European Journal of Cancer 146 (2021) 21–29

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Clinical Trial

Embryonal rhabdomyosarcoma completely resected at diagnosis: The European paediatric Soft tissue sarcoma Study Group RMS2005 experience

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Received 19 September 2020; received in revised form 12 November 2020; accepted 18 December 2020
Available online 7 February 2021

KEYWORDS
Rhabdomyosarcoma;
Soft tissue sarcoma;
Childhood cancer

Abstract ***Background:*** Rhabdomyosarcoma (RMS) is the most common form of soft tissue sarcoma in children. We report the results of the European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS 2005 study, which prospectively evaluated the reduction of chemotherapy in patients with embryonal RMS (ERMS) after initial surgery.

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https://doi.org/10.1016/j.ejca.2020.12.025

Methods: Between October 2005 and December 2016, all patients with localised ERMS with an initial microscopically complete resection (IRS group I) with lymph node-negative (N0) were prospectively enrolled in the low-risk (n = 70, subgroup A; age < 10 years and tumour size ≤ 5 cm) or standard-risk group (n = 108, subgroup B; age ≥ 10 years or tumour size > 5 cm. Subgroup A received 8 courses of vincristine and dactinomycin (VA) for 22 weeks; subgroup B received 4 courses of VA with ifosfamide (IVA) and 5 courses of VA for 25 weeks.

Results: The 5-year event-free survival (EFS) and overall survival (OS) were 90.8% (95% confidence interval [CI]: 85.0–94.4) and 95.7% (95% CI: 90.5–98.1), respectively (n = 178). The EFS and OS were 95.5% (95% CI: 86.8–98.5) and 100% (subgroupA), and 87.8% (95% CI: 79.3–93.0) and 93.0% (95% CI: 84.8–96.8)(subgroup B), respectively. Bearman stage 2 veno-occlusive disease (VOD) occurred in 4 very young patients.

Conclusion: VA treatment for 8 courses was effective and well tolerated by the subgroup of patients with low-risk ERMS (group A). Four courses of IVA and 5 courses of VA instead of 9 courses of IVA also has very good results. Careful monitoring for liver toxicity is important in very young patients.

European union drug regulating authorities clinical trials EUDRACT No. 2005-000217-35.

1. Introduction

Rhabdomyosarcoma (RMS) is the most common form of soft tissue sarcoma in children and young adults. It is an aggressive malignant embryonal tumour that can occur in any part of the body for which the cell of origin is still a matter of debate. There are two main histological subtypes: an embryonal (ERMS) subtype, accounting for approximately 80% of cases, and an alveolar RMS (ARMS) subtype. Thanks to multimodal approaches to treatment (chemotherapy, surgery and radiotherapy), overall survival has increased from 50% to 80% for all patients with localised RMS, irrespective of the location [1].

In many cases, neoadjuvant chemotherapy allows for delayed surgery. In some cases, based on the lesion's size and location, microscopically complete excision is possible and surgery is the first treatment step [2]. Such cases account for 10–15% of patients with localised RMS, and they usually have an excellent outcome [3]. Therefore, reducing the chemotherapy burden without jeopardising survival is the goal for such patients. We report the results of the European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS 2005 study that evaluated the reduction of treatment burden in patients with embryonal RMS (ERMS) after initial microscopically complete surgery.

2. Patients and methods

2.1. Patients

The RMS2005 protocol enrolled patients between October 2005 and December 2016 in 14 countries. The eligibility criteria were age <25 years, histologically confirmed RMS, no evidence of distant metastatic lesions, tumour previously untreated except for primary surgery, no pre-existing illness that could prevent treatment, no previous malignant tumours and an interval between the diagnostic surgery and treatment of <8 weeks.

2.2. Staging

The diagnostic work-up included imaging of the primary tumour by CT and/or MRI scans, a chest CT scan, a radionuclide bone scan, and a bone marrow biopsy and aspirate. At diagnosis, all of the patients were assigned to a specific risk group based on six prognostic factors identified in a common retrospective analysis of prior European protocols: pathology (favourable *ie* ERMS/unfavourable *ie* ARMS), IRS group classification, tumour primary site (favourable/unfavourable), nodal involvement (N0, N1), tumour size and patient age (Table 1). All of the patients with localised ERMS with an initial microscopically complete resection (IRS group I) and lymph node (LN)-negative (N0) status were prospectively enrolled in the low-risk group (subgroup A; age < 10 years and tumour size ≤ 5 cm) or standard-risk group (subgroup B; age ≥ 10 years or tumour size > 5 cm, or patients with paratesticular RMS with favourable characteristics, age < 10 years and tumour size ≤ 5 cm, in whom the initial surgical approach was incomplete). Regional LNs were investigated by imaging, without systematic surgical sampling. Both subgroups were the focus of the current analysis.

2.3. Pathology

The pathological diagnosis was confirmed by local pathologists. National revision and molecular biology

Table 1
Risk stratification for the EpSSG non-metastatic RMS study.

Risk group	Subgroups	Pathology	Post-surgical stage (IRS group)	Site	Node Stage	Size and age
Low risk	A	Favourable	I	Any	N0	Favourable
Standard risk	*B*	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High risk	*E*	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable	I, II, III	Any	N0	Any
Very high risk	*H*	Unfavourable	II, III	Any	N1	Any

Pathology: *Favourable* = all embryonal, spindle cell, botryoid RMS; *Unfavourable* = all alveolar RMS (including the solid-alveolar variant).
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).
Site: *Favourable* = orbit, GU non-bladder prostate (i.e., paratesticular and vagina/uterus) and non-PM head & neck; *Unfavourable* = all other sites (parameningeal, extremities, GU bladder prostate, and 'other site').
Node stage (according to the TNM classification): *N0* = no clinical or pathological node involvement; *N1* = clinical or pathological nodal involvement.
Size and age: *Favourable* = tumour size (maximum dimension) $\leq$ 5 cm ***and*** age $<$ 10 years; *Unfavourable* = all others (i.e., size $>$ 5 cm ***or*** age $\geq$ 10 years).
RMS, rhabdomyosarcoma; EpSSG, European paediatric Soft tissue sarcoma Study Group; IRS, initial microscopically complete resection.

studies were recommended but not mandatory for inclusion in the study.

2.4. Treatment

Primary resections were indicated in accordance with the surgical guidelines for the RMS 2005 protocol, when there was no clear clinical evidence of LN or metastatic disease and when the surgical procedure can achieve a microscopic resection without mutilation. In case of incomplete resection, a primary reoperation was recommended unless it would result in mutilation. In case of a primary orchidectomy with a paratesticular localisation, a reoperation was undertaken to excise the cord at the internal ring, and the treatment was upstaged from subgroup A to subgroup B while avoiding a hemiscrotectomy. The interval between the initial surgery and the chemotherapy, including the primary re-excision, was as short as possible ($\leq$8 weeks).

Adjuvant chemotherapy was provided as follows: subgroup A, 8 courses of vincristine (1.5 mg/m^2, maximum single dose of 2 mg) and dactinomycin (1.5 mg/m^2, maximum single dose of 2 mg, VA, both as single i.v. injection) for 22 weeks; subgroup B, 4 courses of ifosfamide (3 g/m^2 administered daily as a 3-h i.v. infusion for two consecutive days) + VA followed by 5 VA courses for a total of 9 courses for 25 weeks (Table 2). No first-line radiotherapy was undertaken as all of the patients had undergone a primary microscopically complete resection of their ERMS. Evaluation of the toxicity was performed with version 4.0 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute.

2.5. Statistical analysis

Data up to 30/03/2019 were collected via a web-based remote data entry system. Survival probabilities were estimated using the Kaplan-Meier method. The 5-year

Table 2
Treatments for groups A and B. Surgery was followed by chemotherapy.

Group A: Surgery (IRSI)																			
Chemotherapy	V	V	V	V			V	V	V	V	V	V	V	V	V	V	V	V	
	D			D			D			D	D			D	D			D	
Weeks	1			4			7			10	13			16	19			22	
Group B: Surgery (IRSI)																			
Chemotherapy	I	V	V	I	V	V	I			I	V			V	V			V	V
	V			V			V			V	D			D	D			D	D
	D			D			D			D									
Weeks	1	2	3	4	5	6	7			10	13			16	19			22	25

V, vincristine 1.5 mg/m^2 (a maximum single dose of 2 mg) was administered as a single intravenous injection.
D, dactinomycin 1.5 mg/m^2 (a maximum single dose of 2 mg) was administered as a single intravenous injection.
I, ifosfamide 3 g/m^2 was administered daily as a 3-h intravenous infusion, with Mesna (3 g/m^2) and hydration (total dose/course = 6 g/m^2).
IRS, initial microscopically complete resection.

Table 3
Clinical characteristics.

	Subg. A n = 70	Subg. B n = 108	Total N = 178	%
Age (yrs) at diagnosis				
≤1	2	1	3	1.7
1–9	68	35	103	57.9
10–17	-	60	60	33.7
≥18	-	12	12	6.7
Gender				
Female	6	7	13	7.3
Male	64	101	165	92.7
Histology				
Botryoid RMS	3	4	7	3.9
Embryonal RMS	57	99	156	87.7
Spindle cell/Leiomyomatous RMS	10	5	15	8.4
Primary tumour invasiveness (T)				
T1	65	84	149	83.7
T2	4	24	28	15.7
Tx	1	0	1	0.6
Tumour size				
a: ≤ 5 cm	70	43	113	63.5
b: > 5 cm	-	65	65	36.5
Regional lymph node involvement				
N0-No evidence of lymph node involvement	70	107	177	99.4
Nx-No information on lymph node involvement		1	1	0.6
Site of origin of the primary tumour				
Orbit	**-**	**1**	**1**	**0.6**
Head and neck	**2**	**1**	**3**	**1.7**
Neck	**-**	1	1	33.3
Oral cavity	1	-	1	33.3
Retro-auricular	1	-	1	33.3
Bladder-prostate	**3**	**1**	**4**	**2.3**
Bladder	3	1	4	100
Genito-urinary non-Bladder Prostate	**58**	**101**	**159**	**89.3**
Paratesticular**	58	96	154	96.9
Uterus	-	4	4	2.5
Vagina*	-	1	1	0.6
Extremities#	**4**	**2**	**6**	**3.4**
Other sites	**3**	**2**	**5**	**2.8**
Abdominal wall	1	-	1	20.0
Paraspinal without intraspinal extension	1	-	1	20.0
Perianal	1	-	1	20.0
Pelvis	-	1	1	20.0
Penis	-	1	1	20.0

event-free survival (EFS) and overall survival (OS) were reported with 95% confidence intervals (CIs), calculated based on the Greenwood method.

2.6. Ethical issues

This prospective study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (European Union Drug Regulating Authorities Clinical Trials EUDRACT No. 2005-000217-35). All of the participating centres obtained approval from their local regulatory bodies and ethics committees, as well as written informed consent from the patients and/or their parents or legal guardians.

3. Results

Overall, 1760 patients were prospectively enrolled in the RMS 2005 EpSSG study. One hundred and seventy-eight patients had localised ERMS with an initial microscopically complete resection (IRS group I) and LN-negative status (70, 39.3% in subgroup A; 108, 60.7% in subgroup B). Of these 108 patients, 103 were aged ≥10 years or had a tumour size >5 cm, and 5 patients who had a favourable age and size were treated in subgroup B due to an inadequate surgery at diagnosis (2 did not undergo the primary re-excision, 3 underwent the primary re-excision without a hemiscrotectomy). The median age of the population was 7.2 years (range: 0.03–22.5); with 106 (59.6%) < 10 years old. Tumour size was ≤5 cm in 63.5% of cases. Most of the patients were boys (92.7%), reflecting the frequency of the paratesticular location within this group (86.5%). One hundred and fifty-four patients had a paratesticular tumour: 58 (37.7%) in subgroup A, 96 (62.3%) in subgroup B (30 due to age ≥ 10 years, 26 due to a tumour > 5 cm, 33 due to both and 5 patients aged < 10 years and with a tumour ≤ 5 cm in whom the initial surgical approach was inadequate). For 24 patients, the RMS was located at another site (Table 3).

Of the 178 cases, 116 (65.2%) were reviewed by a national pathology panel and 80 (44.9%) slides underwent a secondary review by an international pathology panel. Biomolecular analysis was performed in 104 cases (58%), at the national centres. The histology results were typical ERMS in 156 patients, botryoid in 7 patients and spindle cell/leiomyomatous RMS in 15 patients. All of the 104 tumours tested for *FOXO1* fusion had a fusion-negative status.

3.1. Treatment

Treatment data were available for 176 of 178 enrolled patients; in 176 patients with known data, 63 of 68 patients (92.6%) in subgroup A received VA alone and 5 received a modified chemotherapy regimen in accordance with physician's decision. Ninety of the 108 patients (83.3%) in subgroup B received 4 courses of IVA/and 5 VA, 2 received 8 VA courses, 8 received 9 VA courses and 8 received other chemotherapy regimens in accordance with physician's decision. Seven patients (4%) underwent radiotherapy according to the physician's decision: 5 with questionable margin resections, 1 with an orbital tumour primary site, and 1 for unknown reason; 169 (96%) did not undergo radiotherapy treatment according to protocol guidelines.

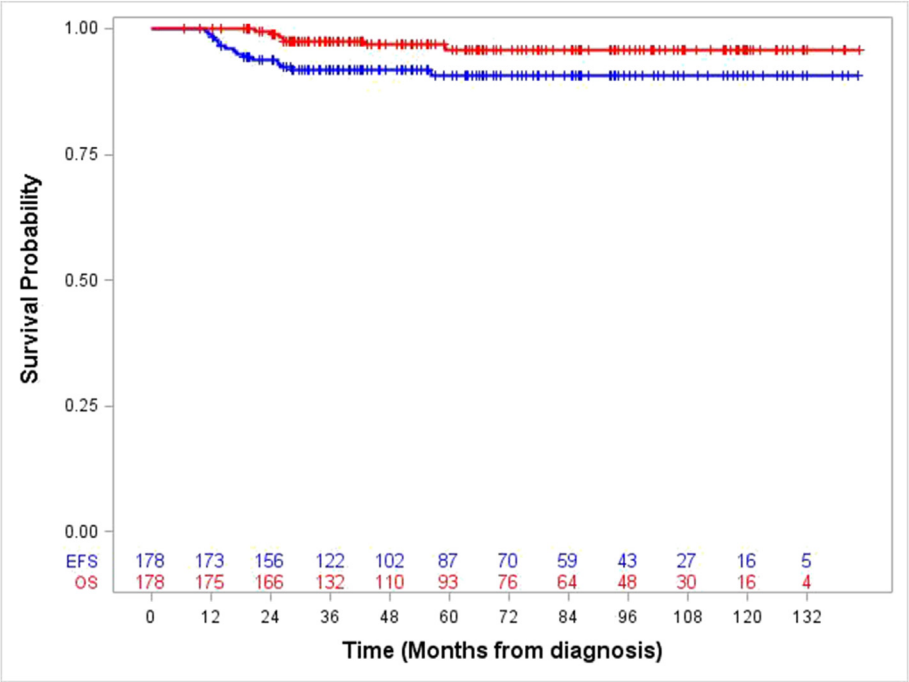

Fig. 1. Event-free and overall survival of the patients with ERMS IRS I. ERMS, embryonal RMS; IRS, initial microscopically complete resection; RMS, rhabdomyosarcoma.

3.2. Toxicity

In the 63 patients treated with VA and evaluated for toxicity, we recorded 15 grade III, 2 grade IV infections, 7 grade III infections and 1 grade IV neuropathy, whereas Bearman stage 2 VOD occurred in 4 very young patients (1, 1.5, 1.5, and 3.9 years old at diagnosis) [4]. In the 90 subgroup B patients treated with 4 courses of IVA/5 VA, we found 17 grade III and 1 grade IV infection, 8 grade III neuropathies; none of the patients

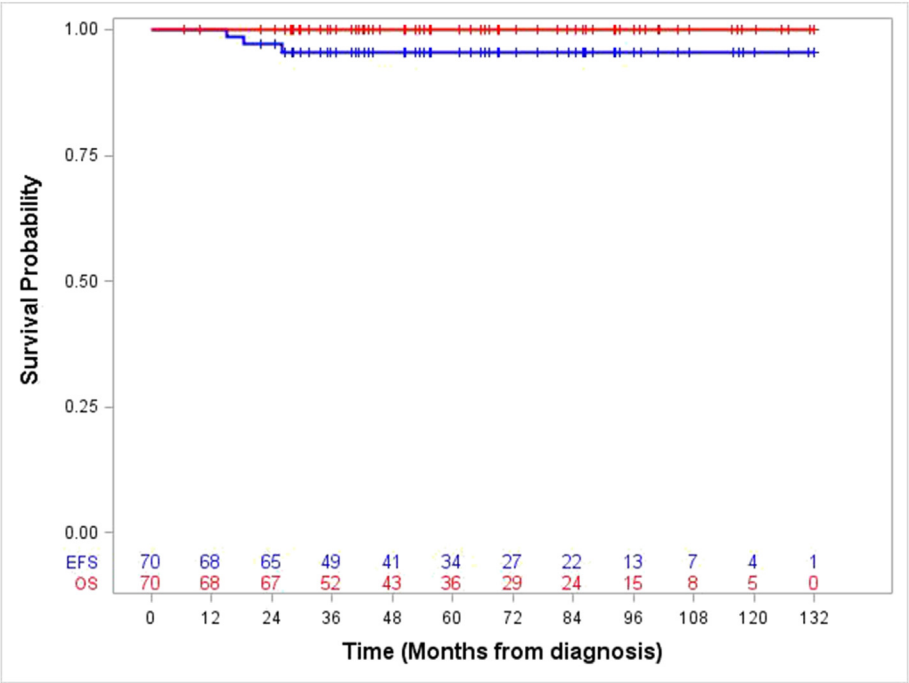

Fig. 2. EFS and OS of the patients with ERMS IRS I in subgroup A. ERMS, embryonal RMS; IRS, initial microscopically complete resection; OS, overall survival; RMS, rhabdomyosarcoma.

had VOD. The long-term toxicities of chemotherapy were not evaluated within this study due to the short follow-up.

3.3. Outcomes

The median follow-up was 65.1 months (IQ range: 36.4–100.7). Fifteen events occurred, comprising 13 patients who relapsed and 2 patients who developed a second tumour (ERMS at another location for one patient with a *TP53* mutation and a non-Hodgkin lymphoma for the other). Relapses occurred locoregionally in 10 patients (77% of all relapses), with LN relapses in 6 and with both LN and distant metastasis in 3 patients. Relapse at distant metastatic sites alone was documented in 3 patients (Table 2). Six patients (all in subgroup B) died of progressive disease, 5 of whom had metastatic relapses and 1 who had a para-aortic nodal relapse (time from the first event to death: 9.1–30.6 months). The other 9 patients were in second complete remission (7 patients; one of them following a second tumour), third complete remission (1 patient), or alive with a second tumour (1 patient). The 5-year EFS and OS were 90.8% (95% CI: 85.0–94.4) and 95.7% (95% CI: 90.5–98.1), respectively, for all of the patients with IRS I ERMS (Fig. 1).The EFS and OS for subgroup A and subgroup B were 95.5% (95% CI: 86.8–98.5) and 100% (Fig. 2), and 87.8% (95% CI: 79.3–93.0) and 93.0% (95% CI: 84.8–96.8), respectively (Fig. 3). In subgroup B, the 5 years EFS was 75.5% (95% CI: 56.3–87.2) for patients with both unfavourable features (age and size) versus 94.2% (95% CI: 85.2–97.8) for patients with only one unfavourable features (size or age)($p = 0.01$).

4. Discussion

Patients with ERMS microscopically completely resected at diagnosis represent a highly selected subgroup of the patients with RMS, and they typically have an excellent outcome [3]. Seventy percent of patients with paratesticular ERMS within RMS 2005 are classified as having IRS group I staging after primary surgery compared with only 4% of patients with ERMS in other locations. Overall there were 24 patients (13.5%) within the EpSSG RMS 2005 study for whom a microscopically complete resection was achieved in another (not paratesticular) site, and similar outcomes were achieved for these patients also.

The currently reported EpSSG study was developed in accordance with the previous European experience. Treatment for completely resected RMS has been progressively reduced in Europe, both in terms of intensity and duration. However, the adoption of only 9 weeks with VA courses had resulted in survival rates lower than expected in the MMT89 protocol [5]. In the subsequent SIOP MMT 95 protocol, the 9 weeks of VA

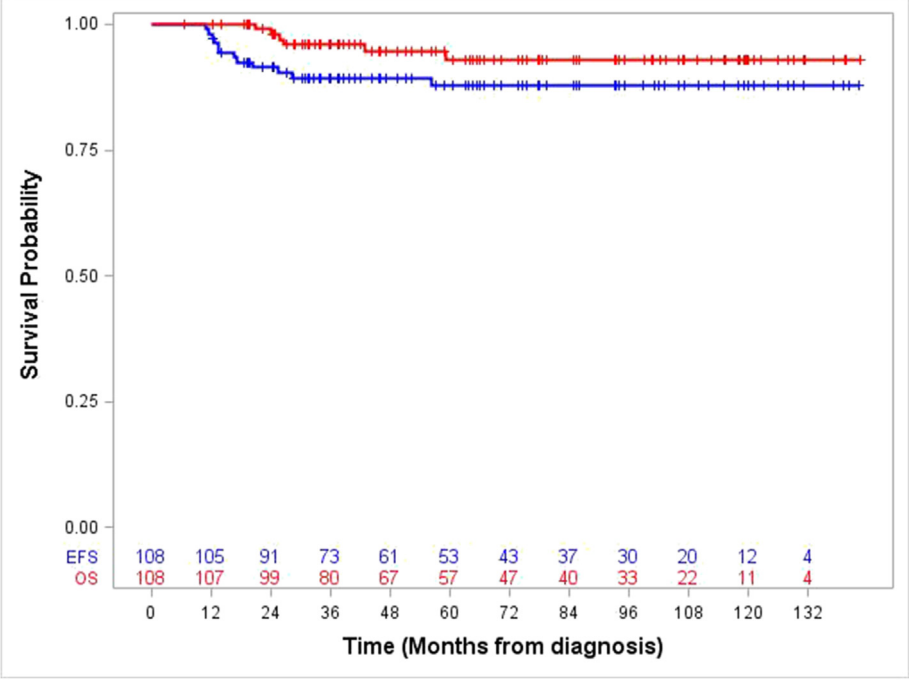

Fig. 3. EFS and OS of the patients with ERMS IRS I in subgroup B. ERMS, embryonal RMS; IRS, initial microscopically complete resection; EFS, event-free survival; OS, overall survival; RMS, rhabdomyosarcoma.

Table 4
F events for the whole population.

group	age (yrs)	tum primary site	T	Size (cm)	Event (1st)	Outcome
A	1.1	Abdominal wall	T1	≤5	2nd tumour	CR2/ AWD
A	1.5	Bladder	T1	≤5	LR	CR2/ AWD
A	3.5	Paratesticular	T2	≤5	MTS	CR2/ AWD
B	**11.3**	**Paratesticular**	**T1**	**> 5**	**LR + MTS (lung)**	**DOD**
B	**15.5**	**Paratesticular**	**T1**	**> 5**	**N**	**DOD**
B	**15.6**	**Paratesticular**	**T1**	**≤ 5**	**MTS**	**DOD**
B	16.1	Paratesticular	T1	>5	2nd tumour	CR2/ AWD
B	16.2	Paratesticular	T1	>5	N	CR2/ AWD
B	16.3	Paratesticular	T2	>5	N + MTS	CR2/ AWD
B	**16.5**	**Paratesticular**	**T1**	**> 5**	**MTS**	**DOD**
B	17.4	Paratesticular	T1	>5	N	CR3/ AWD
B	**18.0**	**Paratesticular**	**T1**	**> 5**	**LR + MTS (bone)**	**DOD**
B	18.7	Paratesticular	T1	≤5	N	CR2/ AWD
B	**19.6**	**Dorsum of penis**	**T2**	**≤ 5**	**LR**	**DOD**
B	19.7	Paratesticular	T1	≤5	LR + N	CR2/ AWD

T, invasiveness of the tumour; LR, local relapse; N, nodal relapse; MTS, metastatic relapse; CR, complete remission; AWD, alive without disease; DOD, dead of disease.

alone, similar to the schedule in MMT89, resulted in suboptimal EFS of 79% at 5 years in the 64 patients (SIOP-MMT95, unpublished data). A combined analysis of the Italian and the German group yielded 5-year survival and EFS rates of 96.1% and 91.3%, respectively, in 164 IRS group I patients. This analysis was restricted to patients with paratesticular tumours, and no differences were reported when the chemotherapy was modified over the years from a regimen containing alkylating drugs and anthracycline (VAIA or VACA protocols) to VA for 22 weeks [6]. The adoption of patient's age and tumour size as strict criteria to select subgroup A patient with low-risk tumour explains the choice of 22 weeks of VA in the RMS 2005 study for this subgroup.

In North American trials, the VA regimen has been adopted in group I favourable histology patients since the IRS-III study (1984–1991), but the duration of treatment was much longer than in European trials. The results of VA alone for low risk (not the same definition as in RMS 2005) was worse, and the failure-free survival (FFS) improved significantly in IRS-IV with the addition of an alkylating agent (total cumulative cyclophosphamide dose, 26.4 g/m^2) [7]. In the IRSG/COG experience on D9602, patients with Group I/IIA were treated with 45 weeks of VA. For the 108 paratesticular patients, the 5-year FFS and OS were 96% and 100%, respectively. Neither tumour size nor patient age were associated with FFS/OS [8]. The excellent results for subgroup "A" in RMS 2005 validate this low burden of treatment approach (without radiotherapy, without alkylating agent) and a 22-week duration of chemotherapy with VA alone. Thus, the reported efficiency/burden of chemotherapy for patients with ERMS IRS I group aged <10 years and with a tumour size ≤5 cm, N0 appears to be optimal.

The worse prognoses in patients ≥10 years of age [9] or with a tumour size > 5 cm [10,11] were considered in the EpSSG RMS 2005 protocol. We decided to consider the two criteria of 'favourable vs. unfavourable age' and 'favourable vs. unfavourable tumour size' together to split this IRS group 1 population into two subgroups: 'A' (low risk) and 'B' (included within standard-risk). Subgroup B was created to upstage some patients from group A, i.e., those with an incomplete primary surgery or an inadequate primary surgery, and patients with a tumour size >5 cm or ≥10 years of age. In group B, 36 of 108 patients (33.3%) had both unfavourable 'age and tumour size'. The aim for subgroup B was to treat with a limited dose of alkylating agents to reduce the risk of relapse, while avoiding significant chemotoxicity. By retaining the alkylating agent in the first 4 chemotherapy courses for subgroup B with the typical total of 9 courses (25 weeks), we succeeded in this aim, with a 93% 5-year OS. On the other hand, the relapse rate was not different for a paratesticular location (11/154; 7%) versus other locations (2/24, 8%). However among the patients with events, 6 of 15 died. All of these patients were in subgroup B, 6 were >10 years of age and 4 of 6 had a tumour size >5 cm (Table 4). With both unfavourable features (age and size), this very selected group has a poorer outcome (75.5%) and an 'escalation' of investigation with retro peritoneal lymph node dissection (RPLND) and chemotherapy should be considered.

The 22 weeks of VA alone (4 courses) was not as well tolerated as expected. Regarding acute toxicity, although the VA regimen may be considered a mild chemotherapy in term of myelosuppression, the potentially serious toxicity of dactinomycin in younger children must be carefully considered [12,13]. In our series, we registered 4 episodes of VODs in subgroup A patients (while none were seen in subgroup B). Three of 4 were older than 1 year but younger than 2 years. We wish to emphasise that physicians should be aware of this potentially serious complication in very young patients treated with VA.

The current analysis did not report data on long-term toxicities due to the short follow-up. Though discussion on late sequelae is therefore above the aim of the present manuscript, based on previous studies reporting moderate renal toxicity with ifosfamide dose of 54 g/m^2 [14], we might assume potential low long-term renal damages in our patients receiving total cumulative ifosfamide

dose of 24 g/m^2. Similarly, we might hypothesise a low degree of gonadal damage because ifosfamide was demonstrated to be associated with a lower risk than cyclophosphamide [15].

Patients with embryonal RMS completely resected at diagnosis continue to have an excellent prognosis and our future EpSSG protocol will maintain 8 courses of VA (22 weeks) for low risk groups with the same criteria (group A). One key distinction between the European and North American approach for lower risk ERMS is the role of routine surgical LN evaluation for paratesticular RMS in patients >10 years old. A common recommendation is under preparation as part of the International Soft Tissue Sarcoma Consortium initiative [16]. This will include a clear plan for optimal staging and risk-adapted treatment for patients with age ≥10 and size >5 cm who appear to be at risk of a poorer outcome.

Author contributions

C.B., M.J., A.F., G.L.D.S. and G.B. contributed to study concepts and study design; C.B., M.J., F.D.C., S.G., H.M., H.G., D.R.V., A.F., G.L.S., I.Z. and G.B. contributed to data acquisition; C.B., G.L.S., I.Z. and G.B. contributed to quality control of data; C.B., G.L.D.S., I.Z. and G.B. contributed to data analysis and interpretation; G.L.S. and I.Z. contributed to statistical analysis; C.B., M.J., F.D.C., S.G., H.M., H.G., A.F., D.R.V., G.L.D.S., I.Z., G.B., JC., V.M.-C. and T.R. contributed to manuscript preparation and manuscript review.

Funding

The overall organisation of this study was supported by the Città della Speranza Foundation, Padova, Italy. In France Dr Bergeron was supported to lead this study by ALBEC (Association Léon Bérard Enfant Cancéreux) grant in 2005. During the course of the RMS2005 study (but not related to it), the EpSSG received unrestricted grants from Chugai and Roche. Dr Chisholm was supported by National Health Service funding to the National Institute for Health Research Biomedical Research Centre of the Royal Marsden Hospital.

Conflict of interest statement

The authors do not have competing interests.

Acknowledgements

The authors would like to thank all of the investigators who worked at the EpSSG centres as well as the patients/families who consented to participate in this trial, thereby contributing to its success. In particular, the authors would like to acknowledge the work of the national coordinators: Adriana Rose (Argentina), Christine Devalck (Belgium), Sima Ferman (Brasil), Peter Mudry (Czech Republic), Christophe Bergeron (France), Myriam Weyl Ben Arush (Israel), Gianni Bisogno (Italy), Heidi Glosli (Norway), Daniela Sejnova (Slovakia), Maja Cesen (Slovenia), Soledad Gallego (Spain), J. Hans Merks (The Netherlands) and Meriel Jenney (United Kingdom and Ireland).

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