Adolescents and young adults with rhabdomyosarcoma treated in the European paediatric Soft tissue sarcoma Study Group (EpSSG) protocols: an observational study

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Summary

Background. Adolescent and young adult (AYA) patients with rhabdomyosarcoma (RMS) are characterised by poorer outcomes compared to children. This observational study aimed to compare the findings of AYA patients (here defined as those aged 15-21 years) with children <15 years enrolled in two prospective clinical protocols developed by the European paediatric Soft tissue sarcoma Study Group (EpSSG) for localised and metastatic RMS.

Methods. The analysis was based on data from the EpSSG RMS 2005 trial (phase 3 randomised trial for localised RMS, open from April 2006 to December 2016) and the EpSSG MTS 2008 protocol (prospective, observational, single-arm study for metastatic RMS, open from June 2010 to December 2016), together involving 108 centers from 14 different countries. For this analysis, patients were categorized according to their age into “children” (age 0-14 years) and “AYA” (15-21 years). To compare adherence to treatment and toxicity between the two age groups, only patients with high-risk localised RMS included in the randomised part of RMS 2005 study were considered.

Findings. The study cohort included 1977 patients, 1720 children and 257 AYA. AYA patients were more likely than children to have metastatic tumours, unfavourable histological subtypes, large tumours, and regional lymph node involvement. AYA patients had significantly lower survival, i.e. 5-year event-free survival was 52.6% (95% CI 46.3-58.6) and 67.8% (95% CI 65.5-70.0) in patients aged ≥15 and <15 years, respectively (p-value <0.0001), while 5-year overall survival was 57.1% (95% CI 50.4-63.1) and 77.9% (95% CI 75.8-79.8) (p-value <0.0001). The multivariable analysis confirmed the prognostic value of age ≥15 years. Modifications of administered chemotherapy occurred in 15.3% and 21.3% of patients ≥15 years and <15 years, respectively. Grade 3-4 haematological toxicity and infection were observed more frequently in children.

Interpretation. The study demonstrated better results for AYA patients than those reported in epidemiological studies (e.g. the EUROCARE-5 study, that reported 5-year OS of 39.6% for patients 15–19 years in the 2000–2007 study period), supporting their inclusion in paediatric RMS trials. It suggests that AYA patients, at least up to 21 years old, can be treated with intensive therapies originally designed for children, with no major tolerability issues. However, our study showed that treatment results were inferior in AYA patients than in children, despite receiving similar therapy. This may suggest that a tailored and intensive treatment strategy may be warranted for these patients.

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Key words:

rhabdomyosarcoma, adolescents, young adults, AYA, clinical trial, age, prognostic factor, outcome, survival, treatment, toxicity

Research in context

Evidence before this study

Several studies have reported that adolescent and young adult (AYA) patients with rhabdomyosarcoma (RMS) are characterised by poorer survival when compared to younger patients. This inferior outcome is likely to be multifactorial; however, differences in clinical management – including lack of referral to experienced centres, lack of inclusion into clinical trials, or less intensive treatments because of decreased tolerance to chemotherapy in older patients – have been suggested to play a role. For the purposes of this report, we have searched PubMed for articles published in English between Jan 1, 1980, and Dec 31, 2021, using the terms "rhabdomyosarcoma", "adolescents", "adults", "AYA", "clinical trial", "protocol", "age", "risk factors", "prognostic factor", "prognosis", "outcome", "survival", "treatment", and "toxicity".

Added value of this study

This study aimed to compare clinical findings, treatment data, toxicity and outcome of RMS patients aged 15-21 years, with children <15 years enrolled in two prospective clinical protocols developed by the European paediatric Soft tissue sarcoma Study Group (EpSSG) for patients with localised and metastatic disease. The added value of this study is that it focused on RMS patients enrolled into EpSSG trials, therefore eliminating the potential impact on survival of a lower recruitment of AYA patients into clinical protocols. To our knowledge, this is the first study aiming to ascertain whether the outcomes of AYA patients (here defined as those aged 15-21 years) were persistently worse compared to children, even when enrolled in the same clinical trials and receiving similar treatment.

The study demonstrated better results than those reported in epidemiological studies, supporting the inclusion of AYA patients with RMS in paediatric trials to receive therapy derived from paediatric protocols. Our study did not report major toxicity and major protocol modifications in older patients compared to children, suggesting that AYA patients, at least up to 21 years old, can be treated with

intensive therapies originally tailored for children, with no major tolerability issues. However, our study showed that treatment results remained significantly worse in AYA patients than in children even when they were treated in the same way.

Implications of all the available evidence

The results of our study support the strategy of the current EpSSG RMS study (i.e. the Frontline and Relapsed Rhabdomyosarcoma [FarRMS] study, opened in 2021) to include adult patients without upper age limit. The inclusion of AYA patients in paediatric trials to receive therapy derived from paediatric protocols, is feasible and can improve the prognosis of AYA patients with RMS.

However, the inferior outcome of AYA patients suggests that a tailored and intensive treatment strategy may be warranted for these patients. Our findings also suggest that in older patients, more aggressive tumour biology may play an important role in the different outcomes. A better understanding of age-related biology factors, including also pharmacokinetic and pharmacodynamic aspects, is needed and may lead to identification of specific targeted treatments.

Introduction

Rhabdomyosarcoma (RMS) is a highly malignant mesenchymal neoplasm with cancer cells characterized by a propensity for myogenic differentiation.[1] Although it is the most frequent soft tissue sarcoma in children and adolescents, it remains a rare tumour, with an annual incidence of 4 per million in the 0-19 years population, and 400 new cases occurring each year across Europe in this age range.[2] RMS is considered a typical tumour of childhood, but it can occur at any age.[3-4]

RMS is an aggressive tumour with a strong propensity to metastasize.[1] However it is often responsive to conventional chemotherapy, and modern paediatric oncology studies report survival rates over 70% for patients with localized disease.[5-8] These achievements have been ascribed to centralisation of care delivered in specialised centres and wide collaboration at national and international levels, with high inclusion rates of paediatric patients into cooperative multi-institutional clinical trials.[9,10] Patient outcomes depend on prognostic variables, including histological subtype and FOXO1 fusion status, tumour resectability, tumour site and size, presence of lymph node or distant metastases.[5-8] Additionally, patient age has an impact on survival, with age over 10 years identified as an adverse prognostic variable in paediatric studies.[11] Poorer outcomes have been reported for adolescents compared to younger patients,[12] and adults carry an even higher risk, with overall survival of adult patients lower than 40%.[3,13-16] The epidemiological EUROCARE-5 study (study period: 2000–2007) reported a 66.6% 5-year relative survival among patients 0–14 years old, as compared to 39.6% for patients 15–19 and 36.4% for 20–39 years of age.[17] The inferior survival of adolescents and even worse survival in adults is likely to be multifactorial,[9,10] and may be influenced by potential differences in tumour biology[18,19] or differences in clinical management, such as diagnostic delay,[20] lack of referral to experienced centers,[21] lack of inclusion into clinical trials,[22] or less intensive treatments because of decreased tolerance to chemotherapy in older patients.[23]

Adolescents and young adults (AYA) are increasingly seen as a distinct category of patients with specific clinical needs.[24] The definition of AYA varies considerably from country to country: whilst

there is agreement that the definition of "adolescence" ranges from 15 to 19 years of age, there is still little consensus regarding the upper age limit of "young adulthood", which has been variously set at 24, 35 and 39 years (with an emerging preference for the broader age range of 15-39 years).[24] The clinical management of AYA patients is challenging, and for many tumour types, this patient group has inferior survival when compared to other age groups. The unsatisfactory survival data reported for AYA patients with RMS prompted the European paediatric Soft tissue sarcoma Study Group (EpSSG) to specifically focus on these patients. The study aimed to analyse clinical findings, treatment data, toxicity and outcome of RMS patients aged 15-21 years and compare them to those 0-14 years old. This study included patients registered onto the EpSSG RMS 2005 trial, for patients with localised RMS, and onto the EpSSG MTS 2008 for patients with metastatic RMS. The main purpose of the analysis was to ascertain whether the outcomes of AYA patients (here defined as those aged 15-21 years at diagnosis) were persistently worse when compared to children, even when enrolled in the same clinical trials and receiving similar treatment.

Methods

Study design and population

The analysis was based on the EpSSG RMS 2005 trial (open from April 2006 to December 2016) and the EpSSG MTS 2008 study (open from June 2010 to December 2016), together involving 108 centres from 14 different countries.

The EpSSG RMS 2005 trial was a multicentre, open-label, randomised controlled, phase 3 trial with two consecutive independent randomisations, the first investigating the role of early dose intensification with doxorubicin and the second exploring the value of a maintenance treatment after standard therapy in patients with high-risk localised RMS. Patients with low, standard, and very high risk localised RMS were also included in RMS 2005 and treated according to standardised guidelines. The methods and results of RMS 2005, including the two randomizations, have been reported elsewhere.[7,8,25,26] Concerning age criteria, patients younger than 25 years were

eligible for inclusion in the study, while patients older than 6 months and younger than 21 years were eligible for the randomizations. Patients were stratified into different risk groups according to six prognostic factors including histological subtype (embryonal versus alveolar; pleomorphic RMS was not included in these studies), Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping, primary tumour site, nodal involvement, tumour size, and patient age (with age <10 years considered favourable and age ≥10 years considered unfavourable). High-risk patients (around 50% of cases) were those with non-metastatic embryonal RMS, incompletely resected at diagnosis (IRS group II or III), localised at unfavourable sites (i.e. parameningeal, extremities, genitourinary bladder-prostate, and other sites), and tumour size >5 cm and/or patient aged ≥10 years (subgroup E); non-metastatic embryonal RMS, incompletely resected (IRS group II or III) and involvement of regional nodes (subgroup F); non-metastatic alveolar RMS without nodal involvement (subgroup G). High-risk patients were considered eligible for the randomizations and received nine cycles of ifosfamide, vincristine and actinomycin-D (IVA) or four cycles of ifosfamide, vincristine, actinomycin-D, and doxorubicin (IVADo) followed by five IVA chemotherapy, plus local treatment (radiotherapy and/or surgery). Patients in clinical remission after the ninth cycle of chemotherapy were randomly assigned to either stop treatment or continue with six 4-week cycles of vinorelbine and oral low dose cyclophosphamide (**Supplemental Table 1**).[7,8]

The EpSSG MTS 2008 study was a prospective, observational, single-arm study for patients with metastatic RMS. Eligibility criteria included age <21 years. Patients were treated with nine cycles of induction chemotherapy comprising four IVADo and five IVA, followed by twelve four-weekly courses of maintenance therapy with vinorelbine and cyclophosphamide; treatment of the primary tumour included surgery and/or radiotherapy, as well as radiotherapy to all metastatic sites, when feasible. The publication with the main results of the EpSSG MTS 2008 is in press.

Procedures

The EpSSG RMS 2005 and MTS 2008 studies were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participating centres obtained approval

from their local authorities and ethics committees, and written informed consent from the patient or their parents/legal guardians.

For the current analysis, patients eligible for the two protocols (RMS 2005 and MTS 2008) and with available data on treatment and outcome, were categorized according to age at diagnosis into "children" (age 0-14 years) and "AYA" (age ≥15 and <21 years). The few cases with age ≥21 years and <25 years registered in the RMS 2005 study but not considered eligible for the randomized trials were excluded from the analysis to make the subgroups of localized and metastatic patients more comparable.

To compare AYA patients and children regarding adherence to the protocol and treatment toxicity, we analysed only patients with high-risk localised RMS included in the two randomisations. Electronic Case Report Forms (eCRFs) were different, in fact, for the different risk groups, and more details on treatment administration and toxicity were collected for randomised patients as compared to the others.

For the aim of this analysis, we considered only major modifications of the chemotherapy program, defined as omission of single agents or omission of full chemotherapy cycle, or delay in chemotherapy administration longer than 2 weeks.

Outcomes

The primary outcome, event-free survival (EFS), was defined as the time from diagnosis to the first event (tumour progression, relapse, refusal of therapy, protocol discontinuation due to toxicity, second malignancies, or death due to any cause) or to the latest follow-up. Regarding secondary outcomes, overall survival (OS) was measured as the time from diagnosis to death due to any cause, or to the latest follow-up. Response to chemotherapy (in high-risk localised patients with measurable disease) was assessed radiologically by measuring tumour volume reduction after three cycles of chemotherapy.[7] Toxicity was evaluated according to the US National Cancer Institute Common Toxicity Criteria, version 3.

Statistical analysis

For statistical analysis, continuous variables were summarised as median and IQR values, and categorical variables were reported as counts and percentages. Survival probabilities were estimated using the Kaplan-Meier method, and the log-rank test was used to assess heterogeneity in survival rates among strata for the following variables: gender (male, female), age at diagnosis (<15years, ≥15years), histology (favorable, unfavorable), tumor primary site (favorable, unfavorable), stage of disease (localised, metastatic), IRS group (I, II, III, IV), T-invasiveness (T1, T2), tumor size (≤5cm, >5cm) and loco-regional nodes involvement (N0, N1). 5-year EFS and 5-year OS with 95% CIs were calculated using the Greenwood method. All the prognostic factors were considered for their effect on EFS and OS using also Cox univariable models to assess hazard ratios (HR) throughout the whole follow-up. A p-value of less than 0.05 was considered significant. Multivariable analysis was performed for EFS and OS including variables with $p<0.25$ at univariable analysis, except IRS due to a collinearity issue with the stage of disease. The Proportional hazards assumption was tested by interacting all the predictor variables with the log-function of survival time. Stratified Cox models were implemented accordingly to not proportional factors and patients with not evaluable size of primary tumor, Tx or Nx were excluded. No significant interactions emerged.

Data collected as of March 10, 2021, were analysed with SAS statistical packages (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data anlaysis, data interpretation or writing the report. AF, BC, GB and JHMM had full access to the raw data, and were responsible for the decision to submit the present paper for publication on behalf of the EpSSG board members.

Results

Overall, 2278 patients were registered, 1900 from EpSSG RMS 2005 and 378 from EpSSG MTS 2008 studies. **Figure 1** shows the study flow diagram. After exclusion of patients not responding to

the eligibility criteria or with missing data, and the exclusion of 14 patients registered in the RMS 2005 study with age between 21 and 24 years, the study cohort included 1977 patients, 1719 enrolled in RMS 2005 and 258 in MTS 2008 studies. Concerning their age, 1720 patients were children (1523 with localised and 197 with metastatic disease) and 257 were AYA (196 with localised tumour and 61 with metastases). No imbalances were founded regarding patient enrolment by year of study

Table 1 describes the main clinical findings of the cohort, comparing the characteristics of patients <15 years with those ≥15 years. AYA were more likely than children to have metastatic tumours (61/257, 23.7% versus 197/1720, 11.5%; p<0.0001), unfavourable histological subtypes (119/257, 46.3% versus 451/1720, 26.2%; p<0.0001), tumour larger than 5 cm (177/257, 68.9% versus 891/1720, 51.8%; p<0.0001), and regional lymph node involvement (109/257, 42.4% versus 339/1720, 19.7%; p<0.0001).

On the contrary, children more often had tumours arising at unfavourable sites including parameningeal, bladder and prostate, extremities, and other sites (1136/1720, 66.0% versus 132/257, 51.4%, p<0.0001). A high proportion (102/257, 39.7%) of AYA patients had tumours in paratesticular and vagina/uterus sites.

Outcome

Outcome data were available for all 1977 patients. Median follow-up for alive patients was 71.0 months (range 1.9-167.7) (IQR 51.1-99.5). Including all patients, the 5-year EFS and OS were 65.9% (95% CI 63.7-67.9) and 75.1% (95% CI 73.1-77.0), respectively. For patients with localised RMS, 5-year EFS and OS were 70.7% (95% CI 68.4-72.8) and 80.5% (95% CI 78.5-82.4), compared to 33.2% (95% CI 27.3-39.2) and 37.0% (95% CI 30.4-43.7) for patients with metastatic disease.

AYA patients had significantly worse survival compared to children. Overall, the 5-year EFS was 52.6% (95% CI 46.3-58.6) and 67.8% (95% CI 65.5-70.0) in patients aged ≥15 and <15 years,

respectively (p-value <0.0001), while 5-year OS was 57.1% (95% CI 50.4-63.1) and 77.9% (95% CI 75.8-79.8) (p-value <0.0001).

Univariable analysis for the whole series of patients is shown in **Supplemental Table 2** and **Supplemental Table 3**, while **Supplemental Table 4** reports univariable analyses for localised and metastatic patients, separately. The multivariable analyses for both EFS and OS are shown in **Supplemental Table 5.** The Cox regression model confirmed the inferior prognosis of patient age ≥15 years, with hazard ratio 1.48 (95% CI 1.20-1.83) for EFS (p-value = 0.0002) and 1.73 (95% CI 1.37-2.19) for OS (p-value <0.0001).

EFS and OS remained significantly different when outcomes for patients with non-metastatic and metastatic disease were analysed separately (**Figure 2**). There were significant differences in survival between histological subgroups, with the exception of those with localised favourable histotypes, as shown in **Table 2**.

Overall, 679 patients out of 1977 developed an event (34.3%) and 496 died. **Table 3** reports the distribution of first events comparing AYA patients and children in the two studies. While a relative high proportion of local failure was recorded in children, regional and metastatic failures were more frequent in patients ≥15 years. Specifically in the RMS 2005 study, metastatic failure comprised 39.7% (29/73) of the events in the AYA group, and 25.4% (111/437) in children (a chi-square test to investigate the difference between metastatic events and other events in the two groups of age resulted in a p-value of 0.011).

Treatment and toxicity

Administered treatment, adherence to the protocol and treatment toxicity were evaluated only in patients with high-risk localised RMS included in the EpSSG RMS 2005 study.

Modifications of the chemotherapy program were reported in 20.7% of the evaluable cases (174/839), including 15.3% (13/85) of patients ≥15 years and 21.3% (161/754) of patients <15 years, with a difference of 6.0% (95% CI 3.5-12.9).

Tumour response evaluation was available for 689 patients with localised high-risk RMS. Response to chemotherapy was reported in 84.4% of patients ≥15 years (7 complete remission and 42 partial remission out of 58 evaluable cases) and in 89.3% of patients <15 years (32 complete remission and 532 partial remission out of 631 cases).

Radiotherapy was given to 84.7% of patients ≥15 years (72/85) and to 80.4% of patients <15 years (609/757). Considering only patients classified as IRS group III, delayed surgery was performed in 51.6% (33/64) and 53.9% (357/662) of patients ≥15 years and <15 years, respectively.

Table 4 describes the different acute Grade 3-4 toxicities in patients with non-metastatic high-grade RMS, enrolled in RMS 2005, randomised to treatment with IVA or IVADo chemotherapy. Hematological toxicity was more frequently reported for patients <15 years. Infection associated with IVA and IVADo chemotherapy, occurred in 33.3% (14/42) and 55.9% (19/34) of AYA patients, and 66.4% (279/420) and 85.0% (232/273) of children (p<0.0001).

Discussion

This study aimed to compare clinical findings, treatment and outcome of RMS patients aged ≥15 and <21 years (here defined as AYA), with children <15 years enrolled in two prospective EpSSG clinical protocols.

The inferior outcome of AYA patients with RMS has been variously reported [3,12-17] and multiple potential factors have been suggested to play a role in this survival difference. Among others, differences in clinical approach and treatment were considered.[9,10,20-23,27,28] Compared to children, AYA patients suffer from a lack of centralization of care and enrolment into clinical trials. Adult patients do not generally have access to paediatric RMS protocols and cooperative prospective studies specifically dedicated to adult RMS have not been developed.[9,16] Limited inclusion of adolescent patients into RMS trials has been observed, yet age cut-off criteria should not act as a barrier for eligibility to participate in clinical trials. A previous EpSSG study compared the number of patients enrolled in EpSSG clinical protocols with the number of cases expected to occur in the

contributing European countries according to incidence rates during the period from 2008 to 2015. The study showed that adolescents were less represented in EpSSG protocols, even though the trials recruited patients up to 21 years of age; whilst 77% of the patients 0–14 years old were included in EpSSG protocols, the percentage dropped to 64% for adolescents (15–19 years).[22]

The current study focused on those RMS patients enrolled into EpSSG trials, therefore eliminating the potential impact on survival of the lower recruitment into clinical trials.

Primarily, our study confirmed that AYA patients with RMS had significantly worse outcomes than children. The 5-year OS was 57.1% in AYA patients and 77.9% in children, and multivariable analysis confirmed the prognostic role of age ≥15 years (hazard ratio 1.73 for OS, 95% CI 1.37-2.19, p-value <0.0001). Outcomes remained statistically worse for AYA patients when different subgroups were analysed, with the exception of patients with non-metastatic favourable histotypes, that achieved similar results to children with the inclusion in a paediatric trial.

The unfavourable clinical presentation of older patients when compared to children has been reported as an important factor explaining the poorer outcomes.[3,13-16] Our study confirmed that AYA patients with RMS were more likely than children to have adverse clinical variables such as distant metastases, regional nodal involvement, alveolar subtype, and large tumour size at diagnosis. Our study also showed significant differences in the pattern of events depending on patient age groups. When treatment failure was observed in patients ≥15 years, this was most frequently metastatic relapse. It remains difficult to speculate on the reasons of the high frequency of distant and lymph nodal metastases at onset, as well as on the significantly higher proportion of AYA patients developing metastatic relapse; however, these finding might potentially be seen indirect markers of intrinsic tumour aggressiveness of RMS arising in AYA patients.

Patients age as continuous variable needs to be investigated in further studies to potentially determine whether a cut-off different from 15 years could better identify where outcomes for younger and older patients diverge,

A further aim of our study was to compare the treatment administered and treatment toxicity in AYA patients and children. Studies have reported that adult patients with RMS have often not received treatment considered standard of care in paediatric patients, and the lower adherence to the principles adopted in paediatric protocols, influenced patient outcomes.[13,16,23,27,28] The concerns that intensive treatments designed for children may be less well tolerated in older patients, has hindered treatment compliance [16] and the smaller experience of adult oncology teams in applying the key concepts of RMS therapy, may also play a role.[13,21,23] In our study, we did not observe major toxicity and major protocol modifications in AYA patients compared to children. It might be questioned that AYA patients might not truthfully report their compliance to the oral maintenance therapy; however, this aspect was considered and therefore great attention was put by local researchers in responsibilizing their patients several times during the therapy. As a matter of fact, modifications of the chemotherapy program were reported in 15.3% () and 21.3% () of patients ≥15 years and <15 years, respectively. Grade 3-4 hematological toxicity and infection were observed more frequently in children than in AYA patients. This finding would suggest that AYA patients, at least up to 21 years old, can be treated with intensive therapies originally designed for children, with no major tolerability issues. It is not known whether this might also be applicable to older adults (the upper age limit of the cohort - i.e. 21 years old - was in fact a major limitation of our study). Pharmacokinetic and pharmacodynamic researches are needed to investigate chemotherapy toxicity according to age, with the possible goal of optimising treatment protocol for different age groups (for example, more intensive treatments for AYA patients).

In conclusion, our study of AYA patients with RMS treated within paediatric clinical trials demonstrated better results than those reported in epidemiological studies: the 5-year OS of 57.1% for patients aged ≥15 and <21 years (treated between 2005 and 2016) compared favourably with the 5-year OS of 39.6% for patients 15–19 years reported by the EUROCARE-5 study (study period: 2000–2007).[17] This finding supports the strategy of the current EpSSG RMS study (i.e. the Frontline and Relapsed Rhabdomyosarcoma [FarRMS] study, opened in 2020) to include adult

patients without an upper age limit. The inclusion of AYA patients in paediatric trials to receive therapy derived from paediatric protocols, is feasible and can improve the prognosis of AYA patients with RMS.

However, our study showed that treatment results remained significantly worse in AYA patients when compared to children even when they are treated in the same way. A tailored treatment strategy may be warranted for these patients including careful staging of regional lymph nodes (given the high frequency of N1 disease), and adoption of more intensive therapy.

Our findings may suggest that in older patients, more aggressive tumour biology may play an important role in the different outcomes. With older age there may be increasing numbers of somatic mutations,[29] high frequency of MYOD1-mutant tumours,[30] and differences in microenvironmental signal modulation[18]. A better understanding of age-related biology factors should be achieved through an integrated and comprehensive approach including the genomic aspects along with multi-professional cooperation of both paediatric and adult sarcoma experts to improve our knowledge of tumorigenesis in AYA patients with RMS. This will potentially lead to the identification of targeted treatments and further improvement of outcomes.

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Tables and figures

Figure 1. Study flow diagram.

Figure 2. Overall survival (OS) according to the age groups, in all series (A) and in patients with localised (B) and metastatic disease (C), respectively. In patients with localised RMS, 5-year OS was 69.7% (95% CI 62.4-75.9) and 81.9% (95% CI 79.8-83.8) in patients aged ≥15 and <15 years (p-value = 0.0004); in patients with metastatic RMS, 5-year OS was 15.8% (95% CI 7.3-27.1) and 44.7% (95% CI 36.8-52.3), respectively (p-value <0.0001).

Table 1. Clinical characteristics of the patients, according to the age categories (children vs AYA). Analysis on patients eligible for the two protocols (RMS 2005 and MTS 2008).

Table 2. 5-year event-free survival (EFS) and overall survival (OS) for different histology subgroups, according to the age categories.

Table 3. Type of first events by age, according to the two different studies (RMS 2005 and MTS 2008).

Table 4. Worst grade of toxicity in patients with localised high-risk RMS, enrolled in the randomised trial, treated in the IVA and in the IVADo arm, respectively, according to the age categories (Fisher exact test; Chi-square test)

Supplemental Table 1. Risk grouping stratification and therapy

Supplemental Table 2. Univariable analysis for the whole series of patients

Supplemental Table 3. Univariable analysis for the whole series of patients, with hazard ratios

Supplemental Table 4. Univariable analyses for localised and metastatic patients

Supplemental Table 5. Multivariable analysis of survival

Declaration of interests

Andrea Ferrari - no conflict of interests

Julia C Chisholm – she has acted in a consulting/advisory role for Bayer

Meriel Jenney – no conflict of interests

Veronique Minard-Colin – no conflict of interests

Daniel Orbach - no conflict of interests

Michela Casanova - no conflict of interests

Gabriela Guillen - no conflict of interests

Heidi Glosli - no conflict of interests

Rick R van Rijn - no conflict of interests

Reineke A. Schoot - no conflict of interests

Alison L. Cameron - no conflict of interests

Timothy Rogers - no conflict of interests

Rita Alaggio - no conflict of interests

Myriam Ben-Arush - no conflict of interests

Henry C. Mandeville - no conflict of interests

Christine Devalck - no conflict of interests

Anne-Sophie Defachelles - no conflict of interests

Beatrice Coppadoro - no conflict of interests

Gianni Bisogno - no conflict of interests

Johannes H M Merks - no conflict of interests

Data sharing statements

Individual participant data are not publicly available since this requirement was not anticipated in the study protocol.

The protocols can be requested through the EpSSG website: https://www.epssgassociation.it/en/.

Contributors statement

- **Conceptualisation and study design –** Ferrari, Bisogno, Merks
- **Literature search -** all authors
- **Data collection** – all authors
- **Data analysis** – Ferrari, Coppadoro, Casanova, Schoot, Bisogno, Merks
- **Data interpretation -** all authors
- **Writing original draft** - Ferrari, Bisogno, Merks
- **Writing review -** all authors
- **Editing -** all authors
- **Final approval** - all authors

AF, BC, GB and JHMM had full access to the raw data, and were responsible for the decision to submit the present paper for publication on behalf of the EpSSG board members.

The corresponding author confirms that all authors have seen and approved of the final text.

570 **Table 1 –** Clinical characteristics of the patients, according to the age categories (children vs AYA). Analysis on
571 patients eligible for the two protocols (RMS 2005 and MTS 2008).
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	Age <15 years n=1720	**Age≥15 years n=257**	**Total (%) n=1977**	**Chi-square test p-value** [a]
Median age (years)	4.7	16.6	5.5	---
Range	0-14.9	15.0-20.8	0-20.8	
IQR (years)	2.6-8.4	15.8-18.0	2.9-11.1	
Protocol				
EpSSG RMS2005	1523 (88.5%)	196 (76.3%)	1719 (87.0%)	**<0.0001**
EpSSG MTS2008	197 (11.5%)	61 (23.7%)	258 (13.0%)	
Gender				
Female	712 (41.4%)	79 (30.7%)	791 (40.0%)	**0.0011**
Male	1008 (58.6%)	178 (69.3%)	1186 (60.0%)	
Histology [b]				
Favourable RMS	1269 (73.8%)	138 (53.7%)	1407 (71.2%)	**<0.0001**
Unfavourable RMS	451 (26.2%)	119 (46.3%)	570 (28.8%)	
Tumour primary site				
Orbit	179 (10.4%)	7 (2.7%)	186 (9.4%)	**<0.0001***
HNnoPM	158 (9.2%)	16 (6.2%)	174 (8.8%)	
HNPM	419 (24.4%)	43 (16.7%)	462 (23.4%)	
GUBP	206 (12.0%)	23 (8.9%)	229 (11.6%)	
GUnoBP	247 (14.4%)	102 (39.7%)	349 (17.7%)	
Extremities	229 (13.3%)	31 (12.1%)	260 (13.2%)	
Other sites	280 (16.3%)	32 (12.5%)	312 (15.8%)	
Unknown	2 (0.1%)	3 (1.2%)	5 (0.3%)	
Tumour primary site [c]				
Favourable site	584 (34.0%)	125 (48.6%)	709 (35.9%)	**<0.0001**
Unfavourable site	1136 (66.0%)	132 (51.4%)	1268 (64.1%)	
IRS Group [d]				
IRS Group I	156 (9.1%)	54 (21.0%)	210 (10.6%)	**<0.0001**
IRS Group II	183 (10.6%)	30 (11.7%)	213 (10.8%)	
IRS Group III	1184 (68.8%)	112 (43.6%)	1296 (65.6%)	
IRS Group IV	197 (11.5%)	61 (23.7%)	258 (13.1%)	
T-invasiveness				
T1	908 (52.8%)	112 (43.6%)	1020 (51.6%)	**0.0078**^
T2	798 (46.4%)	141 (54.8%)	939 (47.5%)	
T0/Tx	14 (0.8%)	4 (1.6%)	18 (0.9%)	
Tumor size				
≤5 cm	808 (47.0%)	74 (28.8%)	882 (44.6%)	**<0.0001**^^
>5 cm	891 (51.8%)	177 (68.9%)	1068 (54.0%)	
Size not available	21 (1.2%)	6 (2.3%)	27 (1.4%)	
Nodal involvement				
N0	1370 (79.7%)	145 (56.4%)	1515 (76.6%)	**<0.0001**^^^
N1	339 (19.7%)	109 (42.4%)	448 (22.7%)	
Nx	11 (0.6%)	3 (1.2%)	14 (0.7%)	
Median fup, months (IQR)				
Non-metastatic	72.8 (52.4-100.8)	74.9 (51.3-102.9)	72.9 (52.4-101.7)	
Metastatic	51.6 (36.5-70.7)	60.5 (37.5-84.7)	52.6 (36.5-72.5)	

573 Excluded patients: * 5 with tumour primary site unknown; ^ 18 T0/Tx; ^^ 27 with size not available; ^^^ 14 Nx
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[a] Chi-square test p-values investigate the differences in the distribution by each clinical characteristic and age groups. The statistical significance level is $p<0.05$.

[b] favourable RMS: embryonal RMS, botryoid RMS, spindle cell RMS;
unfavourable RMS: alveolar RMS, mixed embryonal/alveolar RMS, solid alveolar RMS, not-otherwise-specified RMS;

[c] favourable site: orbit, HNnoPM, GUnoBP
unfavourable site: HNPM, GUBP, extremities, other sites, unknown

[d] IRS Group I: primary complete resection (R0 surgery); IRS Group II: microscopic residual disease (R1 surgery) or primary complete resection but N1; IRS Group III: macroscopic residual disease (R2 surgery or biopsy); IRS Group IV: metastatic disease

Legend:
AYA - adolescents and young adults
EpSSG - European paediatric Soft tissue sarcoma Study Group
RMS - rhabdomyosarcoma
IRS - Intergroup Rhabdomyosarcoma Study grouping
HNnoPM – head & neck, no parameningeal
HNPM - head & neck, parameningeal
GUBP – genito-urinary, bladder & prostate
GUnoBP - genito-urinary, no bladder & prostate

Table 2. 5-year event-free survival (EFS) and overall survival (OS) for different histology subgroups, according to the age categories.

	N	5-yr EFS (95%CI)		p-value	5-yr OS (95%CI)		p-value
		Age <15 years	Age ≥15 years		Age <15 years	Age ≥15 years	
All series	1977	67.8% (65.5-70.0)	52.6% (46.3-58.6)	<0.0001	77.9% (75.8-79.8)	57.1% (50.4-63.1)	<0.0001
Localised RMS	1719	71.6% (69.2-73.9)	63.6% (56.3-69.9)	0.013	81.9% (79.8-83.8)	69.7% (62.4-75.9)	0.0004
Metastatic RMS	258	38.1% (31.0-45.2)	17.7% (9.3-28.2)	0.0002	44.7% (36.8-52.3)	15.8% (7.3-27.1)	<0.0001
Combined series, unfavourable histotypes	570	53.8% (49.0-58.3)	36.8% (28.2-45.4)	<0.0001	64.0% (59.1-68.4)	36.7% (27.5-45.9)	<0.0001
Localised RMSs, unfavourable histotypes	422	62.1% (56.7-67.0)	49.0% (37.4-59.6)	0.015	72.3% (67.0-76.9)	50.2% (37.6-61.5)	0.0003
Metastatic RMS, unfavourable histotypes	148	26.0% (17.5-35.2)	14.3% (5.8-26.5)	0.016	34.3% (24.1-44.8)	12.5% (4.4-25.1)	0.001
Combined series, favourable histotypes	1407	72.8% (70.3-75.3)	66.5% (57.8-73.9)	0.12	82.8% (80.6-84.9)	74.7% (66.2-81.3)	0.058
Localised RMS, favourable histotypes	1297	74.4% (71.8-76.9)	73.1% (64.0-80.3)	0.80	84.8% (82.6-86.8)	82.3% (73.9-88.2)	0.71
Metastatic RMS, favourable histotypes	110	52.0% (40.7-62.1)	25.3% (8.6-46.2)	0.021	56.2% (44.5-66.5)	20.3% (3.9-45.5)	0.037

Legend:
favourable histotypes: embryonal RMS, botryoid RMS, spindle cell RMS;

unfavourable histotypes: alveolar RMS, mixed embryonal/alveolar RMS, solid alveolar RMS, not-otherwise-specified RMS;

Table 3. Type of events by age, according to the two different studies (RMS 2005 and MTS 2008).

	EpSSG RMS2005 study				EpSSG MTS2008 study			
	Age<15 yrs n=437	**Age≥15 yrs n=73**	**Total n=510**	**p-value**	**Age<15 yrs n=119**	**Age≥15 yrs n=50**	**Total n=169**	**p-value**
Local failure	257 (58.8%)	27 (37.0%)	284 (55.7%)	**0.002**	22 (18.6%)	3 (6.0%)	25 (14.9%)	**0.038***
Regional failure	40 (9.2%)	13 (17.8%)	53 (10.4%)		5 (4.3%)	-	5 (3.0%)	
Metastatic failure	111 (25.4%)	29 (39.7%)	140 (27.5%)		88 (74.6%)	44 (88.0%)	132 (78.6%)	
Unknown site of progression	-	-	-		1	-	1	
Other events	29 (6.6%)	4 (5.5%)	33 (6.4%)		3 (2.5%)	3 (6.0%)	6 (3.5%)	

Fisher's exact test p-values
*The patient with unknown site of progressive disease has been excluded.

Legend:
Local failure: local progression, local relapse
Regional failure: regional lymph nodal relapse with or without concomitant local failure
Metastatic failure: metastatic progression or relapse with or without local and/or regional failure
Other events: refusal of therapy, protocol discontinuation due to toxicity, second tumour, dead for other causes

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Table 4. Worst grade of toxicity in patients with localised high-risk RMS, enrolled in the randomised trial, treated in the IVA and in the IVADo arm, respectively, according to the age categories (Fisher exact test; Chi-square test)

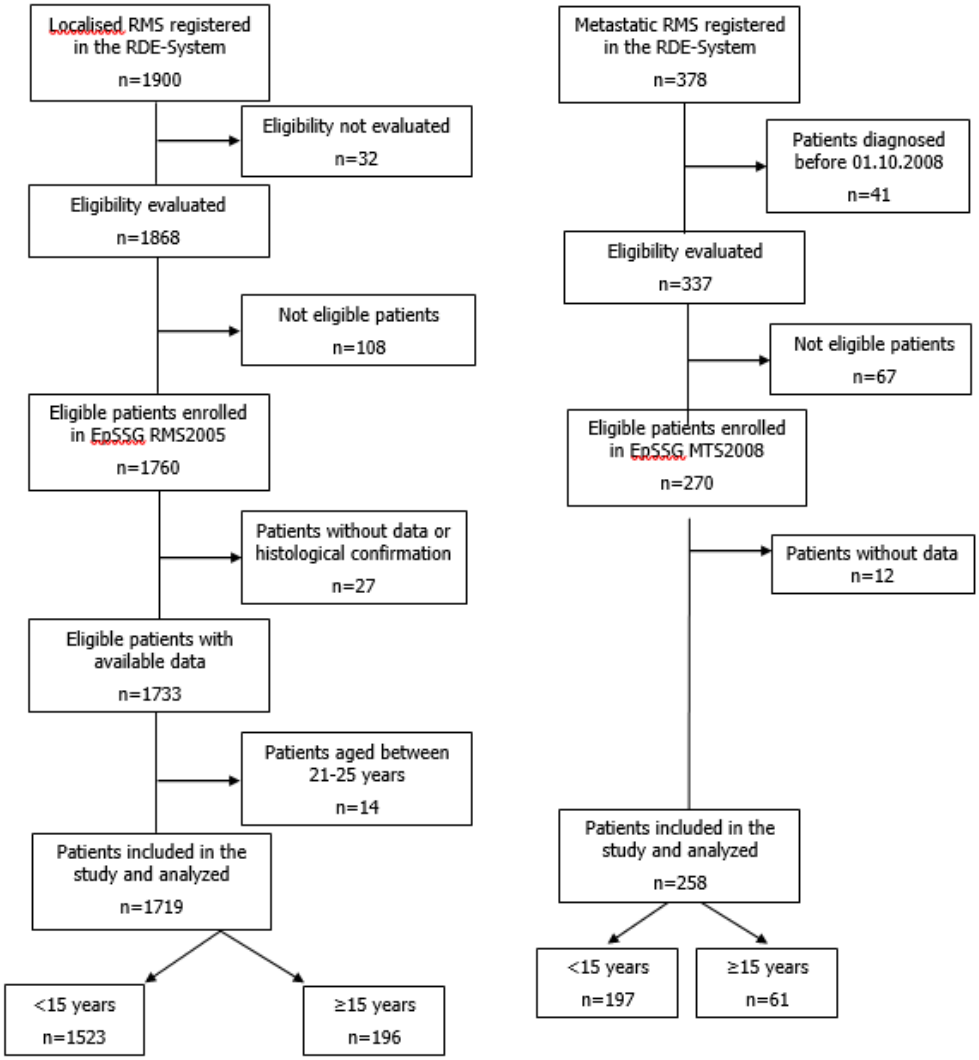
Toxicity category	IVA			IVADo		
	<15yrs n=420	**≥15yrs** n=42		**<15yrs** n=273	**≥15yrs** n=34	
	G_{3-4} (%)	G_{3-4} (%)	p-value	G_{3-4} (%)	G_{3-4} (%)	p-value
Haematological toxicity						
Haemoglobin	241 (57.4%)	7 (16.7%)	<0.0001	211 (77.3%)	14 (41.2%)	<0.0001
Leukocytes	363 (86.4%)	26 (61.9%)	<0.0001	252 (92.3%)	31 (91.2%)	0.74
Neutrophilis	380 (90.5%)	30 (71.4%)	0.0002	259 (94.9%)	32 (94.1%)	0.69
Platelets	132 (31.4%)	5 (11.9%)	0.0074	189 (69.2%)	13 (38.2%)	0.0003
Non-haematological toxicity						
Cardiac	4 (1.0%)	-	0.99	6 (2.2%)	-	0.99
Hepatotoxicity	3 (0.7%)	-	0.99	3 (1.1%)	-	0.99
Infection	279 (66.4%)	14 (33.3%)	<0.0001	232 (85.0%)	19 (55.9%)	<0.0001
Nephrotoxicity	14 (3.3%)	2 (4.8%)	0.65	9 (3.3%)	2 (5.9%)	0.35
Neurology	42 (10.0%)	4 (9.5%)	0.99	25 (9.2%)	2 (5.9%)	0.75
Nausea	76 (18.1%)	5 (11.9%)	0.40	64 (23.4%)	6 (17.6%)	0.45
Gastrointestinal	57 (13.6%)	1 (2.4%)	0.046	92 (33.7%)	12 (35.3%)	0.85
Allergy	-	-	-	1 (0.4%)	1 (2.9%)	0.21
Dermatological	16 (3.8%)	1 (2.4%)	0.99	10 (3.7%)	1 (2.9%)	0.99
Other	38 (9.0%)	2 (4.8%)	0.56	42 (15.4%)	5 (14.7%)	0.99

Legend:

IVA = ifosfamide, vincristine, actinomycin-D

IVADo = ifosfamide, vincristine, actinomycin-D, doxorubicin

622 Figure 1



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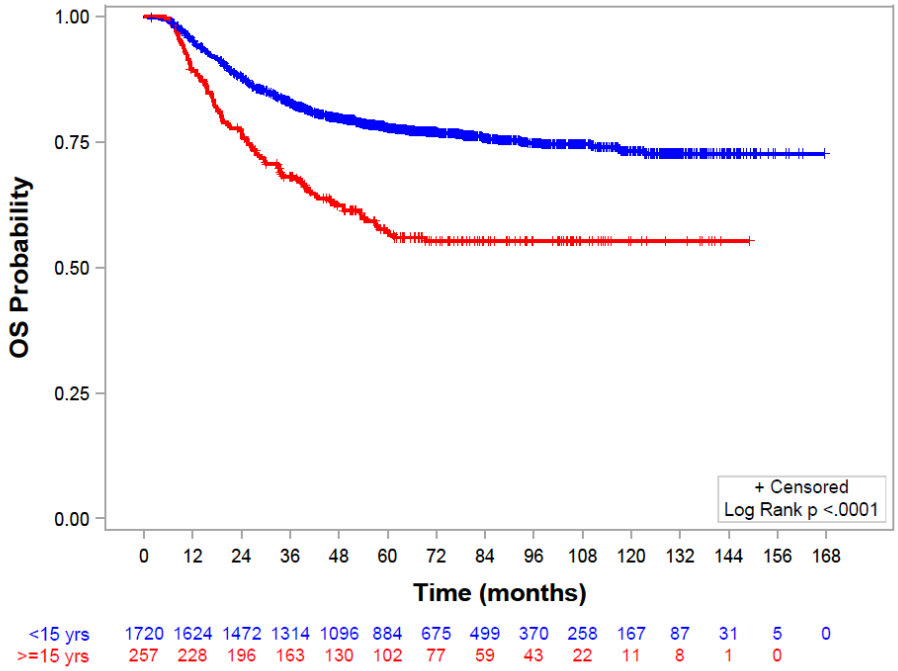
625 Figure 2



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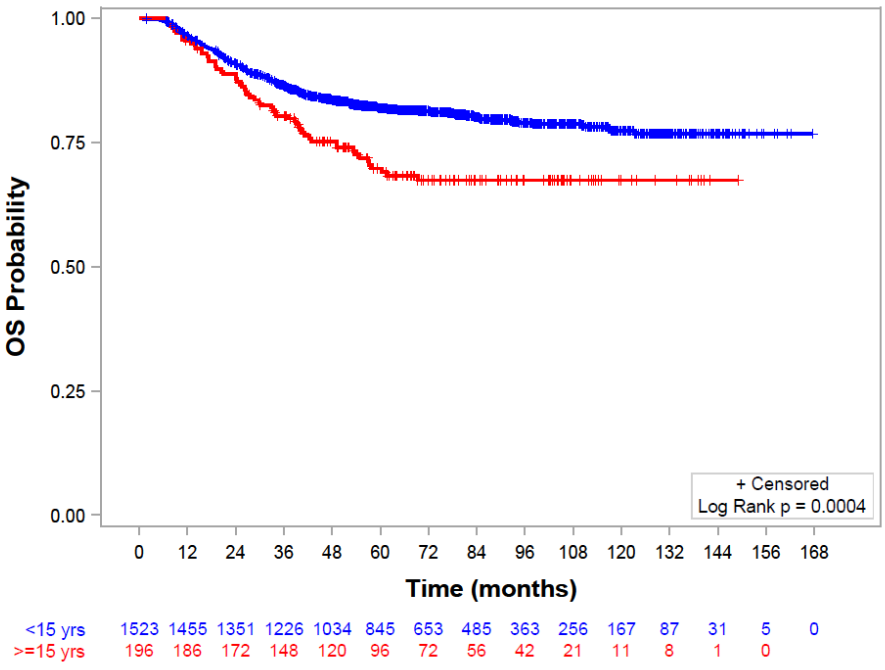

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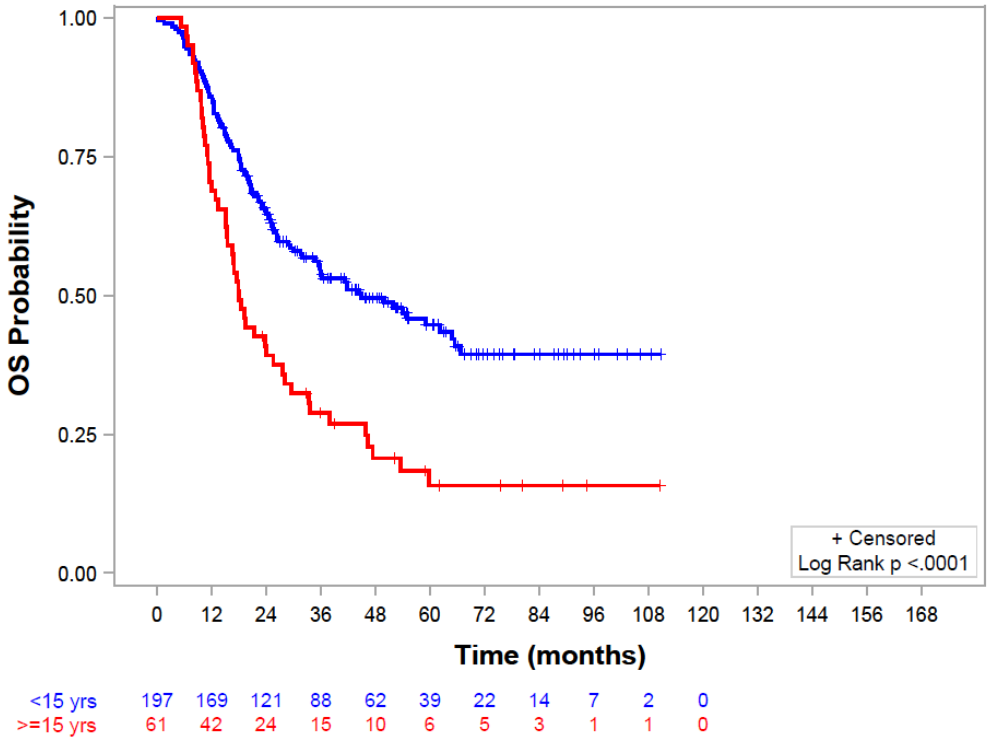
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0.75
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OS Probability
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0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
Time (months)
<15 yrs 197 169 121 88 62 39 22 14 7 2 0
>=15 yrs 61 42 24 15 10 6 5 3 1 1 0

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