [6, 7]. MRTs, regardless of the anatomic site, tend to present at a young age and have an extremely aggressive course with dismal overall survival rates estimated near 23% [5]. In addition to poor overall survival, MRTs in comparison to other pediatric cancers have a high tendency to metastasize early [8]. The tissue of origin of MRTs remains unclear [5, 8]; however, molecular analyses have shown few genetic changes other than the common inactivating mutation of the tumor suppressor *SMARCB1* (also known as *hSNF5, INI1* and *BAF47)* in chromosome band 22q11.2, regardless of their anatomic location, suggesting their common genetic basis [7, 9–13]. Due to their rarity, there is no standardized treatment protocol for MRTs [7] and poor outcomes are common, despite intense chemotherapy and radiotherapy regimens [12]. As such, surgical resection remains central to treatment, and prognostic variables of age, surgery and adjunctive therapies have been evaluated in several studies with varied results [5, 8, 14]. At our institution, the pediatric surgery service typically treats rhabdoid tumors that arise in non-central nervous system (non-CNS) anatomic sites. To better characterize the clinical course and outcome of pediatric and adolescent patients with non-CNS rhabdoid tumors, we analyzed our institutional experience in treating these tumors over a 35-year period, in order to investigate overall survival rates and identify relevant prognostic indicators.

2. Methods

After obtaining institutional review board approval, our institutional database was searched for all patients younger than 22 years of age treated for malignant rhabdoid tumor or atypical teratoid/rhabdoid tumor (AT/RT) between January 1980 and July 2015. The medical records of these patients were reviewed for age at diagnosis, age at diagnosis relative to the full cohort's median age at diagnosis, M1 metastatic status, location of primary tumor (renal or extra-renal), surgical intervention, adjuvant therapies received, and histologic information including *SMARCB1* status. These variables were analyzed for associations with overall survival. The log-rank test was used to compare Kaplan-Meier survival probability distributions, with *P* values adjusted for multiple testing using the false discovery rate

approach. *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using R software (version 3.2.3, R Project for Statistical Computing, Vienna, Austria; www.r-project.org).

3. Results

Nineteen patients (10 female, 9 male) who received treatment at our institution for primary or metastatic non-CNS rhabdoid tumors were identified, with an average age at diagnosis of 3.2 years (median 1.5 y; range, 1.3 mo – 21.8 y). Of these 19 patients, 7 underwent surgery for the primary tumor at other institutions. The anatomic locations of the primary tumors were the kidney (n=10), head and neck (n=5), and the liver, thigh, mediastinum, and retroperitoneum (n=1 each). Histopathologic assessment of *SMARCB1* expression was negative in all 10 patients tested. Metastases were detected at diagnosis in 8 patients, of whom 5 had primary tumors in the kidney; the remaining patients each had a primary tumor in the mediastinum, liver, and left thigh. Patients had metastases in the lung (n=4), brain (n=2), thymus (n=1), and both lung and retroperitoneum (n=1). One patient was diagnosed with a synchronous primary tumor (primitive neuroectodermal tumor of the brain). Surgical margin data were available for review for 17 patients, of whom 8 had R0 resections, 4 had R1 resection, 1 had an R2 resection, and 5 patients only had biopsies performed (Table 1). Median follow-up for all patients was 11.8 months (range, 1.7 mo –16 y). The median follow-up period was 4.2 years (range, 8 mo –16 y) for survivors and 9.8 months (range, 1.7 mo – 2.7 y) for patients who died of disease. Neoadjuvant chemotherapy was given to 8 patients, and adjuvant radiotherapy was administered to 12. Median overall survival was 1.2 years. Only age greater than the median was associated with better outcome, with a median overall survival of 2.7 years (P=0.049). Radiotherapy administration, as part of the multimodal treatment, appeared to be statistically significant with median overall survival of 2.7 years (P=0.002) (Figure 1). However, given our limited sample size, we would caution against a global conclusion based on this P value and we cannot consider radiotherapy to be an independent predictive factor until larger studies have been completed. No survival benefit was observed in association with location of primary tumor or metastatic disease status at diagnosis (Table 2).

4. Discussion

MRTs do not arise in any unique anatomic location; thus, there is no uniform staging system or treatment protocols for these patients. Currently, patients are treated based on protocols classified by the tumor's site of origin [8]. Rhabdoid tumors, regardless of location, continue to have a terrible prognosis. As a rare, aggressive malignancy, there is a dire need for the development of new adjunctive therapies to complement surgical intervention. Surgical treatment of non-CNS MRTs is initially guided by the location. However, preoperative diagnosis is not always possible, as non-CNS MRTs are frequently mistaken for other more common tumors that arise in the location in which they are found [15]. For MRTs presenting in the kidney, the initial management strategy follows that of Wilms tumor. Biopsy of the primary tumor is usually not carried out prior to removal, to avoid rupture of the tumor capsule and consequent spillage of tumor cells [16].

Various chemotherapeutic regimens are used in treating MRTs, including combinations of actinomycin D, carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, methotrexate, and vincristine [1, 7, 8, 14, 17]. While multi-agent regimens are often used, and prior studies have shown that chemotherapy can reduce tumor volume [1], only the inclusion of actinomycin D or doxorubicin in drug regimens has been associated with reductions in the risk of death in a population of non-CNS rhabdoid tumors [14, 17]. In an analysis of patients enrolled in studies conducted by the Société International d'Oncologie Pédiatrique (SIOP) and Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH), patients who received a preoperative regimen of doxorubicin-intensified actinomycin D and vincristine achieved a better response than patients who received actinomycin D and vincristine without doxorubicin [17]. Although chemotherapy plays an essential role in treatment of MRT, our analysis of the 8 (42%) patients who received multidrug chemotherapy regimens, neoadjuvant chemotherapy was not a prognostic indicator for survival. Continuing with our evaluation of adjuvant treatment options, we assessed survival benefit of radiotherapy. Eleven patients (58%) received radiation as part of their multimodal treatment. While the dosage and irradiated field varied between our patients, radiation therapy appeared to result in a statistically significant difference in survival (P=0.002); however, as mentioned previously, larger studies are necessary to definitively show this as a prognostic indicator in survival. Thus, we would conclude that radiotherapy might benefit patients over 1.5 years of age, as others have previously shown [5]. Further studies investigating the utility of radiotherapy in this older age group are clearly warranted.

Studies reviewing patients within the NWTS and trials of the SIOP Renal Tumor Study Group have shown older age at diagnosis portends better survival for renal rhabdoid tumors [1, 5]. Additionally, separate review of extra-renal, extra-CNS rhabdoid tumors also showed older age at diagnosis giving a better prognosis to MRT patients[14]. Our study examining non-CNS rhabdoid tumors similarly shows that age over 1.5 years at time of diagnosis, regardless of anatomic location, has higher overall survival (P=0.049). While this is encouraging, a limitation of our study is the small sample size, which can be attributed to the rarity of this malignancy. National and international collaborative investigations are warranted to enroll a large cohort to further characterize rhabdoid tumors from numerous anatomic locations.

The discovery of a common inactivating *SMARCB1* mutation across all MRTs was a promising step towards directing the search for desperately needed therapeutic options for patients with these tumors. Absence of immunohistochemical staining for *SMARCB1* has already proved to be clinically valuable in confirming the MRT diagnosis regardless of anatomic location [18]. On review of pathology reports of our patients, one was diagnosed with a synchronous primitive neuroectodermal tumor (PNET). While possible diagnoses of metastatic MRT and AT/RT were both considered, after histologic and immunohistochemical analysis, a consensus diagnosis of PNET was made. This patient, however, did not have *SMARCB1* testing conducted due to the year the patient was diagnosed. Had *SMARCB1* testing been conducted, this may have helped elucidate the diagnosis and further assist with treatment selection.

Research has implicated the inactivation of *SMARCB1* in the regulation of *cyclin D1*/CDK4 activation and cell cycle arrest. Restoration of *SMARCB1* expression in deficient cells results in suppression of *cyclin D1* and consequent G1 cell cycle arrest [19, 20]. With this background, as well as *in vivo* studies showing the relation of *cyclin D1* in tumorigenesis of rhabdoid tumors [21, 22], research efforts have progressed to the bedside with a phase 1 multicenter clinical trial exploring CDK4 inhibition in patients with MRT (ClinicalTrials.gov Identifier: NCT01747876). Aside from the loss of *SMARCB1* in MRTs, prior studies that included SNP and exome analysis noted very little variation in MRT genomes[13, 23–25]. Recent studies by Chun et al. found clustering of CG island promoter methylation into two groups that correlated with age at diagnosis, which may provide a biological reason for the apparent survival benefit among older patients[26]. Similar to non-CNS rhabdoid tumors, recent investigations in transcriptomic and epigenetic organization of CNS AT/RTs suggests that these tumors can be subclassified into three distinct molecular subgroups with different preferred locations in the brain, suggesting they may originate from different precursor cells while maintaining their common loss of *SMARCB1*[27].

Another potential target, *EZH2*, which encodes a catalytic subunit of the polycomb repressive complex 2 (PRC2), has similarly been recognized in MRTs. Elevated *EZH2* expression has been observed in primary *SMARCB1*-deficient tumors and pharmacological inhibition of *EZH2* has been shown to induce antiproliferative effects specifically in MRT cell lines with *SMARCB1* deletion [28]. Trials examining the safety and efficacy of EZH2 inhibitors in patients with MRTs are currently under way. Given the dismal prognosis of MRTs despite aggressive chemotherapy regimens, the continued exploration of rational targeted therapies is especially important to achieve progress in managing this disease group.

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Abbreviations

AT/RT	atypical teratoid/rhabdoid tumor
GPOH	Gesellschaft für Pädiatrische Onkologie und Hämatologie (Society for Pediatric Oncology and Hematology)
MRT	malignant rhabdoid tumor
NWTS	National Wilms Tumor Study
PNET	primitive neuroectodermal tumor
PRC	polycomb repressive complex
SIOP	Société International d’Oncologie Pédiatrique (International Society of Pediatric Oncology)

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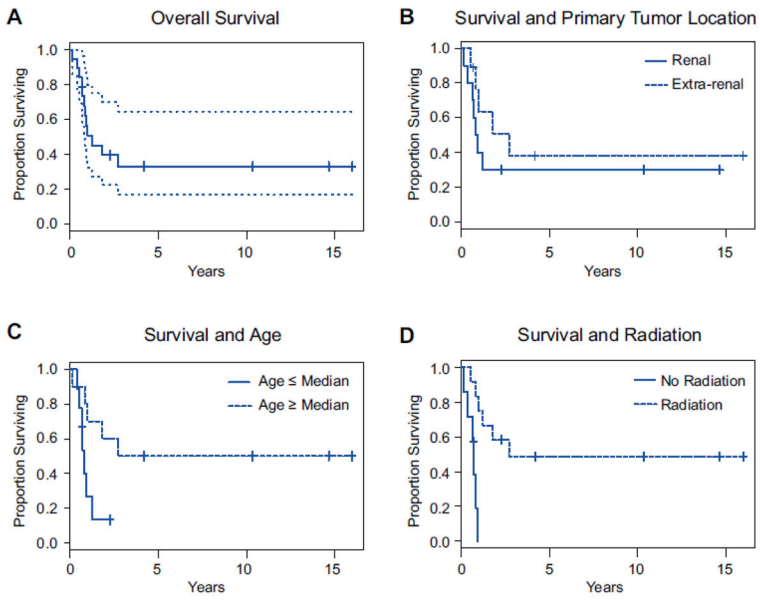

Figure 1. Kaplan-Meier Survival Analyses

(A) Overall survival for the entire cohort. Dotted lines show the 95% confidence interval. (B) Survival stratified by the presence of a renal or extrarenal primary tumor at presentation (*P*=0.321). (C) Survival stratified by age above or below the median age of 1.5 years (*P*=0.049). (D) Survival of patients treated with and without adjuvant radiation therapy (*P*=0.002).

Table 1

Patient Demographics and Disease Characteristics

Pt	Gender	Age at Dx	Alive	Location of Tumor	Mets at Dx	Location of Metastasis	Neoadjuvant Chemotherapy	Radiation	Loss of *SMARCB1*	Resection status	Follow up time
1	F	6.2 mo	No	Kidney	Yes	Brain	No	Yes	--	2	1.2 y
2	M	3.9 y	No	Mediastinum	Yes	Lung	Yes	No	--	Biopsy	10 mo
3	M	2.5 mo	No	Kidney	No	--	No	No	--	0	4.6 mo
4	F	4.9 mo	No	Head/Neck	No	--	Yes	Yes	Yes	Biopsy	6.4 mo
5	M	1.5 y	No	Kidney	Yes	Lung	Yes	No	--	Biopsy	1.7 mo
6	M	1.8 y	Yes	Kidney	No	--	No	Yes	--	0	10.3 y
7	F	8.4 mo	No	Kidney	Yes	Lung	Yes	No	--	0	7.8 mo
8	M	9 mo	Yes	Kidney	Yes	Thymus	Yes	Yes	Yes	1	2.3 y
9	M	3.2 y	No	Head/Neck	No	--	No	Yes	Yes	1	2.7 y
10	F	5 mo	No	Kidney	Yes	Brain	No	No	Yes	1	8.4 mo
11	M	2.2 y	No	Head/Neck	No	--	No	Yes	Yes	Biopsy	11.8 mo
12	F	1.1 y	Yes	Liver	Yes	Lung, Retroperitoneum	Yes	No	--	Biopsy	8.2 mo
13	F	1.3 mo	No	Kidney	No	--	No	No	Yes	0	11 mo
14	F	7.7 y	Yes	Thigh	Yes	Lung	Yes	Yes	Yes	0	4.1 y
15	M	3.6 mo	No	Kidney	No	--	No	Yes	Yes	0	9.6 mo
16	F	6.5 y	Yes	Head/Neck	No	--	Yes	Yes	Yes	0	3.5 y
17	F	6.6 y	Yes	Head/Neck	No	--	No	Yes	--	0	16.0 y
18	M	21.8 y	No	Retroperitoneum	No	--	No	Yes	Yes	Unknown	1.8 y
19	F	1.5 y	Yes	Kidney	No	--	No	Yes	--	1	14.7 y

Table 2

Variables evaluated for correlation with improved survival.

Variable	*P* value*
Age ≥ Median	0.049
Location of Primary Tumor	0.46
Metastasis at Diagnosis	0.53
Radiation Therapy	0.002

*Adjusted for multiple testing using the false discovery rate approach.