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Original article

EXTRARENAL NON-CEREBRAL MALIGNANT RHABDOID TUMOR IN CHILDREN: DOES MAINTENANCE CHEMOTHERAPY PLAY A ROLE IN SURVIVAL?

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Abstract

Introduction: Malignant rhabdoid tumor (MRT) is a highly aggressive disease, mainly affecting infants and small children.

Material and methods: Between January 2007 and May 2021 a retrospective study was conducted at the Hospital de Pediatría J. P. Garrahan in Buenos Aires, Argentina, including 13 patients diagnosed with ERNC-MRT (extra-renal non-cerebral malignant rhabdoid tumor). Event-free survival (EFS) and overall survival (OS) were assessed using the Kaplan-Meier method and compared using the log-rank test.

Results: Seven patients were less than 1 year old, all of them died. Four of 13 had metastatic disease, all of them in the lungs, 2 had locoregional lymph node involvement. Six achieved complete remission, 4 of them remained alive. Five received maintenance therapy (MT) with cyclophosphamide/vinorelbine, 4 were alive at last follow-up. Only one was studied for germline mutations, the result was negative. With a median follow-up of 126 months (range: 72-161), 3 and 5-year EFS and OS were 30.7% and 38.4%, respectively.

Discussion: Although the sample size is small, survival rates are similar or slightly lower than other series. Age was the main prognostic factor. All but one patient that received MT are alive, suggesting that MT might have a role in ERNC-MRT; however, the prognostic significance is not entirely clear since there are multiple confounding factors.

Key words: rhabdoid tumor, extracranial, children, chemotherapy, maintenance chemotherapy

Resumen

Tumor rabdoide maligno extrarrenal extra- cerebral en niños: ¿tiene el mantenimiento un rol en la sobrevida?

Introducción: El tumor rabdoide maligno (TRM) es una enfermedad altamente agresiva que afecta principalmente a lactantes y niños pequeños.

Materiales y métodos: Entre enero de 2007 y mayo de 2021 se realizó un estudio retrospectivo en el Hospital de Pediatría J. P. Garrahan de Buenos Aires, Argentina, incluyendo 13 pacientes diagnosticados con tumor rabdoide maligno extrarrenal extra-cerebral. La sobrevida libre de eventos (SLE) y la sobrevida global (SG) se evaluaron mediante el método de Kaplan-Meier y se compararon mediante la prueba de rango logarítmico.

Resultados: Siete pacientes tenían menos de 1 año al diagnóstico y todos fallecieron. Cuatro de 13 tenían enfermedad metastásica, todos ellos en los pulmones, 2 tenían afectación ganglionar loco-regional. Seis alcanzaron la remisión completa, 4 de ellos sobrevivieron.

Cinco recibieron terapia de mantenimiento (TM) con ciclofosfamida/vinorelbine, 4 estaban vivos en el último control. Solo uno fue estudiado para mutaciones de línea germinal, el resultado fue negativo. Con una mediana de seguimiento de 126 meses (rango: 72-161), la SLE y la SG a 3 y 5 años fue de 30.7 % y 38.4 %, respectivamente.

Discusión: Aunque el tamaño muestral es pequeño, las tasas de sobrevida son similares o ligeramente inferiores a otras series. La edad fue el principal factor pronóstico. El uso de TM prolongó significativamente la sobrevida; sin embargo, la importancia pronóstica no está del todo clara ya que existen múltiples factores confundidores.

Palabras clave: tumor rabdoide, extracraneal, niños, quimioterapia, quimioterapia de mantenimiento

KEY POINTS

- Malignant rhabdoid tumor is a highly aggressive, extremely rare disease, with poor prognosis.
- Treatment modalities include surgical resection (if feasible early and completely), intensive multidrug regimen, and radiotherapy when possible.
- In our series, survival rates were similar to other series reported by high income countries.
- Maintenance therapy could play a role in extrarenal non-cerebral malignant rhabdoid tumors; however, more studies are necessary to reach definitive conclusions.

Malignant rhabdoid tumor (MRT) is an extremely aggressive cancer initially described in small children with kidney tumor location[1]. The disease occurs predominantly in infants younger than 1 year old, accounting for 14% of soft tissues sarcomas in this age group. The yearly rate is 5 per million in infants, decreasing to 0.6, 0.1, and 0.04 per million in children in the age groups of 1-4, 5-9, and 10-14 years, respectively[2,3].

The most common primary site is central nervous system (CNS) (65%) in which it is called Atypical Teratoid/Rhabdoid Tumor (ATRT) and has distinctive clinical and molecular features[3-4]. In the extra-CNS location, the most common primary site is the kidney, especially in children under one year of age[5], while in ERNC-MRT, the location is variable, and the median age is 16.8 months[3,6].

Hypercalcemia was reported with variable frequency, presenting in approximately 9.5% of rhabdoid tumors of the kidney (MRTK)[7]. The association between SWI/SNF chromatin remodeling complex deficiency and hypercalcemia has been described[8].

MRT are characterized by biallelic mutations with loss of function in the SMARCB1 gene, which is a tumor suppressor gene encoding for INI1, or rarely in the SMARCA4 gene (5% of cases) that encodes for RG1[9]. Approximately 25-30% of patients have non-pathogenic germline mutations in SMARCB1 or SMARCA4 and typically they present before the first year of life, frequently with multifocal tumors and extensive disease. Germline pathogenic mutations in SMARCB1 mostly occur as de novo mutations[6], meanwhile, SMARCA4 germline mutations are inherited in more than 50% with incomplete penetrance[10].

Five DNA methylation subgroups have been described: Group 1 – "ATRT-MYC-like", Group 2 – "ATRT-TYR-like", Group 3 – "RTK-like", Group 4 – "Extrarenal MRT-like", Group 5 – "ATRT-SHH-like"[11]. EC-MRT (extracranial-MRT) often shows similarities with the ATRT-MYC-like subgroup in terms of DNA methylation[12]. Until now, it is uncertain whether this characteristic holds any therapeutic significance.

Regarding risk factors, patients less than 1 year and male sex were reported as the group with the worst prognosis[13]. Recently, there have been described two distinct risk groups: standard risk (localized disease, complete surgical resection of primary tumor, and no hereditary genetic mutation), that exhibited a 5-year OS rates 72.2 ± 9.9, and high-risk group (distant metastasis, incomplete tumor resection, and/or presence of a germline mutation), with notably lower 5-year OS rates 32.5 ± 6.2%[14].

Treatment modalities are not uniform due to the rarity of the disease and includes surgical resection (if feasible early and complete), intensive multidrug regimen with high dose of alkylating and anthracyclines, and radiotherapy when possible[1, 6, 13, 15].

The aim of our study was to report the clinical and epidemiological features, therapeutic mo-

dalities, and results in terms of overall and EFS (event-free survival) in a series of patients with ERNC-MRT (extrarenal non-cerebral malignant rhabdoid tumors) treated at a single paediatric centre in Argentina.

Materials and methods

A retrospective study was conducted including 13 patients diagnosed with ERNC-MRT between January 2007 and May 2021 at Hospital de Pediatría J. P. Garrahan, through review of clinical charts. In all patients MRT was histologically diagnosed and confirmed by loss of nuclear expression of INI-1 and/or deletion of the SMARCB1 gene. The patients were staged according to the recommendations of the EpSSG NRSTS 2005 Treatment Protocol[13]. In patients with unresectable tumors at diagnosis the initial surgical approach was biopsy. For postoperative tumor staging the criteria of the Intergroup Rhabdomyosarcoma Study (IRS) was used[16].

The patients received multimodal treatment consisting of surgery, chemotherapy with age- and weight-adapted dose according to the EpSSG-nonRMS2005 protocol[13], EpSSG-nonRMS 2019 addendum[17] or MUV-ATRT[4], and radiotherapy in few cases due to age (radiation therapy was given to patients over 36 months of age per protocol and to those in a palliative care setting according to the criteria of treating physician). Patients who successfully controlled the disease with the initial therapy received MT (maintenance therapy) with Vnb/ Cy (cyclophosphamide/vinorelbine), according to Institutional decision[18]. Adverse events were classified according to the National Institute of Cancer criteria of terminology for adverse events (CTCAE) version 4.0[19]. EFS and OS (overall survival) were assessed using the Kaplan-Meier method, compared using the log-rank test, and analyzed using the Statistical Program Graph Pad Prism version 5.0.

The article was approved by the ethics committee of the Hospital Prof. Dr. Juan P. Garrahan. The article meets the conditions for publication since the confidentiality of patient data has been preserved. As this is a retrospective study, whose information comes from the medical reports, the ethics committee ruled that informed consent text was not necessary.

Results

Thirteen patients were included in the study. Male/Female ratio was 0.6/1.

Clinical features (Table 1)

Median age at diagnosis was 10 months (range: 1-69 months). Seven patients were younger than one year old and in three cases were congenital as defined by diagnosis within the first 4 weeks of life, with a prenatal diagnosis in 2 of them. Three were older than 24 months. The median time from symptom onset to diagnosis was 1.18 months (range: 0.3-4.6), while median time from hospital admission to diagnosis was 0.43 months (range: 0.23-1.48).

Primary tumor site was paraspinal in 4, thoracic 4, liver 3, cavum 1 and cervical 1 (Fig. 1). The most frequent symptom was tumor in 6 patients, followed by spinal cord compression in 4 (Fig. 2).

Figure 1 | Distribution according to primary site

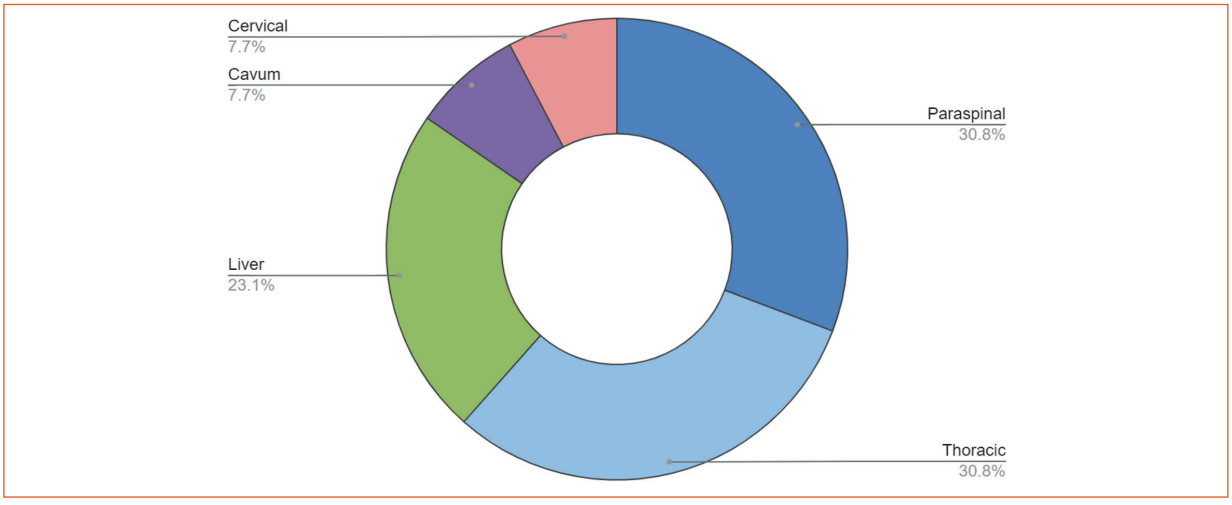
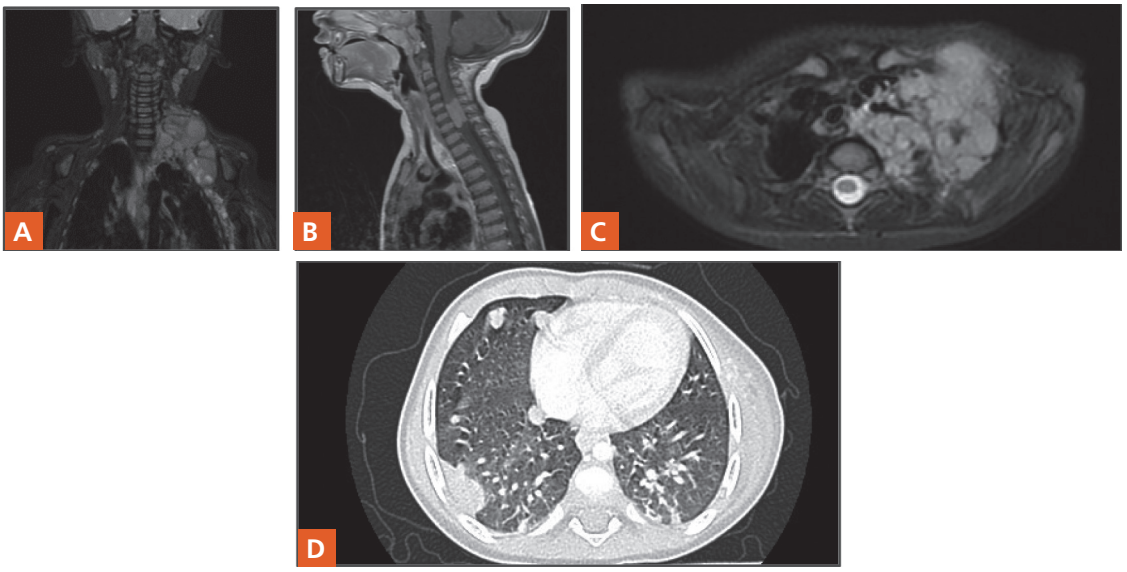


Figure 2 | Example of a 13-month-old patient with primary paraspinal tumors with metastatic lung disease and spinal cord compression at diagnosis. A: Coronal MRI-STIR: Heterogeneous mass with extension to cervical spinal canal. B: Sagittal MRI-T1: Intradural lesion. C: Axial MRI-STIR: Extension and characteristics of tumor. D: Chest CT: Metastatic nodular lung lesions



One patient had locoregional lymph node involvement and 4 had metastatic disease: 3 in the lung and 1 combined lung with locoregional lymph node involvement.

Four patients had hypercalcemia with a maximum level of 16 mg/dl (range: 10.5-16).

Histological, immunohistochemical, and molecular diagnosis

In all patients, the diagnosis was performed based on histological findings, and loss of nuclear expression of INI-1 by immunohistochemical analysis. Determination of the SMARCB1 gene was performed using FISH in 10 patients with a positive result in 6 cases and a negative result in 2 cases. Two samples were not evaluable (Table 1).

Therapeutic modalities (Table 2)

The initial surgical procedure was complete resection in 4 patients [2 IRS I, 1 IRS II, 1 IRS III (rupture during surgery)], surgery for spinal decompression (IRS III) in 4, biopsy only (IRS III) in 5.

Eleven patients received chemotherapy treatment (Table 1). Five received MT after completing chemotherapy. The main adverse event was hematological toxicity (9/10 patients had grade 3-4 toxicity). There were no treatment-related deaths.

After neoadjuvant chemotherapy, complete surgical resection could be performed in 2 patients, both IRS I.

Four patients received radiotherapy, 3 of whom were older than 36 months (one after complete resection, other after subtotal resection, and the third, cavum unresectable, as the only local treatment). One patient under one year of age received radiotherapy with an adapted dose in a palliative care setting.

Two patients underwent biopsy only, without further treatment, considering the rapid progression of the symptoms, with metastatic disease in one case and congenital disease in the other.

Outcome

Six patients completed treatment and achieved CR (3 with surgery, 1 with surgery and radiotherapy and 2 with radiation therapy only), 5 of them received MT and 4 are alive. The only patient who achieved CR but did not receive MT was due to CNS relapse shortly after completing treatment.

Table 1 | Clinical, immunohistochemical and molecular features

Pt	Sex	Age (month)	Primary Site	Presenting symptom	Hyper Ca (mg/dl) (month)	Time to diagno-sis	Stage	Metasta-tic site	INI1 (-) (IHQ)	del 22q11.2 (FISH)
1	F	14	Liver	*Abdominal tumor	10 8.1	1.18 2.7	M* M*	Lung Lung	Loss Loss	ND Negative
2	M	3	Liver	*Abdominal tumor *Congenital				Loco-regional nodes		
3	M	33	Liver	*Abdominal tumor *Constipation	8	2.1	L	-	Loss	Positive
4	F	10	Cervical	*Tumor	9.5	0.7	L	-	Loss	NE
5	M	14	Paraspinal (Cervical)	*Spinal cord compression *Lower limb paresia	11#	0.8	M*	Lung	Loss	Negative
6	F	7	Paraspinal (Thoracic)	*Spinal cord compression *Pain *Loss of developmental milestones *Lower limb paresis	9.5	1.8	L	-	Loss	Positive
7	F	69	Cavum	*Palpebral ptosis *Cordal dystonia *Weight loss	9.5	4.6	L	-	Loss	NE
8	F	1	Thoracic (scapula)	*Tumor *Congenital	10.5#	1.18	L	Loco-regional nodes	Loss	Positive
9	F	51	Thoracic (Costal)	*Tumor	16#	3.6	L	-	Loss	ND
10	M	9	Paraspinal (Dorsal-cervix) Thoracic	*Hemiparesis *Bitonal voice *Loss of developmental milestones *Stiff neck *Difficulty breathing	10.8#	0.3	L	-	Loss	ND
11	F	1	Thoracic	*Swallowing disorders *Congenital	9.1	0.4	L	-	Loss	Positive
12	M	9	(Dia-phragm)	*Cough and difficulty breathing	8.7	1.48	M*	Lung	Loss	Positive
13	F	45	Paraspinal (Dorsal cervix)	*Abdominal and back pain *Urinary incontinence and bladder balloon *Lower limb paresia *Stiff neck	9.9	0.69	L	-	Loss	ND

M: male; F: female; M: metastatic; L: localized; ND: not done*
Congenital: detection within the first 4 weeks of life

Table 2 | Treatment modalities

Pt	Chemotherapy	Surgery (Up-front)	Surgery (After chemotherapy)	Radiotherapy (radiotherapy dose)	Event (months to dg)	Outcome (month to dg)
1	VDCy (1,10, 13, 22, and 28) VCR (2, 3, 11, 12, 14, 15, 23, 29, and 30) CyCE (4, 7, 16, 19, and 25) VNB 25 mg/m²/IV d 1, 8, 15. CFM 25 mg/m²/d PO. (24 m)	Biopsy IRS III	Post 5to. IRS I	No because of age	-	NED (107.3 m)
2	VDCy 1, Progression of lung disease → VNB 25 mg/m²/IV d 1, 8, 15. CFM 25 mg/m²/d PO 30d. → †	IRS III (Tumor rupture)	-	No because of age	PD (local & metastatic) (1.61)	DOD (3.6 m)
3	VDCy (1,10, 13, 22 y 28) VCR (2, 3, 11, 12, 14, 15, 23, 29, and 30) CyCE (4, 7, 16, 19, and 25) VNB 25 mg/m²/IV d 1, 8, 15. CFM 25 mg/m²/d VO. (6 m)	IRS I	-	No because of age	-	NED (128.1)
4	VDCy (1) Progression → †	Biopsy. IRSIII	-	No because of age	PD (local) (0.07)	DOD (0.49)
5	No treatment	Decompressive Laminectomy IRS III	-	No because of age	PD (local) (0.53)	DOD (0.72)
6	VDCy (1,10, 13) VCR (2, 3, 11) CyCE (4, 7) → Progression → †	Decompressive laminectomy IRS III	-	No because of age	PD (local) (3,1)	DOD (0.72)
7	VDCy (1,10, 13, 22, and 28) VCR (2, 3, 11, 12, 14, 15, 23, 29, and 30) CyCE (4, 7, 16, 19, and 25) VNB 25 mg/m²/IV d 1, 8, 15. CFM 25 mg/m²/d VO. (28 m) Progression → †	Biopsy. IRS III	-	(50.4 Gy)	PD (local) (36.7)	DOD (43.2)
8	VDCy (1,10, 13, 22, and 28) VCR (2, 3, 11, 12, 14, 15, 23, 29, and 30) CyCE (4, 7, 16, 19, and 25) Progression → †	IRS I	-	No because of age	PD (metastatic) (7.9)	DOD (8.3 m)
9	VDCy (1,10, 13, 22, and 28) VCR (2, 3, 11, 12, 14, 15, 23, 29, and 30) CyCE (4, 7, 16, 19, and 25) VNB 25 mg/m²/IV d 1, 8, 15. CFM 25 mg/m²/d. PO. (6.3 m)	Biopsy IRS III	Post 2°. IRS I	(50.4 Gy)	-	NED (155.6 m)
10	Doxorubicin/VCR-CFM (1, 2) progression → †	IRS III Decompressive laminectomy	-	No because of age	PD (local) (1.3 m)	DOD (1.84 m)
11	No treatment	Biopsy. IRS III	-	No because of age	PD (local & metastatic) (0.26 m)	DOD (0.49 m)
12	CE (1) VDCy (0, 4, 8) - IE (2, 6) progression → †	Biopsy IRS III	-	15 Gy palliative	PD (local) (2.47 m)	DOD (4.21 m)
13	VDC (1,10, 13, 22 y 28) VCR (2, 3, 11, 12, 14, 15, 23, 29 y 30) CyCE (4, 7, 16, 19 y 25) VNB 25 mg/m²/IV d 1, 8, 15. CFM 25 mg/m²/d. PO. (7.9 m)	IRS III Decompressive laminectomy	-	50.4 Gy	-	NED (72.8 m)

VDC: vincristine/doxorubicin/cyclophosphamide; VCR: vincristine; CFM: cyclophosphamide; VNB: vinorelbine; CyCE: cyclophosphamide/carboplatin/etoposide; CE: carboplatin/etoposide; IE: ifosfamide/etoposide; NED: no evidence of disease; DP: disease progression; †: died of disease; dg: diagnosis

The most common event was progression during treatment, 5/13, who died with a median survival of 3.6 months (range: 0.4-8.3).

The other 2 remaining patients did not receive treatment, and both died at 8 and 16 days after diagnosis.

Survival

With a median follow-up of 126 months (range: 72-161), 3 and 5-year EFS and OS were 38.4% and 30.7%, respectively (Figure 3 a-b). Taking into account the 11 patients who received treatment, the 3 and 5-year EFS and OS were 45.4% and 36.3%, respectively.

All congenital MRT (3 patients) died with a median of 3.5 months (range: 0.4-8). One of them received only palliative treatment. In patients younger than 12 months 3-year EFS and OS was 0%.

The 3-year OS for paraspinal sites was 25%, with a median survival of 2.7 months. The only survivor patient was older than 24 months and was the only one in the group that received radiation therapy.

For hepatic sites, the OS was 66%. One patient died at 3.6 months, the other 2 patients were alive at 107.8 and 128.1 months, respectively. The 3 patients received treatment according to EpSSG NRSTS, without radiotherapy.

Four of 5 patients who received MT are alive, (including 1 with metastatic disease and 1 with unresectable disease - paraspinal location-). The patient who died had an unresectable cavum tumor and survived 49 months since diagnosis. The 3 and 5-year EFS and OS of this group were 100% and 80%, respectively.

The survival rate according to age at diagnosis, primary site, sex, disease stage and type of surgical resection are depicted below (Fig. 4 A-E).

Discussion

MRT are rare, highly aggressive cancers with a high mortality rate[1, 3, 6]. The OS rate in our series was 38.4%, similar to that reported by EpSSG[13], and worse than that reported by the EU-RHAB registry, of 50.1%[14] and by French Group (treatment strategy according to EpSSG-nonRMS addendum 2019), of 47%[17].

All patients showed absence of INI1 expression by immunohistochemistry. SMARCB1 deletion was not found in 2 cases. Negative results could be related to either intragenic mutations (beyond the FISH resolution) or epigenetic silencing of SMARCB1 by microRNA activation[20].

As reported, in our series, survival was significantly worse in children under 1-year old[21,22], being even worse in children with congenital tumors. In our series, congenital rhabdoid tumor 3-year OS was 0% vs 12.6% reported in the literature[23]. Although the worse prognosis of patients under 1 year old was typically related to the lower intensity of treatment[1], the relationship between germline mutation, younger age at diagnosis, and a more aggressive behavior is currently known[22-24]. Only one patient in our series was studied for germline mutations in SMARCB1 or SMARCA4, the result was negative.

Figure 3 | A: Event-free survival. B: Overall survival

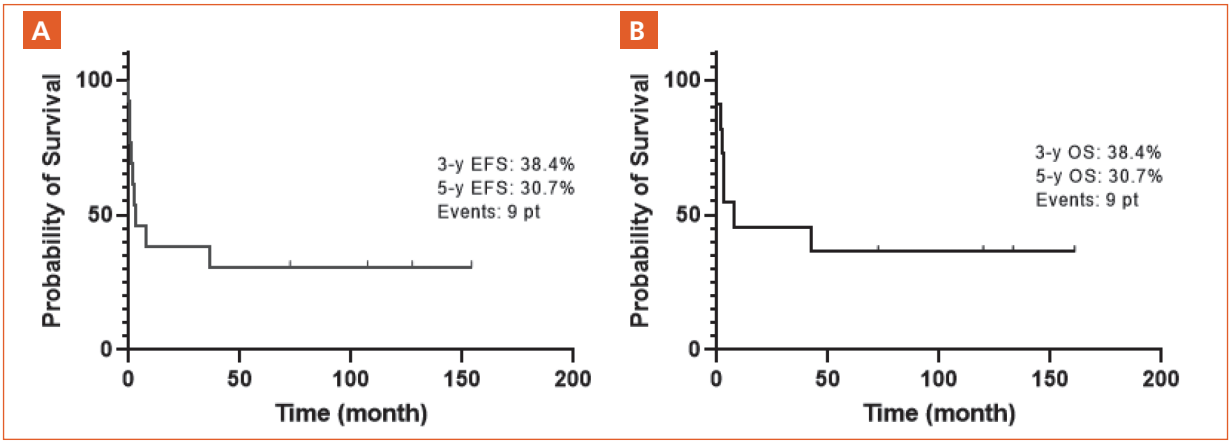
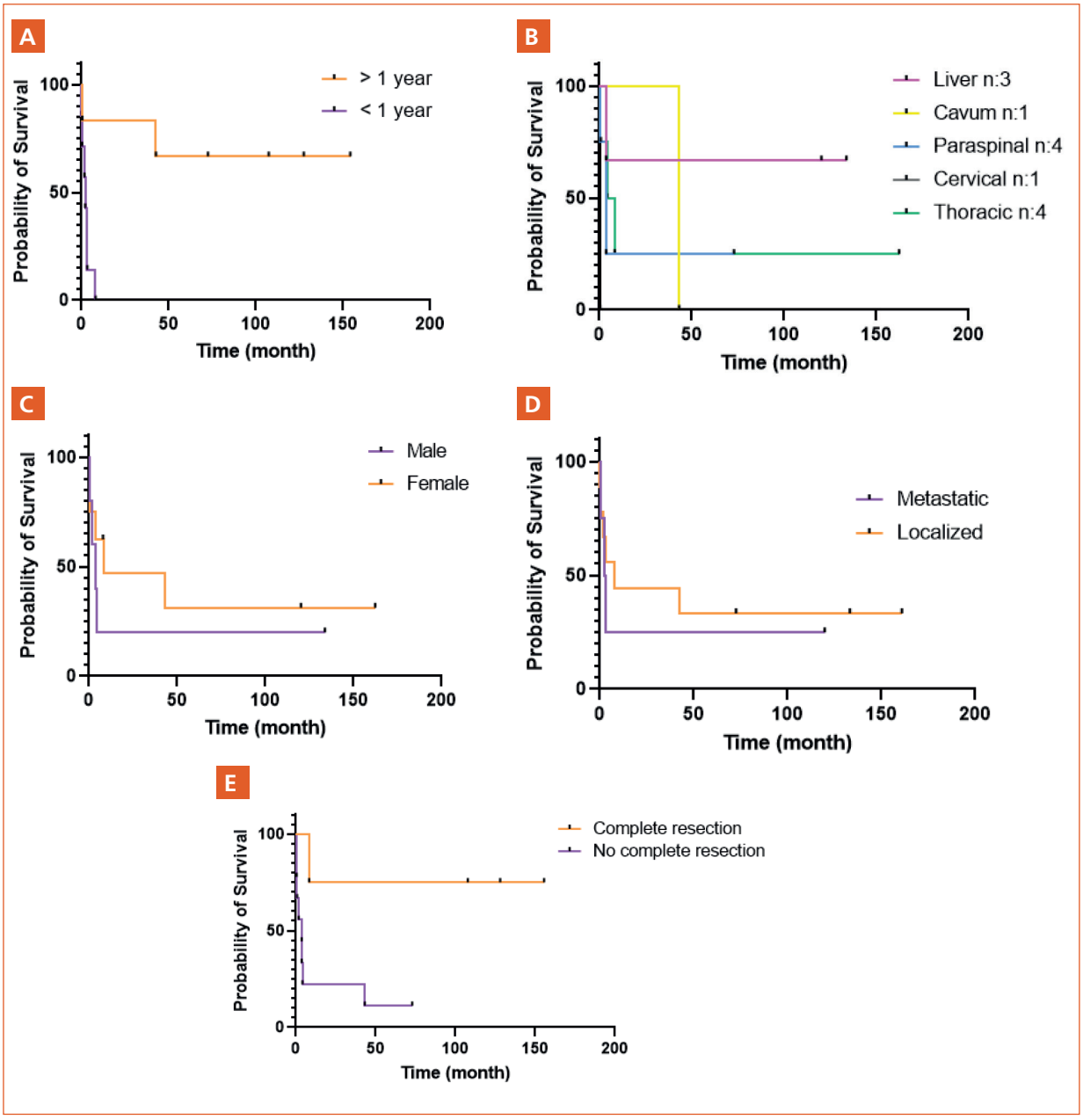


Figure 4 | A: Overall survival according to age, p= 0.0063. B: Overall survival according to localization, p=0.12. C: Overall survival according to patient sex, p= 0.5. D: Overall survival according to disease stage, p= 0.7. E: Overall survival according to surgical resection, p= 0.02



The most frequent metastatic site was the lungs, similar to other series[13, 23]. The presence of metastases is one of the main adverse prognostic factors described, although in our series we did not observe a statistically significant difference between localized and metastatic MRT; this was probably due to the low number of patients.

ERNC-MRT primary site described is variable. In some series the most common site was genitourinary non-bladder/prostate region, followed by the liver and paraspinal region, while for others the head and neck region are more frequent, followed by the liver[3, 13]. In our series, the paraspinal and thoracic location were more frequent, followed by the liver.

The paraspinal location had, in our series, the worst outcome, this could be due to the limitation to perform complete surgical resection and radiotherapy since most patients in this group were younger than 24 months.

Regarding hepatic localization, Trobaugh-Lotrario et al[25] reviewed 34 hepatic MRT and they showed a high mortality rate (88%), usually early during treatment, due to disease or treatment complications. Other series reported 6 patients, of whom 3 died[26]. In a report from the Children's Hepatic Tumors International Collaboration (CHIC) 11 patients with hepatic MRT had an OS 0%[27] and in a recent systematic review OS was 22%[28]. For our series, the outcome for this site is better than reported, nevertheless, we must consider the low number of patients.

Patients who achieved complete resection, either early or delayed surgery, had significantly better survival. In the literature, the type of surgical resection was significant for survival outcomes in some series[14], but not in others[13, 22].

Defining the role of radiotherapy proves challenging as it was administered with curative intent in 3 patients only, all of them older than 36 months. Similar findings were observed in other published series, where the survival benefit of radiotherapy could not be demonstrated, added to the presence of confounding factors like disease progression before radiotherapy or age at diagnosis[1,13]. However, contrasting these results, other series showed a significant improvement in survival rate with radiotherapy, as revealed by both univariate and multivariate analysis[14].

MT (including low-dose metronomic chemotherapy) is a treatment given after induction therapy in the case the tumor achieved complete remission, aiming to treat potential minimal residual disease. It is a well-established treatment strategy for patients with acute lymphoblastic leukemia and neuroblastoma but there is less experience in other pediatric solid tumors. However, in last years, the results of the European pediatric Soft tissue sarcoma Study Group (EpSSG) RMS 2005 trial demonstrated in a randomized trial better survival for high-risk localized rhabdomyosarcoma patients when MT with vinorelbine and low-dose cyclophosphamide was administered. Considering these results, the Children Oncology Group has amended the "intermediate risk trial" to add a similar MT regimen to standard chemotherapy with or without temsirolimus (NCT02567435)[29,30]. Despite this, the use of MT continues to be a poorly studied approach in MRT. In a recent study involving children under 6 months old with MRT diagnosis, the maintenance regimen showed borderline significance in univariate analysis and emerged as an independent prognostic factor in multivariate analysis[22]. However, another series, which included some of the patients from the aforementioned study and added patients with EC-MRT older than 6 months, did not demonstrate a beneficial role for MT[14]. In our series, patients who received MT experienced significantly prolonged survival. Nevertheless, interpreting these results is challenging and there could be a bias in the interpretation due to the low number of patients who received MT, because only those who achieved CR received MT, and all except one were older than 24 months at the time of diagnosis, so patients who enter the MT phase represent a selected group where better survival is expected.

New target therapies, alone or in combination with chemotherapy, would be necessary mainly in patients with unfavorable prognostic factors. In recent years, new therapeutic targets have been reported, some with encouraging results such as histone deacetylase inhibitors, and others with more modest results as inhibitors of EZH2[31-34].

Likewise, the loss of SMARCB1 has been reported to be immunogenic and different clinical studies and case reports have shown favorable results with immune checkpoint inhibitors; both as monotherapy and in combination treatments[35-37].

Different clinical trials with novel therapeutic approaches, including immune checkpoint inhibition and adoptive cell therapy, targeting SWI/SNF subunits and other molecular pathways are ongoing with promising results[38].

In conclusion, ERNC-MRT is a rare disease with a poor prognosis. The survival rates observed in our study were comparable to EpSSG-nonRMS 2005 but slightly lower than reported by EuRhab and EpSSG-nonRMS addendum 2019 series. Age under 1 year was the main prognostic factor.

The use of MT significantly prolonged survival, nevertheless the prognostic significance is not entirely clear since there are multiple confounding factors. More studies are required to confirm these results, with a larger number of patients, and participation in cooperative groups.

One of the limitations of our study was the inadequate assessment of germline SMARCB1 and SMARCA4 mutations and DNA methylation, due to lack of availability to perform both techniques, considering their prognostic relevance and implications for therapeutic decisions. New therapies are urgently needed, especially in the poor prognosis group.

Conflict of interest: None to declare

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