Clinical and Translational Oncology (2021) 23:2460–2473
https://doi.org/10.1007/s12094-021-02654-1

CLINICAL GUIDES IN ONCOLOGY

GEIS-SEHOP clinical practice guidelines for the treatment of rhabdomyosarcoma

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Received: 17 May 2021 / Accepted: 25 May 2021 / Published online: 1 July 2021

Abstract
Rhabdomyosarcoma (RMS) is the most frequent soft tissue sarcoma (STS) in children and adolescents. In Spain the annual incidence is 4.4 cases per million children < 14 years. It is an uncommon neoplasm in adults, but 40% of RMS are diagnosed in patients over 20 years of age, representing 1% of all STS in this age group. RMS can appear anywhere in the body, with some sites more frequently affected including head and neck, genitourinary system and limbs. Assessment of a patient with suspicion of RMS includes imaging studies (MRI, CT, PET-CT) and biopsy. All patients with RMS should receive chemotherapy, either at diagnosis in advanced or metastatic stages, or after initial resection in early local stages. Local control includes surgery and/or radiotherapy depending on site, stage, histology and response to chemotherapy. This guide provides recommendations for diagnosis, staging and treatment of this neoplasm.

Keywords Rhabdomyosarcoma · Alveolar rhabdomyosarcoma · Embryonal rhabdomyosarcoma · Prognostic factors

Methodology

These guidelines have been developed by a multidisciplinary panel of specialists involved in the diagnosis and treatment of rhabdomyosarcoma (RMS) both in children and adults. A bibliographic search of published articles was performed in the PubMed database and international guidelines, such as EpSSG (European Pediatric Soft Tissue Sarcoma Study Group), were consulted [1]. In a telematic meeting, each section was presented by one expert to

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the entire group for discussion and consensus. The panel adopted the Infectious Disease Society of America levels of evidence/grades of recommendation [2].

As pleomorphic rhabdomyosarcoma's behavior is more similar to other adult soft tissue sarcomas, we refer the reader to those specific therapeutic guidelines [3].

Incidence and epidemiology

RMS is the most frequent soft tissue sarcoma (STS) in children, representing 55% of these tumors in Spain [4]. It accounts for 3.7% of all pediatric cancers, with an annual incidence of 4.4 cases per million children younger than 14 years. These figures are similar to those reported by other series both in Europe and the US [5–7]; Asian countries report lower incidences [8, 9]. Incidence is higher among boys (1.5/1 ratio), and in the age group from 1 to 4 years (6.3 cases per million). Most frequently, histological subtypes are embryonal (55–60% of patients) and alveolar (20–25%), while fusocellular/sclerosing is rare [7]. Similar to other pediatric cancers, predisposing factors are identified only in a small fraction of patients. There are known associations with cancer predisposition syndromes (Li-Fraumeni, DICER1…) [10, 11]. Approximately 40% of RMS are diagnosed in patients over 20 years of age. This represents 1% of STS and 0.02% of cancer in adults [12]. Conversely to pediatric RMS, there is a high proportion of the pleomorphic variant [7].

Diagnostic procedures

RMS can appear anywhere on the body, but head and neck (35–50% of cases), genitourinary region (25%) and extremities (20%) are the most frequent sites. Moreover, some locations are more frequently associated with certain histological subtypes, such as the alveolar variant predominant in extremities [13, 14]. Lymph node involvement is common in RMS, mainly in older children and adults, and in the alveolar tumors [15].

Imaging

Ultrasound

It should be used as the first imaging test for any suspicious palpable mass, as well as for abdominal or genitourinary symptoms in children [16].

MRI

The technique of choice for the head and neck, as well as for local staging. With diffusion-MRI techniques, low ADC values are observed in areas with cellular predominance; and intermediate or high ADC values are seen in areas with myxoid and/or necrotic changes [17]. Alveolar RMS associates scattered foci of necrosis with a more heterogeneous enhancement involving muscle, fasciae, bone, and regional lymph nodes [18, 19].

CT

It is usually the first imaging test in older children and adults in head and neck, chest or abdomen locations.

PET/CT

The metabolic activity of RMS tends to be high, and has prognostic value in the baseline study [20]. High SUVmax, SUVpeak, metabolic tumor volume and total-lesion glycolysis are more prevalent among patients with less favorable clinical and pathological features, including unfavorable primary site, alveolar subtype, presence of regional or distant metastasis, and high-risk group.

Plain radiography

Of limited utility in evaluating soft tissue tumors, but it is useful for the initial assessment of calcifications or bone involvement.

Biopsy

Biopsies must be planned to ensure that the scar and the biopsy tract can be easily resected in the definitive surgery or included in the radiotherapy field, and must respect the compartmental anatomy. Endoscopic biopsies are accepted in certain anatomic locations (e.g., urinary tract, biliary tract). Regardless of the technique, hemostasis must be guaranteed to avoid tumor dissemination. Drains should be avoided if possible, and if needed, they should be placed in parallel to the surgical incision and as close as possible. To guarantee an adequate oncologic resection, crossing different anatomical compartments and compromising neurovascular structures should be avoided.

Core needle biopsy (CNB)

This is currently the preferred approach in most situations, as it is less invasive and tumor seeding is rare [22, 23]. If performed under image guidance (mostly ultrasound, but also CT) [24], it allows avoiding necrotic or cystic areas

and prevents possible complications. The needle must be directed toward the peripheral areas of the lesion, those with high metabolism detected on PET/CT, or with clear contrast enhancement on MRI or CT. Usually, 14 or 16G needles, 10–20 mm long, are sufficient, with the number of passes necessary to obtain sufficient tissue to perform histological, immunohistochemical and molecular studies (minimum 4–5 cylinders). Coaxial needles are highly recommended to avoid tumor seeding.

Surgical biopsy

A valid alternative, but currently reserved for those cases where CNB is not feasible, when after two attempts there is not sufficient/valid tissue, or when an excisional biopsy with negative margins can be achieved without mutilation. In the extremities, the incision must be longitudinal to the long axis of the limb.

Fine needle aspiration (FNA)

Not indicated for the initial histological study, however, it could be a valid option for the diagnosis of tumor relapses.

Pathology

RMS is classified into four histologic subtypes: embryonal (ERMS), alveolar (ARMS), spindle cell/sclerosing and pleomorphic, with different histological, immunohistochemical (IHC) and molecular characteristics [25] (Table 1).

1. **ERMS**: predominantly located in the head and neck and genitourinary area. Histologically, the classic form shows myxoid stroma and variable degrees of rhabdomyoblastic differentiation: 1.1 classic (includes botryoid); 1.2 ERMS with predominance of a spindle cell component; 1.3 densely cellular ERMS.

2. **ARMS**: frequently located in deep soft parts of the extremities. Histologically, it is an undifferentiated small, round blue cell tumor, with skeletal muscle differentiation markers: 2.1 classic; 2.2 solid.

3. **Spindle cell/sclerosing RMS**: composed of "herringbone" spindle cells with different components of sclerosis. Four variants have been described based on their molecular features: 3.1 congenital/infantile spindle cell RMS [26, 27]; 3.2 Myo-D1 mutant spindle cell/sclerosing RMS [28]; 3.3 intraosseous spindle cell RMS [29]; 3.4 spindle cell/sclerosing RMS without identifiable genetic alterations.

4. **Pleomorphic RMS**: tumor presenting in adults. It is characterized by a proliferation of spindle or rhabdoid cells with marked pleomorphism. They have complex karyotypes, comparable to undifferentiated pleomorphic sarcomas.

The term RMS N.O.S (not otherwise specified) is not a subtype; it indicates that diagnosis of RMS can be made but no further subtyping is possible. This usually occurs when the biopsy is very small or presents artefacts.

Anaplasia needs to be documented and is defined by the presence of cells with large, lobulated hyperchromatic nuclei (at least three times the size of neighboring nuclei) and atypical mitosis.

Table 1 Histological and molecular classification of RMS

	ERMS	ARMS	Spindle cell/sclerosing RMS
HS	1.1 Classic: myxoid background; rhabdomyoblastic	2.1 Classic: alveolar architectural pattern: fibrous septa upholstered by primitive tumoral cells	Spindle cell tumor with or without sclerosing areas
	1.2 With spindle cell component: spindle cell predominance combined with classic areas	2.2 Solid: sheets of primitive tumoral cells	The cells can be found in cords, nests or microalveoli
	1.3 Densely cellular: solid pattern and variable cellular size and shape differentiation, variable cellularity; cambium layer (botrioid)		
IHQ	Desmin	Desmin	Desmin (diffuse)
	Myogenin (< 80% of cells)	Myogenin (> 80% of cells)	MyoD1 (focal or diffuse in spindle cell/diffuse in sclerosing)
	MyoD1	MyoD1	Myogenin (focal)
MB		FOXO1 + PAX3 (70–90%)	3.1 VGLL2/NCOA2/CI TED
		FOXO1 + PAX7 (10–30%)	3.2 MYOD1
		PAX3-NCOA2, FOXO1-FGFR1 (1–5%)	3.3 TFCP2/NCOA2

RMS: histological subtype (HS); immunohistochemistry (IHC); molecular biology (MB)

Reception and macroscopic study of the specimen

Biopsies and surgical specimens should be sent fresh and provide sufficient material for diagnosis and molecular characterization. All primary and post-chemotherapy resection specimens require evaluation of the margins by the pathologist. The specimen should be inked before incision, weighed, measured, orientated, photographed and, at least, one block per centimeter needs to be sampled. Percentage of necrosis must be documented and all lymph nodes processed.

Diagnostic report

Histological type and subtype (architectural pattern, cell type, stroma, number of mitoses/10HPF, % of necrosis and anaplasia).
In surgical specimens: anatomical location, type of surgical resection, resection margins and minimum distance to the tumor, signs of response to treatment if neoadjuvancy (percentage of necrosis/fibrosis or other regressive changes), vascular invasion, and metastatic lymph nodes.
IHQ stains: negative or positive, localization and extension.
Molecular techniques (FISH, PCR, RT-PCR, NGS) specifying reagents, results and evaluation criteria.

Diagnosis of RMS requires an integration of morphology, IHQ (myogenin, MyoD1 and desmin) and molecular analysis: rearrangements of FOXO1 (FOXO1-PAX3, FOXO1-PAX7, FOXO1-FGFR1) and PAX3 (PAX3-NCOA2) [30] using FISH, RT-PCR or NGS.

Staging and risk stratification

Staging

Local

The initial radiological evaluation (MRI or CT) should include the primary tumor and all anatomical landmarks that may compromise the surgical approach: vascular-nerve tracts, fascial involvement, and bone or adjacent organs [31]. It is important to include regional lymph node stations, especially when using MRI [32].

Metastatic

Chest CT continues to be the technique of choice in the initial assessment of possible pulmonary metastases. PET-CT can increase the accuracy of initial staging, mainly in the detection of lymph node involvement, with high sensitivity (69–100%) and specificity (89–100%) [33]. Nevertheless, sentinel node biopsy detected by ^{99m}Tc-labeled-nanocolloid SPECT/CT remains the technique of choice in the definitive characterization of lymph node involvement [34]. The most recent RMS staging protocols from various cooperative groups include PET-CT as a recommended procedure (**IIB**) [35–37]. It is superior to conventional bone scintigraphy, detecting skeletal involvement thus replacing scintigraphy. Whole-body MRI is an equally valid alternative [38].

Lymph nodes

Adequate sampling of clinically or radiologically suspicious lymph nodes is mandatory at diagnosis and at relapse. Tissue samples can be obtained by FNA, CNB or surgically, depending on each clinical scenario. There is controversy regarding the histological study of non-suspicious lymph nodes, as radiological evaluation (US, MRI) in the case of negative or doubtful findings has been proven insufficient. In cases with high risk of lymph node invasion, PET/CT is recommended [39, 40] and/or biopsy with sentinel lymph node biopsy (SLNB) techniques. Biopsy is particularly recommended in cases of negative clinical and/or radiological examination, but with high risk of involvement. Current recommendations include dual SNLB techniques that should be performed in centers with experience in these procedures [41, 42]. Histological evaluation of the lymph nodes is particularly important in limb and paratesticular tumors > 5 cm in patients > 10 years. At the extremities, regional lymph nodes and "in transit" nodes must be evaluated, as positivity has an impact on treatment and prognosis. The new FaR-RMS Surgical Guidelines of the EpSSG provide a detailed orientation of the lymph nodes to explore depending on the different anatomic locations [43].

Bone marrow examination

Staging of metastatic disease also includes bilateral bone marrow aspirate and biopsy in alveolar tumors. Bone marrow examination may be omitted in patients with tumors < 5 cm, fusion-negative and no lymph node spread [44].

Lumbar puncture

Pre-treatment lumbar puncture is recommended in parameningeal tumors if there is evidence of intracranial/meningeal invasion on imaging studies.

Other studies

Include complete blood counts, biochemistry, echocardiography and hormonal evaluation prior to starting treatment.

Risk group assignment

Risk stratification for RMS is based on both the pretreatment (TNM) staging system and post-surgical grouping system established by the Intergroup Rhabdomyosarcoma Clinical Grouping System (IRS) [44, 45]. The clinical subgroup is determined after the initial surgical procedure, prior to systemic therapy, and is primarily based on the extent of residual tumor after surgery with consideration of regional lymph node involvement. Assignation of the final risk group is completed considering pathology, site and age. Some cooperative groups consider FOXO1 fusion instead of pathology as a risk stratification marker [46].

Table 2 shows final risk group assignment according to the EpSSG guidelines considering all the mentioned risk factors.

Treatment of localized disease

Systemic treatment

Systemic therapy is a cornerstone in the multimodal approach of these patients. With the current multidisciplinary therapy, 5-year overall survival (OS) rates are around 80% in localized disease [47]. Systemic therapy has to be integrated with local therapy (surgery ± radiotherapy) and is adapted, both in duration and regimen, to the patient's risk group (Table 3).

Vincristine, dactinomycin and alkylating agents (ifosfamide or cyclophosphamide) are the main drugs for rhabdomyosarcoma therapy, IVA being the current standard regimen in Europe. More intensive regimens with the addition of other drugs failed to show an improvement in outcome [48, 49].

Regimens without alkylating drugs (VA) or reduced doses of ifosfamide (IVA/VA), can be administered to patients with low or standard risk, without impairing prognosis and with a better toxicity profile [50] (**IIA**) (Table 4).

The addition of anthracyclines did not improve the prognosis of high-risk patients in a randomized study [51], and thus is not recommended (**IA**), although it can be added to the induction chemotherapy in those patients with very high-risk disease (alveolar rhabdomyosarcoma with nodal involvement) [52].

In detail, in patients with initial complete resection (IRS I Group), 8–9 cycles of chemotherapy will be administered based on risk group. Patients in IRS groups II and III, should receive nine cycles of chemotherapy, with local treatment after the first four cycles.

After completing consolidation chemotherapy, in patients with high-risk disease, maintenance chemotherapy with daily oral cyclophosphamide and weekly vinorelbine, for 6 months, proved to increase disease-free survival

Table 2 Risk groups

Risk group	Subgroups	Fusion	IRS group	Site	Node stage	Age and size
LR	A	–	I	Any	N0	Both favorable
SR	B	–	I	Any	N0	One unfavorable
SR	C	–	II, III	Favorable	N0	Any
HR	D	–	II, III	Unfavorable	N0	Any
HR	E	–	II, III	Any	N1	Any
HR	F	+	I, II, III	Any	N0	Any
VHR	G	+	II, III	Any	N1	Any
VHR	H	Any	IV	Any	Any	Any

Risk group

LR low risk, *SR* standard risk, *HR* high risk, *VHR* very high risk

Fusion

FOXO1-PAX3, FOXO1-PAX7, FOXO1-FGFR1, PAX3-NCOA2

Post-surgical stage (according to the IRS grouping)

Group I primary complete resection (R0), *Group II* microscopic residual (R1) or primary complete resection but N1, *Group III* macroscopic residual (R2), *Group IV* distant metastases

Site

Favorable (+) orbit, genital-urinary nonbladder-prostate and nonparameningeal head and neck, *Unfavorable* (−) all other sites (parameningeal, extremities, genital-urinary bladder-prostate and "other site")

Node stage (TNM classification)

N0 no clinical or pathological node involvement, *N1* clinical or pathological nodal involvement

Size and age

Favorable (+) tumor size < 5 cm and age < 10 years, *Unfavorable* (−) tumor size > 5 cm or age ≥ 10 years)

Table 3 Local and systemic treatment

Risk group	Subgroup	Chemotherapy	Local treatment
BR	A	VA × 8	Surgery
RE	B	IVA × 9	Surgery
RE	C	IVAx9 o IVAx5 + 4xVA[a]	Surgery ± Radiotherapy[b]
AR	D	IVA × 9 + 6 maintenance cycles	Radiotherapy ± surgery[c]
AR	E	IVA × 9 + 6 maintenance cycles	Radiotherapy ± surgery[c]
AR	F	IVA × 9 + 6 maintenance cycles	Radiotherapy ± surgery[c]
MAR	G	IVADo × 4 + IVA × 5 + 12 maintenance cycles	Radiotherapy ± surgery[c]
MAR	H	IVADo × 4 + IVA × 5 + 12 maintenance cycles	Radiotherapy ± surgery[c]

[a]Patients will receive a total of nine cycles of VA without radiotherapy if CR has been obtained by secondary surgery. If they receive radiotherapy the treatment will consist of IVAx5 + VAx4

[b]The orbit is considered a favorable site and is usually treated with radiotherapy without surgery if CR to prior chemotherapy. Given that the overall survival benefit is not statistically significant in this subgroup of patients, radiotherapy may be omitted if age or location is considered to be too toxic

[c]Consider surgery only if R0 or R1 is feasible without mutilation. Unfavorable sites are usually treated with radiotherapy alone

Table 4 Treatment schedules (first line and relapse)

IVA	21 day cycle	Daily dose
Ifosfamide	Days 1 and 2	3 g/m^2
Vincristine	Days 1, 8 and 15 (cycles 1 and 2)	1.5 mg/m^2 (maximum 2 mg)
Vincristine	Day 1 (cycles 3–9)	1.5 mg/m^2 (maximum 2 mg)
Actinomycin D (should be omitted during radiotherapy)	Day 1	1.5 mg/m^2 (maximum 2 mg)
IVADo	21 day cycle	Daily dose
Ifosfamide	Days 1 and 2	3 g/m^2
Vincristine	Days 1, 8 and 15 (cycles 1 and 2)	1.5 mg/m^2 (maximum 2 mg)
Vincristine	Day 1 (cycles 3–9)	1.5 mg/m^2 (maximum 2 mg)
Actinomycin D (should be omitted during radiotherapy)	Day 1	1.5 mg/m^2 (maximum 2 mg)
Doxorubicin (should not be given concomitantly with radiotherapy)	Days 1 and 2 (cycles 1–4 only)	30 mg/m^2
Maintenance	28 day cycle	Daily dose
Oral cyclophosphamide	25 mg/m^2 orally daily for 28 days (continuously)	
Vinorelbine	Days 1, 8 and 15	25 mg/m^2
VIT	21 day cycle	Daily dose
Vincristine	Day 1 and 8	1.5 mg/m^2 (maximum. 2 mg)
Irinotecan	Days 1–5	50 mg/m^2
Temozolomida	Days 1–5	125 mg/m^2
VCDE	21 day cycle	Daily dose
Vincristine	Day 1	1.5 mg/m^2 (maximum 2 mg)
Cyclophosphamide	Day 1	1.5 g/m^2
Doxorubicin	Days 1–3	20 mg/m^2
Etoposide	Days 1–3	150 mg/m^2
TVD	21 day cycle	Daily dose
Topotecan	Days 1–5	1.5 mg/m^2
Vincristine	Days 5 and 6 continuous infusion	1 mg/m^2 (maximum 1 mg/day)
Doxorubicin	Days 5 and 6 continuous infusion	22.5 mg/m^2

(DFS) and OS, in a randomized trial [53], and is part of the standard therapy in this risk group (**IA**). The use of maintenance chemotherapy is also recommended in those patients with very high-risk disease after completion of consolidation chemotherapy if there is evidence of disease remission (**IIA**).

Local treatment

Surgery

Local disease control, with surgery and/or radiotherapy, is the keystone of multimodal treatment in patients with RMS. The type of treatment depends on: patient's age, histological subtype, tumor biology, anatomical location, tumor size and response to chemotherapy. Surgical principles for the treatment of pediatric RMS can be extrapolated to adult patients. The post-surgical grouping system is an independent risk factor for every tumor location. However, in most cases, definitive surgery will take place after neoadjuvant chemotherapy (four cycles in localized disease and six in metastatic). Surgical consultation to reference centers is highly advised, given its impact on prognosis and the possible functional and technical implications. The treating surgical team must be able to predict the quality of resection, and whether it will imply the resection of anatomical structures or organs, or even, mutilating procedures. If so, the appropriate reconstructive procedures must be foreseen and scheduled at optimal timing.

When surgical resection carries a high probability of mutilation, other treatment options must be explored, mainly radiotherapy. However, mutilating procedures might be preferable or necessary in certain situations. A list of the procedures considered mutilating can be consulted [43].

The surgical report must reflect the quality of resection achieved. For the correct evaluation of the surgical specimen by the pathologists, the surgeon must make an orientative drawing of the tumor and mark the critical points with sutures. The quality of the resection will be determined by the worst surgical margin:

1. **R0** or microscopically complete resection. This can be "Wide" (*en bloc* resection surrounded by healthy tissue) or "Compartmental" (*en bloc* resection with the entire anatomical compartment). R0 resection should be the goal.
2. **R1** or microscopically incomplete resection. This happens when the tumor or its pseudocapsule is exposed on the resection surface, or when the surgical margins present microscopic involvement, without residual macroscopic remains. In the event of a pseudocapsule rupture and tumor leakage, the field must be thoroughly washed, margins widened and reported by the surgeon, since it will require the addition of local radiotherapy.
3. **R2** or macroscopically incomplete resection. It occurs when a macroscopic residual tumor is left in situ.

The timing of the definitive tumor resection defines a series of conditions:

Primary resection: complete resection with curative intent (R0) performed at the time of diagnosis, as long as this does not imply a vital risk or mutilation, always in the absence of lymph node or metastatic disease. Debulking is not recommended as initial treatment [54]. In the vast majority of cases, particularly in children, an R0 resection at diagnosis will be impossible, so obtaining biopsies and initiating neoadjuvant treatment would be the most adequate route.

Pre-treatment re-excision: refers to a second resection performed after a R1 or R2 primary resection, with the aim of reaching negative margins (R0). It can serve to avoid overstaging the patient, thus reducing the intensity of subsequent treatment.

Delayed excision: the definitive surgery that is carried out after completing the neoadjuvant treatment (chemotherapy ± radiotherapy). Its objective is to achieve a R0/R1 resection of the residual mass. These are mainly conservative surgeries generally combined with radiation therapy, although in some patients, R0 resection can avoid it. If all neoadjuvant options have been exhausted, "mutilating" procedures may be warranted. Brachytherapy, which can offer enormous benefits in individual patients (e.g., bladder or vaginal tumors), should be considered when planning surgery [55, 56]. Debulking surgery does not appear to afford benefits, so preoperative radiation therapy should be considered instead. In the case of preoperative radiotherapy, possible surgical complications must be taken into account, recommending scheduling the surgery in the window between the 4th and 6th weeks after the last session.

Radiotherapy

Treatment recommendations are based on the best current evidence and these guidelines apply to all ages. A retrospective study reported that treatment according to pediatric schedules could improve outcomes in adult patients [57]. Good local control requires the combination of surgery and radiotherapy and outcomes are better when both modalities are used. If it is decided to reduce the radiotherapy dose to minimize the long-term effects, the surgeon should plan the surgery according to the absence or reduced irradiation. Stratification in different risk groups is the basis for determining treatment intensity. It was applied in the EpSSG study (RMS 2005) which reported a significant improvement in outcome. Eighty-five percent of patients with localized

high-risk RMS received radiotherapy and the 3-y EFS was 67%. For very high-risk patients the EFS was 56%, significantly better than those obtained in historical controls [51, 52] (Table 3).

Time of administration: according to EpSSG RMS2005, local treatment, either second surgery or radiotherapy, is administered at week 13 after the 4th cycle of induction chemotherapy.

Technique: the EpSSG RMS2005 study recommended a 3D technique, but the high rates of significant long-term morbidity in pediatric patients and the evolution of irradiation techniques available today make it advisable to use highly conformal techniques, such as single or rotational intensity modulated radiotherapy (IMRT). Proton therapy (excluding extremity localization) should be considered as an option, provided that adequate treatment times can be met and there is a dosimetric benefit to organs at risk. Brachytherapy should be considered as the preferred option in patients with genito-urinary, bladder, prostate, vaginal or perineal tumors, as long as the volume to be irradiated can be treated with this technique. This assessment should be carried out by a radiation oncologist together with a surgeon with experience in brachytherapy treatments.

Dose for the primary tumor: the dose is determined by histology, tumor response to induction chemotherapy and IRS staging group (Table 5).

Dose for the lymph nodes involved: only patients with positive lymph nodes at diagnosis should be irradiated. In those cases where lymph node involvement achieved a complete response, or in case of complete resection, the dose to be administered over the area of initial involvement is 41.4 Gy in 23 fractions. In cases of persistent disease at the time of irradiation, a boost dose of 9 Gy in five fractions should be administered to the residual macroscopic disease, with a total dose of 50.4 Gy, regardless of the histology.

Treatment of metastatic disease

Systemic treatment

The prognosis of these patients is clearly worse, with an OS at 3 and 5 years of 34% and < 20% respectively, according to a combined multivariate analysis of European and American groups [58]. In this study, age (< 1 year or > 10 years), unfavorable location, bone or bone marrow involvement and the presence of three or more metastatic sites were defined as poor prognostic factors. The 3-year EFS was 50%, 42%, 18%, 12% and 5% for patients without any, one, two, three or four of these adverse prognostic factors, respectively. In adults, a 5-year OS of 4.3% [59] has been reported, but could be improved when pediatric treatment protocols are applied [7].

In metastatic RMS, the combination of systemic and local treatment may also achieve complete remissions, although local and distant relapses are frequent. Despite many clinical trials attempting to improve outcomes by adding new agents to standard VAC/IVA chemotherapy, or substituting one or more components of VAC/IVA chemotherapy, to date, no chemotherapy regimens have been shown to be more effective [60, 61]. Thus, the standard systemic treatment in metastatic RMS would be IVA or VAC (**IIA**) adding anthracyclines [62] (**IIIC**) (e.g., IVADo regimen in induction followed by IVA in consolidation). If the disease is controlled at the end of consolidation chemotherapy, maintenance treatment with daily oral cyclophosphamide and weekly intravenous/oral vinorelbine seems indicated, since it has shown significant improvement in overall survival in high-risk RMS [53] (**IIIB**). However, to date, intensification with high doses of chemotherapy has not been shown to be beneficial [63] (**IVB**).

Table 5 Radiotherapy dose for primary tumor by histology and IRS group (age > 3 years)

IRS group	Embryonal RMS	Alveolar RMS
I	No radiotherapy	41.4 Gy in 23 fractions
II a, b y c	41.4 Gy in 23 fractions	41.4 Gy in 23 fractions
III followed by		
Complete resection in a second stage	36 Gy in 20 fractions (if partial response) 41.4 Gy in 23 fractions (if stable disease)	41.4 Gy in 23 fractions
Incomplete surgical resection	50.4 Gy in 28 fractions	50.4 Gy in 28 fractions
Complete clinical response, no second surgery	41.4 Gy in 23 fractions	50.4 Gy in 28 fractions
Partial response (PR), stable disease or progression without surgery	50.4 Gy in 28 fractions + boost 5.4 Gy in 3 fractions 45 Gy in 25 fractions if orbital location and PR	50.4 Gy in 28 fractions + boost 5.4 Gy in 3 fractions

Local treatment

Radiotherapy

With scant evidence, international recommendations support the use of systematic irradiation of all sites that are technically feasible and where the risk/benefit analysis is appropriate. It is not known whether there are subgroups that may benefit more than others, given the prognostic differences also in metastatic disease [64]. Retrospective analyses suggest adequate disease control with irradiation of all metastatic lesions, mainly in the pediatric population **(IVB).** Therefore, according to a retrospective series, aggressive local treatment of metastatic disease, including surgery and radiotherapy in combination when feasible, may have an impact on EFS (35% vs. 16–20%) and OS (44% vs. 18%) [65]. The survival benefit of total lung irradiation with a dose of 15 Gy in 10 fractions in patients with pulmonary metastases is also unclear, although it seems to improve local lung control [66, 67] **(IIIC).** Prognostic group stratification in metastatic disease could modulate treatment intensity, as it does in localized disease [58].

Response assessment

Response assessment, before and after a specified number of chemotherapy cycles or radiotherapy, is based on imaging criteria. These criteria can evaluate the decrease or increase in size of the selected target lesions (morphological criteria); or can evaluate changes in various biological features of the tumor (functional criteria): glycidic metabolism (PET/CT), vascular permeability (DCE-MRI, DCE-CT), necrosis (PET/CT, diffusion MRI). Morphological criteria are the most commonly used, due to their greater simplicity and easy standardization. They can be one-dimensional (RECIST 1.1), two-dimensional (OMS) or three-dimensional (3D). Some publications show discrepancies in up to 20% of cases between them, without any clear advantages [68]. In the pediatric RMS response assessment, both EpSSG and the Children's Oncology Group (COG) preferred volumetric quantification as standard criteria, by estimating 3 orthogonal axes: in the axial plane of maximum length (a), its perpendicular (b) and the skull axis [$(\pi/6) \times a \times b \times c$]. Computer-assisted volumetric assessment offers more accurate and reproducible values, although it is more cumbersome for routine clinical practice [69]. The EpSSG RMS2005 protocol included a first assessment of response after three cycles of chemotherapy that required at least a minimal partial response (mPR) to continue with the same line of treatment. However, the COG group does not recommend any change in treatment unless progressive disease is identified at this timepoint [70]. In adults, RECIST 1.1 is more common as a reference for response assessment. Although the evidence is still limited, PET/CT plays an important role in the assessment of tumor metabolic response after chemotherapy induction, being a better predictor of response than morphological criteria [71]. Data published by a single Institution demonstrated that a complete metabolic response on FDG-PET after induction chemotherapy was associated with improved progression-free survival (PFS; 72% vs. 44%, $p=0.01$). Similarly, high SUVmax values appear more prevalent in patients from high-risk groups, with unfavorable localization, alveolar RMS histology, or presence of metastases [21]. The current trend in RMS is to use morphological and functional criteria (PET/CT, dynamic-enhancement MRI, diffusion MRI) in a combined way to evaluate the response to treatment [72, 73].

Treatment at relapse

Patients refractory to first-line treatment or those who relapse after initial treatment have a dismal prognosis. Patients with ERMS initially treated with alkylating agents (IVA or VAC) and patients with ARMS constitute the group with the worst prognosis at relapse (5-y EFS 10%), while patients with ERMS stage I who did not receive alkylating agents (VA only) constitute a group with better prognosis (5-y EFS 50%). Moreover, relapses that occur within the first 3 years after diagnosis and metastatic relapses have less chance of cure than later local relapses [74].

Systemic treatment

Treatment differs depending on the time of relapse and previous treatment (Table 4). Reported schemas of chemotherapy include doxorubicin, ifosfamide, and etoposide [75], as well as different schedules with the combination of vincristine and irinotecan (VI) [76].

In a recent study conducted by the EpSSG group [77], the combination VI with temozolomide (VIT) demonstrated superiority over VI alone. The majority of patients included in the study had had relapses (89%) compared with those with refractory disease (11%). The objective response rate was 44% in the VIT arm vs. 31% in the VI arm. The VIT arm achieved a significantly better OS than VI, although toxicity, mainly hematological, was higher in the VIT arm.

The VIT scheme is considered the new standard of treatment of the EpSSG group for these patients. (**III**, **B**). If there is no response to VIT, or a new progression occurs, the following combinations are proposed:

1. Consider including the patient in a clinical trial.
2. In patients who did not receive doxorubicin previously: VCDE (vincristine, cyclophosphamide,

doxorubicin, etoposide) or TVD (topotecan, vincristine, doxorubicin) [63, 78].

3. In patients who did not receive maintenance previously: vinorelbine–cyclophosphamide [79].

4. Other options in patients previously treated with anthracyclines: topotecan/carboplatin alternating with cyclophosphamide/etoposide (EpSSG RMS2005, second line) or cyclophosphamide/topotecan [80].

Evaluation of response should be performed every two cycles and local treatment (surgery and/or radiotherapy) delivered as soon as possible.

Duration of treatment: with the VIT scheme, if there is an objective response and toxicity is tolerable, up to a total of 12 cycles are administered. With the VCDE and TVD regimens, the duration of treatment is not established.

Late relapses (> 3 years from diagnosis): these patients have a better prognosis and the use of standard first-line chemotherapy type IVA or VAC can be considered.

Local treatment

Surgery

Depending on the previous treatments, different therapeutic options can be considered. If cure is still a possibility and radiotherapy is not feasible, surgery is the most effective treatment, and even mutilating procedures can be justified [81, 82] On the contrary, when cure is not a realistic possibility, but it is feasible to prolong survival or improve the quality of life of the patient, interventional radiology offers a wide range of minimally invasive procedures [83, 84].

Radiotherapy

Recommendations of local treatment with radiotherapy cannot be established. Cases must be evaluated individually to reach a consensus on the options.

Follow-up

There is no evidence for a standard follow-up policy, but we propose some general recommendations (Table 6). The same techniques used at diagnosis should be consistently applied and by criteria of radioprotection, we recommend reducing the use of CT in favor of plain X-ray. The prognosis of patients with localized RMS is generally favorable with an OS of 80%. However, for patients with unfavorable prognostic factors the figures are not so positive. When planning the monitoring strategy, the kinetics of events is relevant. In general, the mean time for relapse is 1.43 years (range 0.13–13.5 years) [85]; while in paratesticular tumors, the mean is 0.9 (range 0.1–6.2 years) [86], and in alveolar parameningeal tumors it is 0.5 years (range 0.2–2.1 years) [87]. Therefore, it seems prudent to establish a follow-up calendar that ranges from the end of treatment to up to 5–10 years after completion. However, relapses beyond 5 years are very rare and, as recently published [88], the detection of incidental relapses in planned controls does not seem to affect

Table 6 Follow-up evaluations

On treatment	1st evaluation	2nd evaluation	3rd evaluation	4th evaluation
Low risk	At the end of treatment			
Standard risk	After 3 cycles	At the end of treatment		
High or very high risk	After 3 cycles	After 9 cycles	After 3 months of maintenance	At the end of maintenance

After treatment	Year 1	Year 2	Year 3	Year 4–5	Year 6–10
Localized disease at diagnosis					
Physical exam + blood lab	Every 3 months	Every 4 months	Every 4 months	Every 6 months	Every 12 months
US ± CT or MRI primary location	Every 3 months	Every 4 months	Every 4–6 months	Every 6–12 months	If clinical suspicion
Thorax X-ray/CT (at least alternating the first 2 years)	Every 3 months	Every 4 months	Every 4–6 months	Every 6–12 months	Every 12 months
Metastatic disease at diagnosis					
Physical exam + blood lab	Every 3 months	Every 4 months	Every 4 months	Every 6 months	Every 12 months
US ± CT or MRI primary location or other metastasis	Every 3 months	Every 4 months	Every 4–6 months	Every 6–12 months	If clinical suspicion
Thorax X-ray/CT (at least alternating the first 2 years)	Every 3 months	Every 4 months	Every 4 months	Every 6–12 months	Every 12 months
PET-CT[a]	[a]Optional	If clinical suspicion	If clinical suspicion	If clinical suspicion	If clinical suspicion

[a]The first control should be performed at least 6 months after completing radiotherapy

subsequent survival. In addition, the risk associated with any of the routine tests (anesthesia, radiation) should also be considered. It is, therefore, essential to educate the patients/parents about the warning signs/symptoms.

Patient-centered care

Patients diagnosed of RMS should be attended at reference centers with expert multidisciplinary teams (MDT) available. Reference sarcoma centers should provide a discussion panel to assess the better treatment option and to offer potential enrolment in active clinical trials [89, 90]. Moreover, they should be able to offer a second opinion when required. MDT must be patient and family-centered, considering their physical, psychosocial and spiritual needs.

Once the cancer has been overcome, patients are at a higher risk of developing health issues many years after initial diagnosis, due either to the disease or as result of treatment-related toxicity [91]. Once treatment has ended, potential long-term effects will rely on different risk factors such as type of treatment received and age at the time of therapy. Scheduling an end-of-treatment clinic could be of valuable help. Also, an individualized follow-up treatment-plan (IFUTP) should be designed with the following aims:

1. Early detection of relapse.

2. Screening and early detection of second primary tumors.

3. Shared care with the Local Community Care Team to assure a continuous medical surveillance that guarantees health and long-term wellbeing [92], by developing prevention strategies and health promotion.

4. Early diagnosis and appropriate treatment of unforeseen events and long-term treatment sequelae including:

Neuro cognitive assessment and tailored academic curriculum in schools. There is a higher risk of developing learning difficulties and issues about being accepted by equals [93].

*Psychosocial assessment*Psychosocial assessment since diagnosis. Continuous monitoring should be undertaken to detect potential disfunction or learning and psychosocial morbidity.

Cardiotoxicity monitoring. Main cardiac risk factors are represented by previous treatment including anthracyclines, radiation therapy and some medical conditions such as obesity, high blood pressure, hypercholesterolemia and diabetes. High-risk patients would require a cardiological assessment i.e., EKG, Echo performed yearly, or every 2–5 years based on dose of cardiotoxic therapy received.

Fertility. Patients with fertility potential must agree to use appropriate contraception during treatment period. Those patients at high risk of infertility based on the treatment planned, should be offered an age-appropriate fertility preservation technique.

Acknowledgements We thank Ms. Helena Kruyer for English correction. GEIS (Grupo Español de Investigación en Sarcomas): S. Gallego, D. Bernabeu, N. Hindi, C. Mata, C. Marquez, J. Orcajo, G. Ramírez, C. Romagosa, C. Valverde, R. Vergés. SEHOP (Sociedad Española de Hematología y Oncología Pediátrica): S. Gallego, A. Juan Ribelles, C. Marquez, C. Mata, G. Ramírez, D. Ruano, P. Rubio.

Author contributions All authors: conceptualization, methodology, writing and editing, approval of the final version of the manuscript.

Funding Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

References

1. https://www.skion.nl/workspace/uploads/Protocol-EpSSG-RMS-2005-1-3-May-2012_1.pdf.
2. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis. 2001;15(33):139–44.
3. Garcia del Muro X, de Alava E, Artigas V, Bague S, Braña A, Cubedo R, Spanish Group for Research on Sarcoma, et al. Clinical practice guidelines for the diagnosis and treatment of patients with soft tissue sarcoma by the Spanish group for research in sarcomas (GEIS). Cancer Chemother Pharmacol. 2016;77:133–46.
4. Pardo Romaguera E, Muñoz López A, Valero Poveda S, Porta Cebolla S, Barreda Reines MS, Fernández Delgado R, et al. Cáncer infantil en España. Estadísticas 1980–2018. Registro Español de Tumores infantiles (RETI-SEHOP). 2019.
5. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995 National Cancer Institute SEER Program. Bethesda: NIH Pub No. 99-4649; 1999.
6. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer. 2013;49:684–95.
7. Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A. Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2600 patients. J Clin Oncol. 2009;27:3391–7.
8. Nakata K, Ito Y, Magadi W, Bonaventure A, Stiller CA, Katanoda K, et al. Childhood cancer incidence and survival in Japan and England: a population-based study (1993–2010). Cancer Sci. 2018;109:422–34.
9. Stiller CA, Parkin DM. International variations in the incidence of childhood soft-tissue sarcomas. Paediatr Perinat Epidemiol. 1994;8:107–19.
10. Nichols KE, Malkin D, Garber JE, Li FP. Germ line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomark Prev. 2001;10:83–7.
11. Skapek SX, Ferrari A, Gupta AA, Lupo PJ, Butler E, Shipley J, et al. Rhabdomyosarcoma. Nat Rev Dis Primers. 2019;5:1.
12. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. Cancer J Clin. 2019;69:7–34.

13. Freling NJM, Merks JHM, Saeed P, Balm AJM, Bras J, Pieters BR, et al. Imaging findings in craniofacial childhood rhabdomyosarcoma. Pediatr Radiol. 2010;20(40):1723–38.
14. McCarville MB, Spunt SL, Pappo AS. Rhabdomyosarcoma in pediatric patients: the good, the bad and the unusual. Am J Roentgenol. 2001;176:1563–9.
15. Hayes-Jordan A, Andrassy R. Rhabdomyosarcoma in children. Curr Opin Pediatr. 2009;21:373–8.
16. Park K, van Rijn R, McHugh K. The role of radiology in paediatric soft tissue sarcomas. Cancer Imaging. 2008;8:102–15.
17. Inarejos Clemente EJ, Navallas M, Martínez B, de la Torre I, Suñol M, Munuera Del Cerro J, Torner F, et al. MRI of rhabdomyosarcoma and other soft-tissue sarcomas in children. Radiographics. 2020;40:791–814.
18. Saboo SS, Krajewski KM, Zukotynski K, Howard S, Jagannathan JP, Hornick JL, et al. Imaging features of primary and secondary adult rhabdomyosarcoma. Am J Roentgenol. 2012;199:W694-703.
19. van Vliet M, Kliffen M, Krestin GP, van Dijke CF, Vliet M, Kliffen M, et al. Soft tissue sarcomas at a glance: clinical, histological, and MR imaging features of malignant extremity soft tissue tumors. Eur Radiol. 2009;19:1499–511.
20. El-Kholy E, El Nadi E, Hafez H, Ahmed S, Younes A, El-Kenanii N, et al. Added predictive value of 18F-FDG PET/CT for pediatric rhabdomyosarcoma. Nucl Med Commun. 2019;40:898–904.
21. Sa R, Liu D, Zhao H, Hou S, Lin Q, Guan F. Utility of [(18) F] fluoro-deoxyglucose positron emission tomography/computed tomography for staging and therapy response evaluation in pediatric rhabdomyosarcoma: a case series and literature review. Front Med (Lausanne). 2020;7:281.
22. Berger-Richardson D, Swallow CJ. Needle tract seeding after percutaneous biopsy of sarcoma: risk/benefit considerations. Cancer. 2017;123:560–7.
23. Barrientos-Ruiz I, Ortiz-Cruz EJ, Serrano-Montilla J, Bernabeu-Taboada D, Pozo-Kreilinger JJ. Are biopsy tracts a concern for seeding and local recurrence in sarcomas? Clini Orthop Relat Res. 2017;475(2):511–8.
24. Chowdhury T, Barnacle A, Haque S, Sebire N, Gibson S, Anderson J, et al. Ultrasound-guided core needle biopsy for the diagnosis of rhabdomyosarcoma in childhood. Pediatr Blood Cancer. 2009;53(3):356–60.
25. Parham DM, Barr FG. Classification of rhabdomyosarcoma and its molecular basis. Adv Anat Pathol. 2013;20:387–97.
26. Alaggio R, Zhang L, Sung YS, Huang SC, Chen CL, Bisogno G, et al. A molecular study of pediatric spindle and sclerosing rhabdomyosarcoma: identification of novel and recurrent VGLL2-related fusions in infantile cases. Am J Surg Pathol. 2016;40:224–35.
27. Mosquera JM, Sboner A, Zhang L, Kitabayashi N, Chen CL, Sung YS, et al. Recurrent NCOA2 gene rearrangements in congenital/infantile spindle cell rhabdomyosarcoma. Genes Chromosomes Cancer. 2013;52:538–50.
28. Agaram NP, LaQuaglia MP, Alaggio R, Zhang L, Fujisawa Y, Ladanyi M, et al. MYOD1-mutant spindle cell and sclerosing rhabdomyosarcoma: an aggressive subtype irrespective of age. A reappraisal for molecular classification and risk stratification. Mod Pathol. 2019;32:27–36.
29. Le Loarer F, Cleven AHG, Bouvier C, Castex MP, Romagosa C, Moreau A, et al. A subset of epithelioid and spindle cell rhabdomyosarcomas is associated with TFCP2 fusions and common ALK upregulation. Mod Pathol. 2020;33:404–19.
30. Hibbitts E, Chi YY, Hawkins DS, Barr FG, Bradley JA, Dasgupta R, et al. Refinement of risk stratification for childhood rhabdomyosarcoma using FOXO1 fusion status in addition to established clinical outcome predictors: a report from the Children's Oncology Group. Cancer Med. 2019;8:6437–48.
31. Freling NJM, Merks JHM, Saeed P, Balm AJM, Bras J, Pieters BR, et al. Imaging findings in craniofacial childhood rhabdomyosarcoma. Pediatr Radiol. 2010;40:1723–38.
32. Jawad N, McHugh K. The clinical and radiologic features of paediatric rhabdomyosarcoma. Pediatr Radiol. 2019;49:1516–23.
33. Norman G, Fayter D, Lewis-Light K, Chisholm J, McHugh K, Levine D, et al. An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: systematic review. BMJ Open. 2015;5:e006030.
34. Wagner LM, Kremer N, Gelfand MJ, Sharp SE, Turpin BK, Nagarajan R, et al. Detection of lymph node metastases in pediatric and adolescent/young adult sarcoma: Sentinel lymph node biopsy versus fludeoxyglucose positron emission tomography imaging-A prospective trial. Cancer. 2017;123:155–60.
35. Bethesda MD. PDQ Childhood Rhabdomyosarcoma Treatment. National Cancer Institute. 2020. https://www.cancer.gov/types/softtissuesarcoma/hp/rhabdomyosarcoma-treatment-pdq. Accessed 12 July 2020.
36. Lim HJ, Johnny Ong CA, Tan JW, Ching Teo MC. Utility of positron emission tomography/computed tomography (PET/CT) imaging in the evaluation of sarcomas: a systematic review. Crit Rev Oncol Hematol. 2019;143:1–13.
37. Völker T, Denecke T, Steffen I, Misch D, Schönberger S, Plotkin M, et al. Positron emission tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial. J Clin Oncol. 2007;25:5435–41.
38. Gennaro N, Marrari A, Renne SL, Cananzi FCM, Quagliuolo VL, Di Brina L, et al. Multimodality imaging of adult rhabdomyosarcoma: the added value of hybrid imaging. Br J Radiol. 2020;93:20200250.
39. Terwisscha van Scheltinga SEJ, Wijnen M, Martelli H, Rogers T, Mandeville H, Gaze MN, et al. Local staging and treatment in extremity rhabdomyosarcoma. A report from the EpSSG-RMS2005 study. Cancer Med. 2020;9:7580–9.
40. Federico SM, Spunt SL, Krasin MJ, Billup CA, Wu J, Shulkin B, et al. Comparison of PET-CT and conventional imaging in staging pediatric rhabdomyosarcoma. Pediatr Blood Cancer. 2013;60:1128–34.
41. National Cancer Institute. Sentinel Lymph Node Biopsy. 2011
42. Parida L, Morrisson GT, Shammas A, Hossain AKM, McCarville MB, Gerstle T, et al. Role of lymphoscintigraphy and sentinel lymph node biopsy in the management of pediatric melanoma and sarcoma. Ped Surg Int. 2012;28:571–8.
43. Rogers T, Smeele L, Scheltinga STV, Corti FD, Guillén Burrieza G, Smeulders N, et al. Surgery guidelines rhabdomyosarcoma, long version, FaRMS protocol, EpSSG [Internet]. https://www.epssgassociation.it/en/.
44. Weiss AR, Lyden ER, Anderson JR, Hawkins DS, Spunt SL, Walterhouse DO, et al. Histologic and clinical characteristics can guide staging evaluations for children and adolescents with rhabdomyosarcoma: a report from the Children's Oncology Group Soft Tissue Sarcoma Committee. J Clin Oncol. 2013;31:3226.
45. Lawrence W, Anderson JR, Gehan EA, Maurer H. Pretreatment TNM staging of childhood rhabdomyosarcoma. A report of the Intergroup Rhabdomyosarcoma Study Group. Cancer. 1997;80:1165–70.
46. Missiaglia E, Williamson D, Chisholm J, Wirapati P, Pierron G, Petel F, et al. PAX3/FOXO1 fusion gene status is the key prognostic molecular marker in rhabdomyosarcoma and significantly improves current risk stratification. J Clin Oncol. 2012;30:1670–7.
47. Arndt CA, Stoner JA, Hawkins DS, Rodeberg DA, Hayes-Jordan AD, Paidas CN, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan,

and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol. 2009;27:5182–8.
48. Hawkins DS, Chi YY, Anderson JR, Tian J, Arndt CAS, Bomgaars L, et al. Addition of vincristine and irinotecan to vincristine, dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: a report from the Childrens Oncology Group. J Clin Oncol. 2018;36:2770–7.
49. Oberlin O, Rey A, Sanchez de Toledo J, Jenney JEM, Scopinaro M, Bergeron C, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society of Pediatric Oncology MMT95 study. J Clin Oncol. 2012;30:2457–65.
50. Ferrari A, Bisogno G, Casanova M, Meazza C, Piva L, Cecchetto G, et al. Paratesticular rhabdomyosarcoma: report from the Italian and German Cooperative Group. J Clin Oncol. 2002;20:449–55.
51. Bisogno G, Jenney M, Bergeron C, Gallego Melcon S, Ferrari A, Oberlin O, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet Oncol. 2018;19:1061–71.
52. Gallego S, Zanetti I, Orbach D, Ranchere D, Shipley J, Zin A, et al. Fusion status in patients with lymph node-positive (N1) alveolar rhabdomyosarcoma is a powerful predictor of prognosis: experience of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). Cancer. 2018;124:3201–9.
53. Bisogno G, de Salvo GL, Bergeron C, Gallego G, Merks JM, Kelsey A, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20:1566–75.
54. Cecchetto G, Bisogno G, De Corti F, Dall'Igna P, Inserra A, Ferrari A, et al. Biopsy or debulking surgery as initial surgery for locally advanced rhabdomyosarcomas in children?: The experience of the Italian Cooperative Group studies. Cancer. 2007;110:2561–7.
55. Schmidt A, Warmann SW, Eckert F, Ellerkamp V, Schaefer J, Blumenstock G, et al. The role of reconstructive surgery and brachytherapy in pediatric bladder/prostate rhabdomyosarcoma. J Urol. 2020;204:825–34.
56. Chargari C, Haie-Meder C, Guérin F, Minard-Colin V, de Lambert G, Mazeron R, et al. Brachytherapy combined with surgery for conservative treatment of children with bladder neck and/or prostate. Int J Radiat Oncol Biol Phys. 2017;98:352–9.
57. Ferrari A, Dileo P, Casanova M, Bertulli R, Meazza C, Gandola L, et al. Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. Cancer. 2003;98:571–80.
58. Oberlin O, Rey A, Lyden E, Bisogno G, Stevens MC, Meyer WH, Carli M, Anderson JR. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. J Clin Oncol. 2008;26:2384–9.
59. Bergamaschi L, Bertulli R, Casanova M, Provenzano S, Chiaravalli S, Gasparini P, et al. Rhabdomyosarcoma in adults: analysis of treatment modalities in a prospective single-center series. Med Oncol. 2019;36:59.
60. Malempati S, Weigel BJ, Chi YY, Tian J, Anderson JR, Parham DM, et al. The addition of cixutumumab or temozolomide to intensive multiagent chemotherapy is feasible but does not improve outcome for patients with metastatic rhabdomyosarcoma: a report from the Children's Oncology Group. Cancer. 2019;125:290–7.
61. McDowell HP, Foot AB, Ellershaw C, Machin D, Giraud C, Bergeron C. Outcomes in paediatric metastatic rhabdomyosarcoma: results of The International Society of Paediatric Oncology (SIOP) study MMT-98. Eur J Cancer. 2010;46:1588–95.
62. Bergeron C, Thiesse P, Rey A, Orbach D, Boutard P, Thomas C, et al. Revisiting the role of doxorubicin in the treatment of rhabdomyosarcoma: an up-front window study in newly diagnosed children with high-risk metastatic disease. Eur J Cancer. 2008;44:427–31.
63. Peinemann F, Kröger N, Bartel C, Grouven U, Pittler M, Erttmann R, et al. High-dose chemotherapy followed by autologous stem cell transplantation for metastatic rhabdomyosarcoma—a systematic review. PLoS ONE. 2011;6:e17127.
64. Arush MB, Minard-Colin V, Mosseri V, Defachelles AS, Bergeron C, Algret N, et al. Does aggressive local treatment have an impact on survival in children with metastatic rhabdomyosarcoma? Eur J Cancer. 2015;51:193–201.
65. Mohan AC, Venkatramani R, Okcu MF, Nuchtern JG, Vasudevan SA, Mahajan A, et al. Local therapy to distant metastatic sites in stage IV rhabdomyosarcoma. Pediatr Blood Cancer. 2018;65:e26859.
66. Liu AK, Stinauer M, Albano E, Greffe B, Tello T, Maloney K. Local control of metastatic sites with radiation therapy in metastatic Ewing sarcoma and rhabdomyosarcoma. Pediatr Blood Cancer. 2011;57:169–71.
67. Cameron A, Chisholm J, Elze MC, Casanova M, Geoerger B, Gaze M. Role of radiotherapy to primary/metastatic sites in pediatric patients with metastatic rhabdomyosarcoma in the BERNIE study. J Clin Oncol. 2017;35(suppl):10541.
68. Schoot RA, McHugh K, Van Rijn RR, Kremer LCM, Chisholm JC, Caron HN, et al. Response assessment in pediatric rhabdomyosarcoma: can response evaluation criteria in solid tumors replace three-dimensional volume assessments? Radiology. 2013;269:870–8.
69. Orsatti G, Beltrame V, Crimì F, Frigo AC, Bisogno G, Stramare R. Radiologic response assessment in pediatric soft tissue sarcoma: computed-assisted volume evaluation. J Pediatr. 2017;182:327-334.e2.
70. Rosenberg AR, Anderson JR, Lyden E, Rodeberg DA, Wolden SL, Kao SC, et al. Early response as assessed by anatomic imaging does not predict failure-free survival among patients with Group III rhabdomyosarcoma: a report from the Children's Oncology Group. Eur J Cancer. 2014;50(4):816–23.
71. Casey DL, Wexler LH, Fox JJ, Dharmarajan KV, Schoder H, Price AN, et al. Predicting outcome in patients with rhabdomyosarcoma: role of (18)FDG positron emission tomography. Int J Radiat Oncol Biol Phys. 2014;90:1136–42.
72. Voss SD. Functional and anatomical imaging in pediatric oncology: which is best for which tumors. Pediatr Radiol. 2019;49:1534–44.
73. Pourmehdi Lahiji A, Jackson T, Nejadnik H, von Eyben R, Rubin D, Spunt SL, et al. Association of tumor [(18)F]FDG activity and diffusion restriction with clinical outcomes of rhabdomyosarcomas. Mol Imaging Biol. 2019;21:591–8.
74. Pappo AS, Anderson JR, Crist WM, Wharam MD, Breitfeld PP, Hawkins DS, et al. Survival after relapse in children and adolescents with rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. J Clin Oncol. 1999;17:3487–93.
75. Lager JJ, Lyden ER, Pappo AS, Meyer WH, Breitfeld PP. Pooled analysis of phase II window studies in children with contemporary high-risk metastatic rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol. 2006;24:3415–22.
76. Mascarenhas L, Lyden ER, Breitfeld PP, Walterhouse DO, Donaldson SS, Paidas CN, et al. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first

relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2010;28:4658–63.
77. Defachelles AS, Bogart E, Casanova M, Merks H, Bisogno G, Calareso G, et al. Randomized phase 2 trial of the combination of vincristine and irinotecan with or without temozolomide, in children and adults with refractory or relapsed rhabdomyosarcoma (RMS ASCO 2019 (Abstract #250271). J Clin Oncol. 2019. https://doi.org/10.1200/JCO.2019.37.15_suppl.10000.
78. Chisholm JC, Machin D, McDowell H, McHugh K, Ellershaw C, Jenney M, et al. Efficacy of carboplatin given in a phase II window study to children and adolescents with newly diagnosed of metastatic soft tissue sarcoma. Eur J Cancer. 2007;43:2537–44.
79. Casanova M, Ferrari A, Bisogno G, Merks JHM, De Salvo GL, Meazza C, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. Cancer. 2004;101:1664–71.
80. Saylors RL, Stine KC, Sullivan J, Kepner JL, Bernstein ML, Harris MB, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol. 2001;19:3463–9.
81. Hayes-Jordan A, Doherty DK, West SD, Raney RB, Blakely ML, Cox CS, et al. Outcome after surgical resection of recurrent rhabdomyosarcoma. J Pediatr Surg. 2006;41:633–8.
82. Dantonello TM, Int-Veen C, Schuck A, Seitz G, Leuschner I, Nathrath M, et al. Survival following disease recurrence of primary localized alveolar rhabdomyosarcoma: recurrent alveolar rhabdomyosarcoma outcomes. Pediatr Blood Cancer. 2013;60:1267–73.
83. Susa M, Kikuta K, Nakayama R, Nishimoto K, Horiuchi K, Oguro S, et al. CT guided cryoablation for locally recurrent or metastatic bone and soft tissue tumor: Initial experience. BMC Cancer [Internet]. 2016;16:798.
84. Grilley-Olson JE, Webber NP, Demos DS, Christensen JD, Kirsch DG. Multidisciplinary management of oligometastatic soft tissue sarcoma. Am Soc Clin Oncol Educ B. 2018;38:939–48.
85. Dantonello TM, Int-Veen C, Winkler LI, Schuck A, Schmidt BF, et al. Initial patient characteristics can predict pattern and risk of relapse in localized rhabdomyosarcoma tobias. J Clin Oncol. 2008;26:406–13.
86. Hammond WJ, Farber BA, Price AP, Wolden SL, Heaton TE, Wexler LH, et al. Paratesticular rhabdomyosarcoma: importance of initial therapy. J Pediatr Surg. 2017;52:304–8.
87. Bradley JA, Indelicato DJ, Uezono H, Morris CG, Sandler E, de Soto H, et al. Patterns of failure in parameningeal alveolar rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2020;107:325–33.
88. Vaarwerk B, Mallebranche C, Affinita MC, van der Lee JH, Ferrari A, Chisholm JC, et al. Is surveillance imaging in pediatric patients treated for localized rhabdomyosarcoma useful? Eur Exp Cancer. 2020;125:823–31.
89. Bate J, Wingrove J, Donkin A, Taylor R, Whelan J. Patient perspectives on a national multidisciplinary team meeting for a rare cancer. Eur J Cancer Care. 2019;28:12971.
90. Blay JY, Sleijfer S, Schöffski P, Kawai A, Brodowicz T, Demetri GD, Maki RG. International expert opinion on patient-tailored management of soft tissue sarcomas. Eur J Cancer. 2014;50:679–89.
91. Punyko JA, Gurney JG, Scott Baker K, Hayashi RJ, Hudson MM, Liu Y, et al. Physical impairment and social adaptation in adult survivors of childhood and adolescent rhabdomyosarcoma: a report from the Childhood Cancer Survivors Study. Psychooncology. 2007;16:26–37.
92. Vaarwerk B, Schoot RA, Maurice-Stam H, Slater O, Hartley B, Saeed P, et al. Psychosocial well-being of long-term survivors of pediatric head-neck rhabdomyosarcoma. Pediatr Blood Cancer. 2019;66:e27498.
93. Tonning Olsson I, Brinkman TM, Wang M, Ehrhardt MJ, Banerjee P, Mulrooney DA, et al. Neurocognitive and psychosocial outcomes in adult survivors of childhood soft-tissue sarcoma: a report from the St Jude Lifetime Cohort. Cancer. 2020;126:1576–84.