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Malignant Rhabdoid Tumors of the Liver Are Associated With Inferior Outcomes Compared to Other Extracranial Rhabdoid Tumors

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ABSTRACT

Background: Extracranial malignant rhabdoid tumors (eMRT) are rare, highly aggressive pediatric neoplasms. While the liver is a relatively common anatomic site of presentation, the clinical course of patients with hepatic eMRT (eMRT-L) is not well described.

Methods: We retrospectively analyzed 30 children affected by eMRT-L treated on a consensus regimen provided by the European Rhabdoid Registry (EU-RHAB). Clinical characteristics, radiology features according to the Pre-Treatment Extent of Tumor (PRETEXT) system, treatment details, and outcome were assessed. We employed patients with rhabdoid tumors of the kidney (RTK; $n = 30$) and other eMRT ($n = 60$) as controls.

Results: Median age at diagnosis was 8 months (range: 0–53 months), 16 of 30 patients (55%) presented with metastatic disease. R0 resection was achieved in seven patients (23%). Most tumors showed PRETEXT Stage ≥3 (66%) and frequently exhibited PRETEXT annotation factors. One-year overall and event-free survivals were both 17% (95% confidence interval: 7.5–37). Compared to RTK

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CR, complete remission; E, extrahepatic tumor; EFS, event-free survival; eMRT, extracranial malignant rhabdoid tumor; eMRT-L, extracranial malignant rhabdoid tumor of the liver; EURHAB, European Rhabdoid Registry; F, multifocal tumor; HDCT, high-dose chemotherapy; HR, hazard ratio; ICE, ifosfamide, carboplatin, etoposide; M, distant metastases; MR, minor response; MRT, malignant rhabdoid tumor; N, lymph node metastases; OS, overall survival; P, portal venous involvement; PD, progressive disease; PR, partial response; PRETEXT, Pre-Treatment Extent of Tumor; PV, pathogenic variant; R, tumor rupture; RT, radiotherapy; RTK, rhabdoid tumor of the kidney; SCUD, small cell undifferentiated liver tumor; SD, stable disease; SIOPEL, Childhood Liver Tumors Strategy Group; TTP, time to progression; V, hepatic venous/inferior vena cava involvement; VCA, vincristine, cyclophosphamide, actinomycin D.

and other eMRT, patients with eMRT-L had significantly inferior outcomes (hazard ratios 2.47 and 4.39, respectively). Complete resection and absence of metastases were associated with improved survival. Consolidation therapies (i.e., radiotherapy or high-dose chemotherapy) were only rarely used.

Conclusions: EMRT-L represents a distinct high-risk subgroup within the eMRT spectrum, characterized by inferior survival despite standardized multimodal therapy. Current treatment approaches demonstrate limited efficacy. Our results highlight the urgent need for prospective, collaborative studies to refine risk stratification and to evaluate novel treatment options.

1 | Introduction

Extracranial malignant rhabdoid tumors (eMRT) are aggressive neoplasms affecting infants and very young children [1]. They are characterized by biallelic inactivation of *SMARCB1* and rarely *SMARCA4*, resulting in loss of function of these components of the SWI/SNF chromatin remodeling complex [2]. Beyond these hallmark alterations, malignant rhabdoid tumors (MRT) typically lack additional recurrent genetic abnormalities [3]. In a subset of cases, tumors arise in the context of a germline pathogenic variant (PV) in *SMARCB1 or SMARCA4*, rhabdoid tumor predisposition syndrome (RTPS 1 or 2) [4].

eMRT occur at any anatomical site, with the kidney—referred to as rhabdoid tumor of the kidney (RTK)—being the most commonly affected [1]. Despite multimodal treatment regimens, the prognosis remains dismal, with long-term overall survival (OS) ranging from 18.5% to 45% [1, 5–7].

A first case of hepatic malignant MRT (eMRT-L) was described in 1982 by Gonzales-Crussi et al. [8]. Subsequent reports have highlighted the tumor's fulminant clinical development and poor response to standard therapy [9]. Nevertheless, robust data on this subgroup remain limited, as most available information comes from isolated case reports and small case series [10].

Up to this point, the prognostic relevance of tumor site in eMRT remains uncertain. Previous publications could not show a significant difference in survival between renal and non-renal tumors, but rarely focused on systematic investigations of specific sites such as eMRT-L [6, 7, 11, 12].

Our present study provides an extensive characterization of eMRT-L in patients of the EU-RHAB registry. We describe the clinical behavior of this rare entity and identify challenges to inform future therapeutic strategies.

2 | Materials and Methods

2.1 | Patient Cohort and Study Design

Inclusion criteria encompassed a primary rhabdoid tumor of the liver, diagnosed according to WHO criteria in patients aged 0–18 years. Written informed consent from legal guardians was required. We obtained basic patient data, such as age, metastatic status, and treatment details, from the European Rhabdoid Registry (EU-RHAB), a collaborative European project dedicated to collecting and analyzing clinical and biological data on pediatric rhabdoid tumors. As part of the data submission process, clinical and treatment information was systematically recorded using structured case report forms completed by the treating institutions. Any missing information was collected through direct contact with the treating sites. Molecular analyses for somatic and germline alterations were performed as described [13, 14] or with locally available methods, including fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, and Sanger or next-generation sequencing of *SMARCB1/SMARCA4*.

The EU-RHAB registry has received continuous ethical approval from the ethics committee of the University of Münster (ID 2009-532-f-S, latest amendment 2021).

2.2 | Comparison Cohorts

To contextualize results, published [6] data from the EU-RHAB registry were updated, and two comparison cohorts (60 patients with eMRT, 30 with RTK) were established. To this end, information on survival and potential events was brought up to date while the underlying patient set remained unchanged. eMRT-L cases were separated from this historical cohort and comprise, together with newly registered cases, the dedicated cohort reported here.

2.3 | Treatment

All patients had been treated according to the EU-RHAB consensus recommendation. Treatment consisted of surgical resection whenever feasible, combined with alternating courses of chemotherapy, including doxorubicin, ICE (ifosfamide, carboplatin, etoposide), and VCA (vincristine, cyclophosphamide, actinomycin D), as well as radiotherapy (RT) or high-dose chemotherapy (HDCT—thiotepa/carboplatin) at the treating physician's choice. Further details regarding the EU-RHAB recommendations are given elsewhere [6, 15].

2.4 | Radiological Assessments

Initial cross-sectional imaging of 27 patients was re-evaluated by an independent pediatric radiologist (22 magnetic resonance imaging [MRI], 5 computed tomography [CT]). Tumors were classified into PRETEXT (Pre-Treatment Extent of Tumor) groups and assigned annotation factors, as defined by Towbin et al. [16]. The PRETEXT system divides the liver into four sections to determine the extent of tumor involvement. Additional annotation factors capture further features: caudate lobe involvement (C), extrahepatic tumor extension (E), multifocality (F), distant

metastases (M), lymph node metastases (N), portal venous involvement (P), tumor rupture (R), and hepatic venous/inferior vena cava involvement (V).

Response to therapy was categorized into complete remission (CR), partial response (PR; >50% reduction), minor response (MR; 25%–50% reduction), stable disease (SD), and progressive disease (PD; increase >25% or new tumor lesions).

2.5 | Statistical Analysis

Statistical comparisons used the Kruskal–Wallis test, chi-square test, and Fisher's exact test. Post hoc pairwise comparisons were performed using Dunn's test and pairwise Fisher's exact tests, with Holm's method applied to adjust for multiple comparisons. Survival outcomes and impact of risk factors were assessed using Kaplan–Meier analyses and univariate Cox proportional hazards models. We defined event-free survival (EFS) as the time from the detection of the tumor to the first progression, relapse, or death from any cause. Overall survival (OS) was defined as the time from detection of the tumor to death due to any cause. Time to progression (TTP) was defined as the time from administration of the first chemotherapeutic agent to the first documented event. All statistical analyses were conducted using R (version 4.4.1) [17].

3 | Results

3.1 | Patient Characteristics

3.1.1 | Demographics and Clinical Data

The characteristics of 30 patients with eMRT-L are summarized in Table 1. Median age at diagnosis was 8 months (range: 0–53 months). Sixteen patients (55%) presented with distant tumor involvement (extrahepatic M^+ or synchronous tumor), including one with a synchronous atypical teratoid rhabdoid tumor. Multifocal hepatic tumors were observed in 10 patients (33%).

We stratified patients into standard-risk ($n = 10$) or high-risk ($n = 20$) groups according to established criteria [1]. Only patients with gross total resection (GTR), absence of a germline (likely) PV, and M0 at diagnosis qualified as standard-risk cases.

Initial serum alpha-fetoprotein (AFP) levels were available in 26 patients (median: 40.35 ng/mL) (Figure S1). In all but one case, AFP values demonstrated physiologic levels for the respective age. The single case with elevated AFP was classified as MRT by both histology and genetic analyses.

3.1.2 | Comparison to Other Cohorts

Patients with eMRT-L were significantly younger compared to other eMRT (8 vs. 18 months, $p = 0.017$). GTR was significantly less frequent compared to RTK (37% vs. 73%, $p = 0.043$), but showed no evident difference compared to other eMRT. Frequencies of germline PV and distant tumor involvement differed significantly overall; however, pairwise comparisons of eMRT-L and other cohorts were unremarkable (Table 1).

3.1.3 | Molecular Genetic Findings

Somatic genetic testing was available for 22 patients, revealing PVs in *SMARCB1* ($n = 21$) and *SMARCA4* ($n = 1$). Alterations were predominantly large deletions; point mutations appeared only in the context of germline variants. Inactivating biallelic variants were confirmed in 19 cases. In the remaining three patients, we identified only one pathogenic allele; the alteration of the second allele most likely remained undetected due to methodological limitations.

DNA-methylation profiling, conducted in nine cases as part of previous studies [18], consistently allocated tumors within the same high-risk subgroup (eMRT high risk I).

Germline analyses were available for 29 patients, revealing germline alterations in two of them.

In all cases, genetic findings were concordant with loss of protein expression on immunohistochemistry.

3.2 | Treatment and Clinical Course

3.2.1 | Chemotherapy and Toxicity

An overview of clinical course, therapy adaptations, and metastatic patterns at diagnosis is depicted in Figure 1. All eMRT-L patients received at least one course of EU-RHAB therapy (mean 5.47 courses), significantly fewer when compared to extrahepatic eMRT (7.18, $p = 0.012$) and RTK (7.0, $p = 0.037$). All available toxicity data showed at least one Grade 3 or 4 hematologic toxicity per patient. Serious adverse events included three cases of veno-occlusive disease (all in patients <7 months, none of whom had received RT or HDCT) and one severe pneumonia. One patient (No. 5) died from septic shock after achieving CR, after the development of uncontrolled arterioportal venous fistulas.

Ten patients initially received non-EU-RHAB chemotherapy, most commonly according to protocols of the International Childhood Liver Tumors Strategy Group (SIOPEL) due to either delayed biopsy or pathology misdiagnosis, resulting in initial treatment for suspected hepatoblastoma. Following progression, therapies were adapted individually.

3.2.2 | Surgical Interventions

In seven patients, an R0 resection of all detectable disease was achieved, eight had R1/R2 resections, and 14 patients underwent diagnostic biopsies only (exemplary case; see Figure S2). Patient No. 8 received a liver transplantation; however, upon retrospective review of imaging, pulmonary metastases had already been present at the time of transplant surgery. Median time to resection was 3.2 months following presentation.

3.2.3 | Consolidation Therapies

RT was administered in five patients (17%), significantly less frequently than in extrahepatic eMRT (65%, $p < 0.001$). Indi-

TABLE 1 | Clinical characteristics by localization.

Characteristic	eMRT-L ($N = 30$)[a]	eMRT ($N = 60$) [a,b]	RTK ($N = 30$)[a,b]	Global p-value[c]
Age (months)	8 (0, 53)	18 (0, 206) **$p = 0.017$***	10 (1, 166) $p = 0.413$	**0.014***
Sex				0.067
Female	10 (33%)	29 (48%)	19 (63%)	
Male	20 (67%)	31 (52%)	11 (37%)	
Germline (likely) pathogenic variant	2 (6.9%)	8 (17%) $p = 0.304$	8 (33%) $p = 0.094$	**0.048***
(NA)	1	13	6	
Distant location involved[d]	16 (55%)	16 (27%) $p = 0.156$	14 (47%) $p = 0.781$	**0.020***
(NA)	1	0	0	
Gross total resection (primary tumor)	11 (37%)	26 (43%) $p = 0.477$	22 (73%) **$p = 0.043$***	**0.008***
Risk group				0.7
HR	20 (67%)	42 (75%)	19 (70%)	
SR	10 (33%)	14 (25%)	8 (30%)	
(NA)	0	4	3	
Number of EU-RHAB courses	5.47 (2.86)	7.18 (2.65) **$p = 0.012$***	7.00 (2.27) **$p = 0.037$***	**0.011***
PD on chemotherapy	19 (63%)	22 (37%) $p = 0.061$	10 (33%) **$p = 0.043$***	**0.021***
HDCT	1 (3.3%)	12 (20%) $p = 0.16$	9 (30%) $p = 0.054$	**0.025***
RT	5 (17%)	39 (65%) **$p < 0.001$***	13 (43%) $p = 0.077$	**<0.001***

Abbreviations: eMRT, extracranial malignant rhabdoid tumor (extrahepatic, extrarenal); eMRT-L, extracranial malignant rhabdoid tumor of the liver; HDCT, high-dose chemotherapy; HR, high risk; RT, radiotherapy; RTK, rhabdoid tumor of the kidney; SR, standard risk.

[a]Median (Min, Max); *n* (%); Mean (SD).

[b]Pairwise post hoc tests (Holm-adjusted, *p*-values), comparing each group to the eMRT-L cohort.

[c]Global test across all three cohorts: Kruskal–Wallis rank sum test; Pearson's chi-square test; Fisher's exact test.

[d]Distant location involved: extrahepatic metastasis/synchronous tumor.

*$p \leq 0.05$ is considered statistically significant.

cations varied: One patient (No. 3) received irradiation as a preventive measure following chemotherapy, while two patients (No. 4 and 9) underwent simultaneous radio-chemotherapy. Two additional patients (No. 6 and 12) were treated in a palliative setting following relapse. Four patients received RT with photons, one with protons. Doses ranged from 19.5 to 45 Gy. One patient (No. 7) received HDCT.

Patients with eMRT-L (20%) received consolidation therapy (RT or HDCT) significantly less often when compared to RTK (57%, $p = 0.02$) and extrahepatic eMRT (70%, $p < 0.001$).

3.2.4 | Treatment Response

CR was achieved in six patients, PR in seven, and MR in five. Four patients demonstrated SD, while the remaining showed insufficient disease control. Among the 18 patients who achieved CR, PR, or MR, the median time from start of chemotherapy to best response was 1.5 months.

3.3 | Survival and Prognostic Factors

Overall prognosis was poor, with 1-year OS and EFS rates both at 17% (95% confidence interval [CI]: 7.5–37) (Figure 2A). Median OS and EFS were 5.6 months (95% CI: 4.4–9.2) and 3.5 months (95% CI: 3–6.1), respectively. At 5 years, OS and EFS were both 10% (95% CI: 3.4–29). All three long-term survivors had localized disease, had undergone R0 resection, and had completed nine courses of chemotherapy.

Events included 23 cases of disease progression or relapse and four deaths (one likely treatment-related). First sites of

progression (PD) were lungs (9), liver (5), and peritoneum (1). Eight patients experienced multifocal relapses/progressions, all involving the liver (four with peritoneal spread, three with pulmonary metastases, and one with mediastinal involvement). Sixty-three percent of patients experienced PD while on chemotherapy. Median TTP was only 2.8 months.

Prognostic analysis indicated that distant metastases, incomplete resection, and high-risk status significantly correlated with inferior survival. Other variables displayed no significant associations (Figure 2B, Table S1).

Compared to patients with eMRT and RTK, patients with eMRT-L had inferior outcomes. Five-year OS was 56% (95% CI: 45–70) in eMRT and 34% (95% CI: 20–57) in RTK. Five-year EFS followed a similar pattern, with 43% (95% CI: 32–58) in eMRT and 35% (95% CI: 22–58) in RTK (Figure 3).

Cox regression confirmed significantly inferior survival for patients with eMRT-L, with hazard ratios (HR) of 4.39 (95% CI: 2.52–7.63, $p < 0.001$) compared to other eMRT and 2.47 (95% CI: 1.36–4.48, $p = 0.003$) to RTK. Direct comparison between eMRT and RTK revealed no significant differences (HR 0.56, 95% CI: 0.31–1.02, $p = 0.058$).

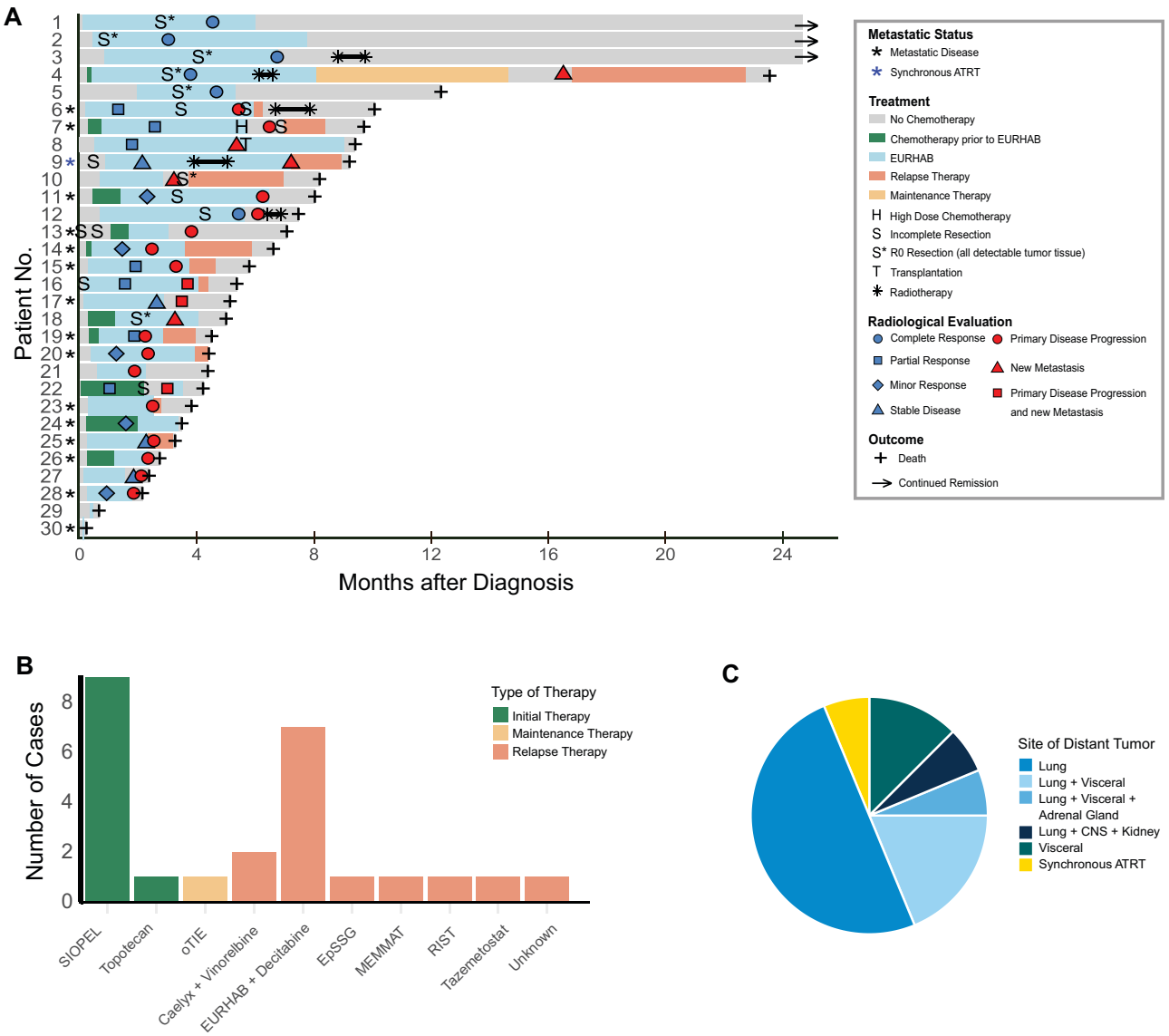

FIGURE 1 | Clinical courses, treatment strategies, and metastatic patterns. (A) Swimmer's plot of 30 patients with eMRT-L. The time points of the best radiological response and first progression/relapse are indicated. Only surgeries aimed at tumor reduction are shown (i.e., no diagnostic biopsies). Data for Patient No. 9 refer only to hepatic disease; the patient died from pelvic metastases and peritoneal carcinomatosis. At the time of abdominal progression, intracranial disease remained stable. (B) Overview of therapy regimens deviating from the EU-RHAB consensus regimen. Only the chemotherapeutic agents actually administered are listed. SIOPEL: International Childhood Liver Tumors Strategy Group (cisplatin, doxorubicin, carboplatin); oTIE: oral trofosfamide, idarubicine, and etoposide; EpSSG: European paediatric Soft Tissue Sarcoma Study Group (vincristine, doxorubicin, cyclophosphamide); MEMMAT: thalidomid, fenofibrate, celecoxib, etoposide, cyclophosphamide, and bevacizumab; RIST: dasatinib, rapamycin. (C) Distribution of extrahepatic tumor sites at diagnosis (16 patients). CNS, central nervous system (1 patient); ATRT, atypical teratoid rhabdoid tumor.

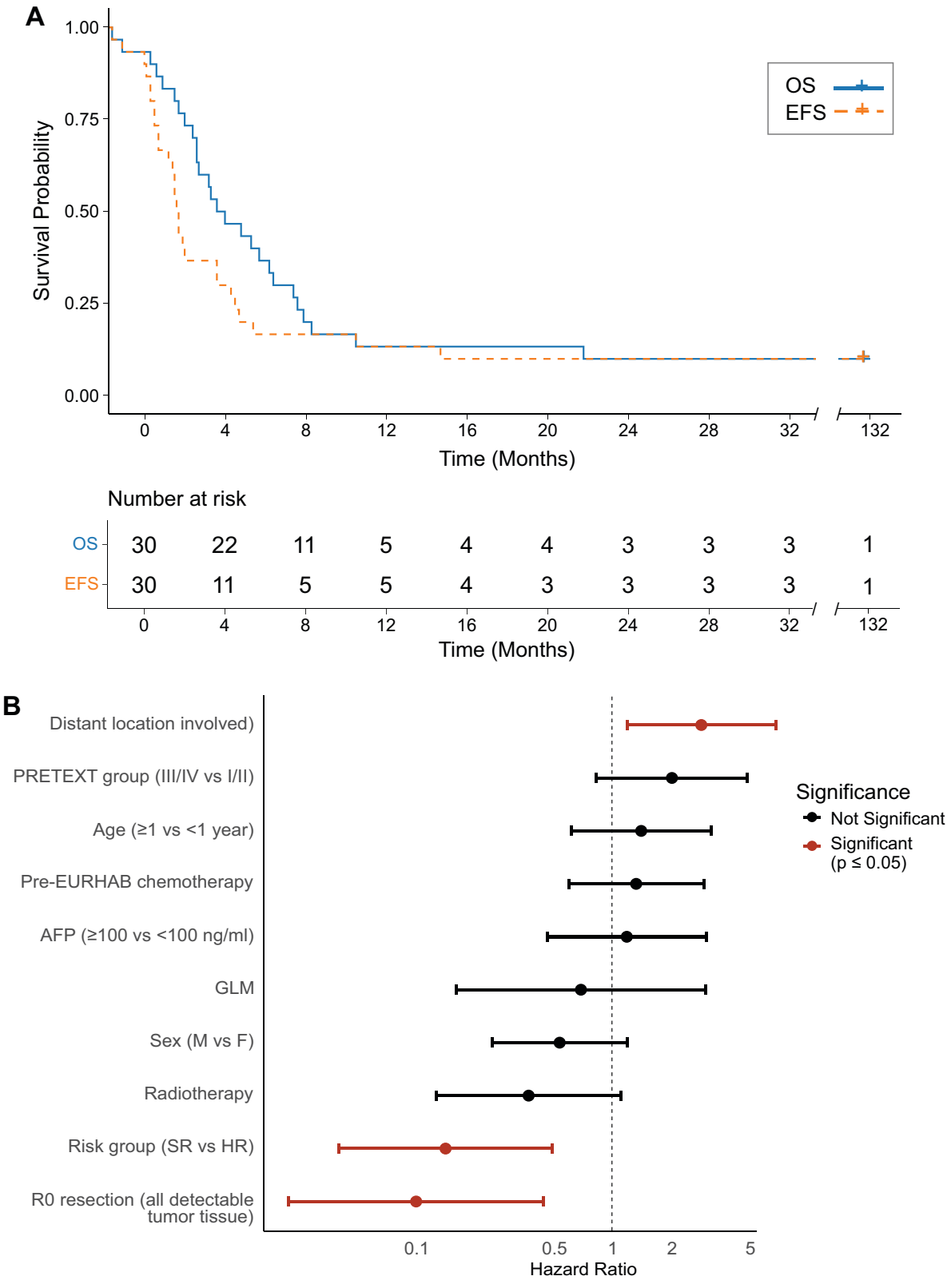

FIGURE 2 | Survival outcomes and risk factors in patients with eMRT-L. (A) Kaplan–Meier curve for overall survival (OS) and event-free survival (EFS). (B) Forest plot of hazard ratios for clinical variables. AFP, alpha-fetoprotein; HR, high risk; SR, standard risk.

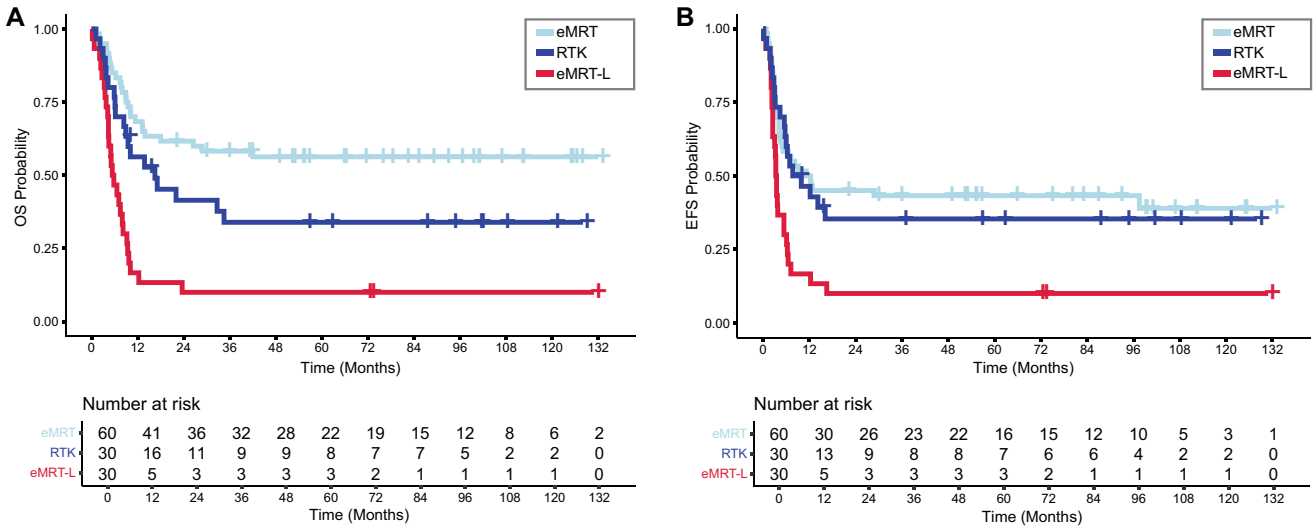

FIGURE 3 | Survival outcomes for overall survival (A) and event-free survival (B) in the different cohorts. eMRT-L, extracranial rhabdoid tumor of the liver; eMRT, extracranial malignant rhabdoid tumor (extrahepatic, extrarenal); RTK, rhabdoid tumor of the kidney.

Age-stratified survival analyses (<12 vs. ≥12 months) are depicted in Figure S3. Among patients less than 12 months, Cox regression indicated an inferior outcome for eMRT-L compared to eMRT (HR 2.86, 95% CI: 1.37–5.88, $p = 0.005$), whereas the difference to RTK was not significant (HR 1.72, 95% CI: 0.85–3.57, $p = 0.13$). In patients ≥12 months, survival of eMRT-L was markedly inferior, with hazard ratios of 7.69 (95% CI: 3.13–20.0, $p < 0.001$) versus eMRT and 5.26 (95% CI: 1.75–16.67, $p = 0.003$) versus RTK.

3.4 | Radiological Findings

Initial imaging available for 27 patients displayed large tumors with a median diameter of 12.6 cm (range: 6.4–21 cm). Exemplary MRI features and treatment responses are depicted in Figure 4A,B. Most patients presented with higher PRETEXT stages, with 44% classified as Stage III and 22% as Stage IV (Figure 4C). PRETEXT annotation factors were highly prevalent (Figure 4D), with extrahepatic disease (E) observed in 70.4% of patients, including six cases of peritoneal carcinomatosis. These were categorized as "E" according to the PRETEXT system, but as distant tumor involvement in the clinical context of Table 1 and Section 3.3, leading to some discrepancy concerning the amount of clinically reported metastases.

Factors P, F, and M were significantly linked to inferior survival. Others were not significantly associated with prognosis (Figure 4E, Table S2).

4 | Discussion

Although the liver is frequently cited as a common primary site in larger series of eMRT [1, 7, 12], data on eMRT-L are scarce. A key diagnostic consideration is the distinction of eMRT-L from small cell undifferentiated hepatoblastoma (SCUD). Current evidence supports the notion that tumors lacking SMARCB1(INI1) expression should be classified as rhabdoid tumors, as it has direct implications for prognosis and treatment [19–21]. In this context, it is noteworthy that in our cohort, AFP levels did not impact survival, and even in the single case with pathologically elevated AFP, MRT diagnosis was unequivocally confirmed by histology and genetic testing.

The most comprehensive summary of eMRT-L data is by Fuchs et al., who performed a case review of 55 published cases of eMRT-L, consisting mainly of single case reports or small series [10]. By including SCUD as presumed eMRT-L, they increased their cohort to 96 patients and reported a 2-year OS of 16% (95% CI: 5–31). Cornet et al. described six patients treated according to protocol EPSSG/NRSTS, with three long-term survivors, all nonmetastatic [22]. Fazlollahi et al. report one remarkable long-term survivor among six patients who presented with pulmonary metastases and achieved durable remission subsequent to aggressive treatment, including R0 resection, chemotherapy, and extensive radiotherapy [23].

In a recent retrospective analysis, Trobaugh-Lotrario et al. reclassified 11 patients initially diagnosed as SCUD and treated as hepatoblastoma as really being eMRT-L, based on loss of SMARCB1(INI1) expression [24]. No patient survived beyond 1.5 years following diagnosis.

Considering therapeutic approaches, the EU-RHAB consensus regimen, while effective in other extracranial MRT [6], demonstrated limited efficacy in eMRT-L. Whether this difference reflects intrinsic biological factors or a combination of high M^+ rates and low resectability remains unclear.

Of note, three cases of veno-occlusive disease occurred in very young patients, possibly related to the combination of young age and hepatic tumor burden. Accordingly, omission of actinomycin D should be considered in patients less than 1 year of age with eMRT-L, given its known association with this toxicity.

Age, a commonly reported favorable prognostic factor in MRT [6, 11, 25, 26] and also observed for eMRT-L by Fuchs et al. [10], was not associated with outcome in our eMRT-L cohort. Upon

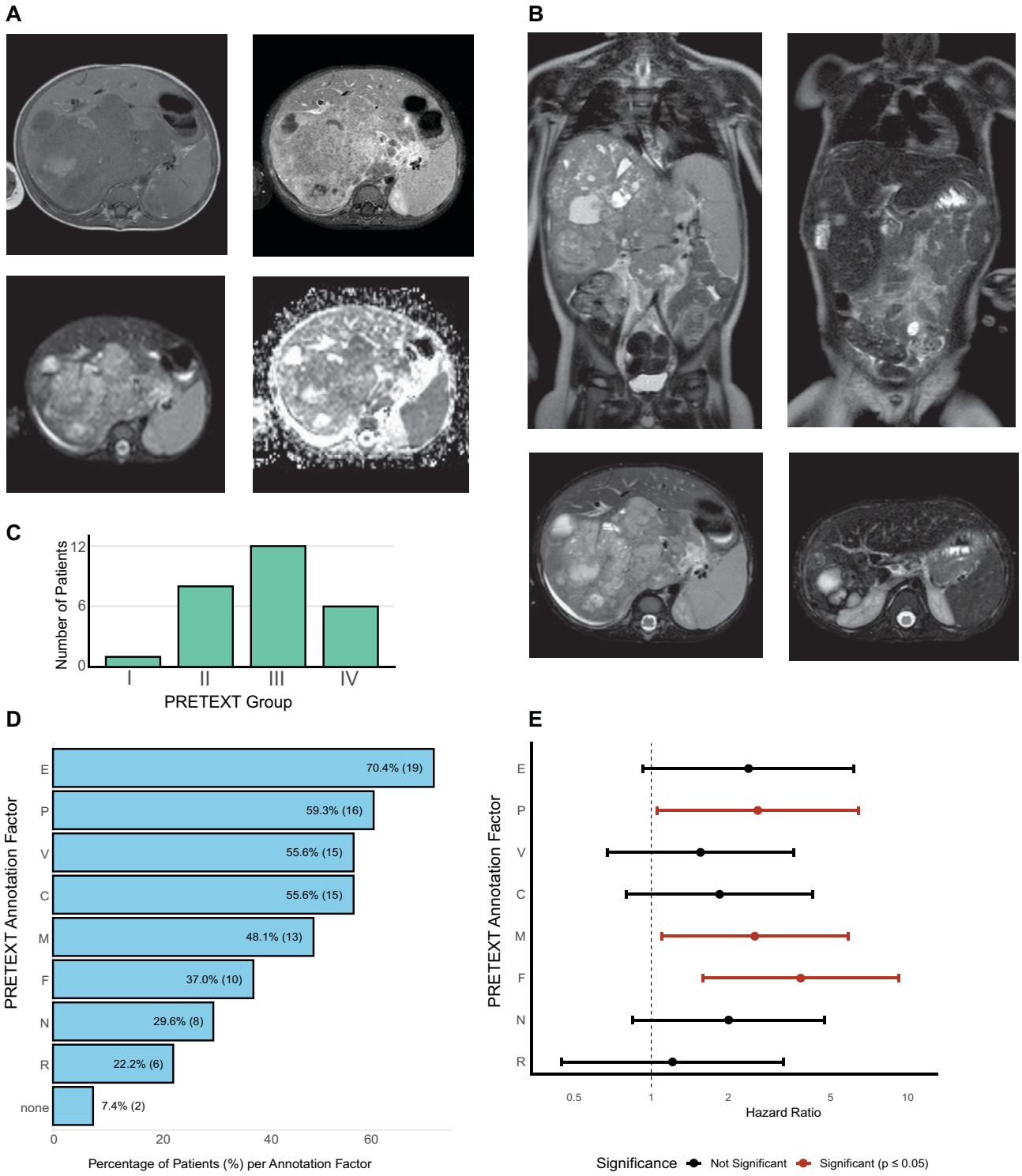

FIGURE 4 | Radiological aspects. (A) Axial MRI images of the tumor at diagnosis (Patient No. 6). Top row: T1-weighted image (left) reveals partially necrotic and hemorrhagic components within the tumor. Fat-saturated, contrast-enhanced T1-weighted image (right) shows heterogeneous enhancement of the lesion. Bottom row: Diffusion-weighted imaging (left) and corresponding apparent diffusion coefficient map show multifocal areas of diffusion restriction. (B) Coronal and axial T2-weighted MRI of the tumor at diagnosis (left) and after four courses of EU-RHAB chemotherapy, prior to tumor-reducing surgery (right). At diagnosis, imaging shows a large, heterogeneous, exophytic tumor originating from the right liver lobe with extrahepatic extension, inferior vena cava occlusion, aortic displacement, and pulmonary and lymph node metastases. Post therapy, marked tumor regression is seen with predominantly cystic residuals in the right liver lobe, regression of extrahepatic spread, restored delineation of the IVC, and normalized aortic position. (C) Distribution of PRETEXT groups. (D) Distribution of PRETEXT annotation factors; proportion and absolute numbers of patients exhibiting each factor. C, caudate lobe involvement; E, extrahepatic disease; F, multifocality; M, distant metastases; N, lymph node metastases; P, portal venous involvement; R, tumor rupture; V, hepatic venous/inferior vena cava involvement; none, patients with tumors without any PRETEXT annotation factors. (E) Forest plot of hazard ratios for individual PRETEXT annotation factors.

age-stratified analyses (<12 vs. ≥12 months), survival was consistently poor and remained inferior to non-hepatic eMRT in both strata. Compared to RTK, outcomes of eMRT-L were likewise inferior, although the difference reached statistical significance only among patients diagnosed at ≥12 months. Given the limited sample size, these findings should be interpreted with caution. Nevertheless, they suggest that age-related treatment restrictions alone cannot explain the unfavorable outcomes observed in eMRT-L and that the primary tumor site likely contributes substantially to prognosis (e.g., through surgical inaccessibility).

Of note, the eMRT comparison cohort appears older than in the originally published EU-RHAB series. This shift results from the methodological separation of patients with RTK and eMRT-L, both with noticeably lower age at diagnosis. Paired with the partially poorer prognosis of these excluded subgroups, long-term survival rates (5-year OS: 56%) of the remaining eMRT cohort appear favorable, but should not be directly compared to other large series including younger patients and more heterogeneous tumor sites, such as the large COG cohort (median age 12 months, 4-year OS: 30.6%) [12] or the French experience (median age 17.5 months; 2-year OS: 47.6%, extrahepatic eMRT only: 53%) [7].

R0 resection had a strong impact on survival but was only rarely achieved. Alternative surgical strategies, such as liver transplantation, have been proposed and warrant consideration in selected cases [27]. Our series highlights the need for careful staging and selection, as illustrated by one case in which undetected pulmonary metastases led to early post-transplantation progression and death.

Consolidative treatment was rarely administered, as many patients did not reach a stage allowing such approaches due to progression. The use of radiotherapy was further limited by the young age of patients, while uncertainty regarding the benefit of HDCT in eMRT and RTK, as shown by retrospective analyses reporting no clear advantage in a cohort of 58 patients with RTK, may have contributed to its restrained use [28].

Although our data did not show a significant benefit of radiotherapy, small numbers and heterogeneous indications preclude definitive conclusions regarding its effectiveness. Other studies have reported a benefit in its use for eMRT [5, 6, 11]. Melchior et al. observed improved outcomes in patients with RTK who received RT and were further able to show survival improvement in patients who were irradiated at higher stages [29]. By contrast, a large series of the EPSSG failed to provide a consistent survival benefit [1, 7]. Similarly, a NWTSG report suggests improved outcomes with RT. However, this effect was no longer evident when adjusting for patient age [30]. Yet, RT merits broader consideration in eMRT-L, particularly in cases of incomplete resection.

Finally, while prior studies suggested inferior outcomes in patients treated within hepatoblastoma protocols [10], initial treatment with SIOPEL regimens had no impact in our cohort, likely due to the early switch to EU-RHAB in most cases. However, even with timely adjustment to a rhabdoid-specific regimen, durable responses remained rare. AFP-negative liver tumors should undergo early biopsy using INI1 immunohistochemistry to prevent misdiagnosis and allow for timely consideration of surgery.

To improve radiologic characterization of eMRT-L, we applied the PRETEXT system, which—although developed and validated for hepatoblastomas—offers a structured and reproducible framework.

Most cases presented with advanced PRETEXT stages and a high number of annotation factors. Only two patients had none, while the remaining 25 showed at least one factor considered high risk in hepatoblastoma [31]. Fuchs et al. similarly reported higher PRETEXT stages (III/IV) in over 85% of patients. In contrast to hepatoblastoma data reported by the Children's Hepatic Tumors International Collaboration (V: 10%, P: 10%, F: 18%, R: 5%, E: 4%) [32], the radiological profile of eMRT-L appears markedly more aggressive. In our series, E was present in over 70%, and more than half of the patients exhibited P and hepatic V. This highly infiltrative growth pattern may help explain the considerable surgical challenge when attempting R0 resection.

Notably, only selected annotation factors (P, F, M) were significantly associated with inferior survival. The PRETEXT stage itself did not correlate with outcome, neither in our cohort nor in prior eMRT-L studies [10]. These findings raise doubts concerning the suitability of PRETEXT as a prognostic tool in eMRT-L. Future adaptations of the system may be needed to capture its distinct growth pattern. Novel approaches will require larger, prospective datasets generated in collaborative clinical trials. Improved radiologic stratification tools may support earlier risk-adapted treatment decisions.

While our findings provide new insights, several limitations must be acknowledged. Despite being the largest dedicated eMRT-L cohort to date, the small absolute number of patients reduces statistical power. The retrospective design and voluntary contribution of data introduce selection bias. Radiologic classification might be affected by inconsistencies of imaging modalities, quality, and protocols. Recent insights into mosaicism suggest possible underreporting of RTPS. This may also explain the comparatively low rate of germline mutations in our cohort [33, 34]. Differentiation between metastatic disease and synchronous tumors was based on clinical and radiological criteria as well as germline mutation status, as molecular analyses comparing tumor tissue from different sites were not available, limiting the accuracy of classification in patients with multifocal presentations. Finally, therapeutic decisions, such as the use of radiotherapy or HDCT and the timing of surgery, were ultimately made by the treating institutions, introducing further variability.

Our findings emphasize the highly aggressive nature of eMRT-L, reflected in a long-term survival rate of only 10%. The results suggest that eMRT-L should be considered a high-risk entity within extracranial MRT, a notion supported by their classification within the same unfavorable high-risk group in recent methylation-based molecular analyses [18].

Given the limited effectiveness of current therapies, intensification or innovative treatment strategies are necessary. Prospective trials evaluating novel and targeted therapies such as immune

checkpoint inhibition [35, 36] or epigenetically active agents [37, 38] are needed [39].

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Conflicts of Interest

J. Gerss: consulting fees from Ecker + Ecker, QUIRIS Healthcare, TESARO Bio; honoraria from Roche Pharma and TESARO Bio; payment for TOMAHAWK study, University Clinics Schleswig-Holstein (Germany), Ruxo-BEAT trial, RWTH Aachen University (Germany), and EMERGE Cryo study, ASKLEPIOS proresearch (Germany). R. Furtwängler: teaching fees from Recordati Rare Diseases. The remaining authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Figure S1: AFP level at diagnosis. **Figure S2**: Intraoperative findings in Patient No. 11 with eMRT-L and pulmonary metastases. (A and B) Intraoperative views of the liver: large tumor with infiltration of the mesocolon. (C) View during pulmonary metastasectomy. (D) Preoperative coronal T2-weighted MRI showing extent of the hepatic tumor. **Figure S3**: Overall survival by age at diagnosis and subgroup. (A) Patients less than 12 months at diagnosis. (B) Patients ≥12 months at diagnosis. eMRT-L: extracranial rhabdoid tumor of the liver; eMRT: extracranial malignant rhabdoid tumor (extrahepatic, extrarenal); RTK: rhabdoid tumor of the kidney. **Table S1**: Univariate Cox-Regression Clinical Factors **Table S2**:Univariate Cox-Regression PRETEXT Annotation Factors