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

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Summary

Background Adolescent and young adult patients with rhabdomyosarcoma often have poorer outcomes than do children. We aimed to compare the findings of adolescent and young adult patients with children enrolled in two prospective clinical protocols.

Methods This retrospective observational analysis was based on data from the European paediatric Soft tissue sarcoma Study Group (EpSSG) rhabdomyosarcoma 2005 trial (phase 3 randomised trial for localised rhabdomyosarcoma, open from April, 2006, to December, 2016) and the EpSSG MTS 2008 protocol (prospective, observational, single-arm study for metastatic rhabdomyosarcoma, open from June, 2010, to December, 2016), which involved 108 centres from 14 different countries in total. For this analysis, patients were categorised according to their age into children (age 0–14 years) and adolescents and young adults (age 15–21 years). For the analysis of adherence to treatment and toxicity, only patients with high-risk localised rhabdomyosarcoma included in the randomised part of the rhabdomyosarcoma 2005 study were considered. The primary outcome of event-free survival (assessed in all participants) was defined as the time from diagnosis to the first event (eg, tumour progression, relapse) or to the latest follow-up. Secondary outcomes were overall survival, response to chemotherapy, and toxicity.

Findings Our analysis included 1977 patients, 1720 children (median age 4·7 years; IQR 2·6–8·4) and 257 adolescents and young adults (16·6 years; 15·8–18·0). 1719 patients were from the EpSSG rhabdomyosarcoma 2005 study (1523 aged <15 years and 196 aged 15–21 years) and 258 patients were from the EPSSG MTS 2008 study (197 aged <15 years and 61 aged 15–21 years). Adolescent and young adult patients were more likely than were children to have metastatic tumours (61 [23·7%] of 257 *vs* 197 [11·5%] of 1720; p<0·0001), unfavourable histological subtypes (119 [46·3%] *vs* 451 [26·2%]; p<0·0001), tumours larger than 5 cm (177 [68·9%] *vs* 891 [51·8%]; p<0·0001), and regional lymph node involvement (109 [42·4%] *vs* 339 [19·7%]; p<0·0001). Adolescent and young adult patients had lower 5-year event-free survival (52·6% [95% CI 46·3–58·6] *vs* 67·8% [65·5–70·0]; p<0·0001) and lower 5-year overall survival (57·1% [50·4–63·1] *vs* 77·9% [75·8–79·8]; p<0·0001) than did children. The multivariable analysis confirmed the inferior prognosis of patients aged 15–21 years (hazard ratios 1·48 [95% CI 1·20–1·83; p=0·0002] for poorer event-free survival and 1·73 [1·37–2·19; p<0·0001] for poorer overall survival). Modifications of administered chemotherapy occurred in 13 (15·3%) of 85 adolescents and young adults, and in 161 (21·4%) of 754 children. Grade 3–4 haematological toxicity and infection were observed more frequently in children than in adolescent and young adult patients.

Interpretation This study found better outcomes for adolescent and young adult patients than those reported in epidemiological studies (eg, the EUROCARE-5 study reported 5-year overall survival of 39·6% for patients aged 15–19 years in the 2000–07 study period), suggesting that adolescent and young adult patients, at least up to age 21 years, can be treated with intensive paediatric therapies with no major tolerability issues and should be included in paediatric rhabdomyosarcoma trials. However, the inferior outcomes in adolescent and young adult patients compared with those in children, despite receiving similar therapy, suggest that a tailored and intensive treatment strategy might be warranted for these patients.

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Introduction

Rhabdomyosarcoma is a highly malignant mesenchymal neoplasm with cancer cells characterised 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 cases per million in those aged 0–19 years, and 400 new cases occurring each year across Europe in this age

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Research in context

Evidence before this study

Several studies have reported that adolescent and young adult patients with rhabdomyosarcoma have poorer survival than do younger patients. This inferior outcome is likely to be multifactorial; however, differences in clinical management—including infrequent referrals to experienced centres, low enrolment into clinical trials, or less intensive treatments because of decreased tolerance to chemotherapy—have been suggested to play a role. For the purposes of this report, we 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". The studies identified in the search formed the background information for the current analysis and were included in the Referenced list.

Added value of this study

To our knowledge, this is the first study to ascertain whether the outcomes of adolescent and young adult patients (here defined as those aged 15–21 years) were persistently worse than in children when enrolled in the same clinical trials and receiving similar treatments. We compared clinical findings, treatment data, toxicity, and outcome by age category of patients with rhabdomyosarcoma enrolled in two prospective clinical protocols developed by the European paediatric Soft tissue sarcoma Study Group (EpSSG). By focusing on patients enrolled into EpSSG trials, we could eliminate the potential impact on survival of a lower recruitment of adolescent and young adult patients into clinical trials. We found better survival data than those reported in epidemiological studies, supporting the inclusion of adolescent and young adult patients with rhabdomyosarcoma in paediatric trials to receive therapy derived from paediatric protocols. Our study did not report major toxicity and major protocol modifications in the two age groups, suggesting that adolescent and young adult patients, at least up to age 21 years, 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 adolescent and young adult patients than in children, even with the same treatment strategies.

Implications of all the available evidence

Our findings support the strategy of the current EpSSG rhabdomyosarcoma study (ie, the Frontline and Relapsed Rhabdomyosarcoma [FarRMS] study, opened in 2021) to include adult patients without an upper age limit. The inclusion of adolescent and young adult patients in paediatric trials to receive therapy derived from paediatric protocols is feasible and can improve the prognosis of adolescent and young adult patients with rhabdomyosarcoma. However, the inferior outcome of these patients suggests that a tailored and intensive treatment strategy might be warranted. Our findings also suggest that in older patients, more aggressive tumour biology might play an important role in the different outcomes. A better understanding of age-related biology factors (including pharmacokinetic and pharmacodynamic factors) is required and could lead to identification of specific targeted treatments to improve outcomes in adolescents and young adults.

range.[2] Rhabdomyosarcoma is considered a typical tumour of childhood but can occur at any age[3–4] Although this aggressive tumour has a strong propensity to metastasise,[1] it is often responsive to conventional chemotherapy. Paediatric oncology studies in the past 10–15 years report survival rates of more than 70% for patients with localised 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, and presence of lymph node or distant metastases.[5–8] Additionally, patient age has an effect on survival, with age older than 10 years has been identified as an adverse prognostic variable in paediatric studies.[11] Poorer outcomes have been reported for adolescents than for younger patients,[12] and adults carry an even higher risk of severe outcomes, with overall survival of adult patients lower than 40%.[3,13–16]

The epidemiological EUROCARE-5 study (study period 2000–07) reported a 66·6% 5-year relative survival among patients 0–14 years old, as compared with 39·6% for patients aged 15–19 years, and 36·4% for those aged 20–39 years.[17] The inferior survival of adolescents and even worse survival in adults is likely to be multifactorial,[9,10] and might be influenced by potential differences in tumour biology[18,19] or differences in clinical management, such as diagnostic delay,[20] infrequent referral to experienced centres,[21] poor enrolment into clinical trials,[22] or less intensive treatments because of decreased tolerance to chemotherapy in older patients.[23]

Adolescents and young adults are increasingly seen as a distinct category of patients with specific clinical needs.[24] The definition of adolescents and young adults varies considerably from country to country. In oncology studies, although adolescence is usually defined as age 15–19 years, 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 for adolescents and young adults).[24] The clinical management of adolescent and young adult patients is challenging. For many tumour types, this patient group has inferior survival compared with other age groups. The unsatisfactory survival data reported for adolescent

and young adult patients with rhabdomyosarcoma prompted the European paediatric Soft tissue sarcoma Study Group (EpSSG) to specifically focus on these patients. In this study, we aimed to analyse clinical findings, treatment data, toxicity, and outcome of patients with rhabdomyosarcoma aged 15–21 years and compare them to those aged 0–14 years. This study included patients registered onto the EpSSG rhabdomyosarcoma 2005 trial, for patients with localised rhabdomyosarcoma, and onto the EpSSG MTS 2008 for patients with metastatic rhabdomyosarcoma. The main aim of the analysis was to ascertain whether the outcomes in adolescent and young adult patients (here defined as those aged 15–21 years at diagnosis) were persistently worse than those in children when enrolled in the same clinical trials and receiving similar treatments.

Methods

Study design and participants

The retrospective analysis was based on the EpSSG rhabdomyosarcoma 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 academic centres and hospitals from 14 different countries (Argentina, Belgium, Brazil, Czech Republic, France, Ireland, Israel, Italy, Norway, Switzerland, Slovenia, Spain, the Netherlands, and the UK).

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 investigating the value of a maintenance treatment after standard therapy in patients with high-risk localised rhabdomyosarcoma. Patients with low, standard, and very high-risk localised rhabdomyosarcoma were also included in the rhabdomyosarcoma 2005 trial and treated according to standardised guidelines. The methods and results of rhabdomyosarcoma 2005, including the two randomisations, have been reported elsewhere.[7,8,25,26] Concerning age criteria, patients younger than age 25 years were eligible for inclusion in the study, while patients older than 6 months and younger than 21 years were eligible for the randomisation. Patients were stratified into different risk groups according to six prognostic factors, including histological subtype (embryonal *vs* alveolar; pleomorphic rhabdomyosarcoma 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 (about 50% of cases) were those with non-metastatic embryonal rhabdomyosarcoma, incompletely resected at diagnosis (IRS group II or III), localised at unfavourable sites (ie, parameningeal, extremities, genitourinary bladder-prostate, and other sites), and tumour size more than 5 cm or patients aged 10 years or older (subgroup E); non-metastatic embryonal rhabdomyosarcoma, incompletely resected (IRS group II or III) and involvement of regional nodes (subgroup F); and non-metastatic alveolar rhabdomyosarcoma without nodal involvement (subgroup G). High-risk patients were considered eligible for the randomisations 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 cycles of IVA chemotherapy, plus local treatment (radiotherapy or surgery, or both). 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 (appendix pp 1–2).[7,8]

See Online for appendix

The EpSSG MTS 2008 study was a prospective, observational, single-arm study for patients with metastatic

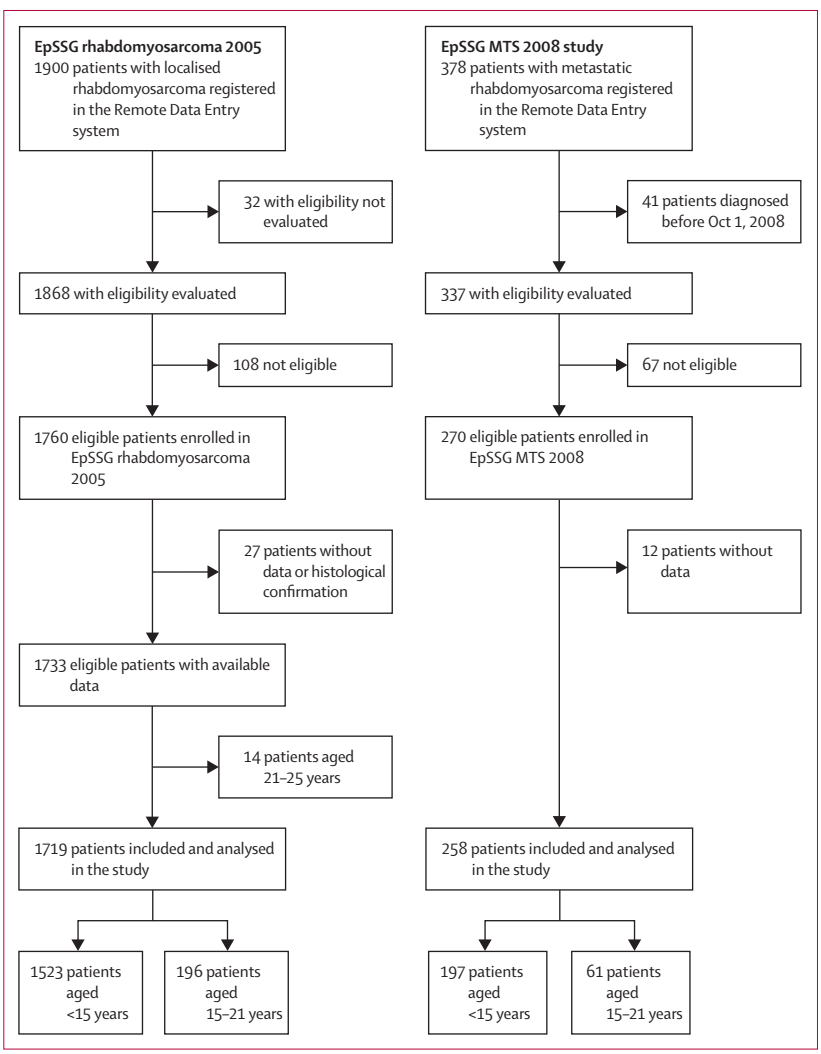

Figure 1: **Study profiles for EpSSG rhabdomyosarcoma 2005 and EpSSG MTS 2008**
EpSSG=European paediatric Soft tissue sarcoma Study Group.

	Younger than age 15 years (n=1720)	Age 15–21 years (n=257)	Total (n=1977)	p value*
Age				
Median age, years	4·7	16·6	5·5	..
Range	0–14·9	15·0–20·8	0–20·8	..
IQR	2·6–8·4	15·8–18·0	2·9–11·1	..
Protocol				
EpSSG rhabdomyosarcoma 2005	1523 (88·5%)	196 (76·3%)	1719 (86·9%)	<0·0001
EpSSG MTS 2008	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†				
Favourable	1269 (73·8%)	138 (53·7%)	1407 (71·2%)	<0·0001
Unfavourable	451 (26·2%)	119 (46·3%)	570 (28·8%)	..
Tumour primary site				
Orbit	179 (10·4%)	7 (2·7%)	186 (9·4%)	<0·0001
Head and neck, no parameningeal	158 (9·2%)	16 (6·2%)	174 (8·8%)	..
Head and neck, parameningeal	419 (24·4%)	43 (16·7%)	462 (23·4%)	..
Genito-urinary, bladder and prostate	206 (12·0%)	23 (8·9%)	229 (11·6%)	..
Genito-urinary, no bladder and prostate	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‡				
Favourable site	584 (34·0%)	125 (48·6%)	709 (35·9%)	<0·0001
Unfavourable site	1136 (66·0%)	132 (51·4%)	1268 (64·1%)	..
Intergroup Rhabdomyosarcoma Study grouping§				
I	156 (9·1%)	54 (21·0%)	210 (10·6%)	<0·0001
II	183 (10·6%)	30 (11·7%)	213 (10·8%)	..
III	1184 (68·8%)	112 (43·6%)	1296 (65·6%)	..
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 (54·9%)	939 (47·5%)	..
Unknown or unspecified	14 (0·8%)	4 (1·6%)	18 (0·9%)	..
Tumour size, cm				
≤5	808 (47·0%)	74 (28·8%)	882 (44·6%)	<0·0001
>5	891 (51·8%)	177 (68·9%)	1068 (54·0%)	..
Size not available	21 (1·2%)	6 (2·3%)	27 (1·4%)	..

(Table 1 continues on next page)

rhabdomyosarcoma. Eligibility criteria included age 21 years or younger. Patients were treated with nine cycles of induction chemotherapy comprising four cycles of IVADo and five cycles of IVA, followed by 12 4-week cycles of maintenance therapy with vinorelbine and cyclophosphamide. Treatment of the primary tumour included surgery or radiotherapy, as well as radiotherapy to all metastatic sites, when feasible. The publication of the main results of the EpSSG MTS 2008 is in press.[27]

For more on **EpSSG** see https://www.epssgassociation.it/en/

The EpSSG rhabdomyosarcoma 2005 and MTS 2008 studies were done 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 also obtained written informed consent from the patient or their parents or legal guardians.

Procedures and outcomes

For the current analysis, patients eligible for the two protocols (rhabdomyosarcoma 2005 and MTS 2008) and with available data on treatment and outcome, were categorised according to age at diagnosis into children (age 0–14 years) and adolescents and young adults (age ≥15 and <21 years). The few participants aged 21 years or older and younger than age 25 years registered in the rhabdomyosarcoma 2005 study but not considered eligible for the randomisation were excluded from the analysis to make the subgroups of patients with localised and metastatic disease more comparable. To compare adolescent and young adult patients and children regarding adherence to the protocol and treatment toxicity, we analysed only patients with high-risk localised rhabdomyosarcoma included in the two randomisations. Electronic case report forms were different for the different risk groups, and more details on treatment administration (such as administered dose for each chemotherapy cycle) and toxicity (details on any grade of toxicity and specific type of adverse event) were collected for randomly assigned patients compared with other patients. For this analysis, we considered only major modifications of the chemotherapy programme, defined as omission of single agents or omission of full chemotherapy cycle, or delay in chemotherapy administration longer than 2 weeks.

The primary outcome, event-free survival, 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 and was assessed in all participants. Secondary outcomes, were overall survival, response to chemotherapy, and toxicity. Overall survival was measured as the time from diagnosis to death due to any cause, or to the latest follow-up, and was assessed in all participants. Response to chemotherapy was assessed in high-risk localised patients with measurable disease, by measuring radiological tumour volume reduction after three cycles of chemotherapy.[7] Administered treatment, adherence to the protocol, and treatment toxicity were only evaluated in patients with high-risk localised rhabdomyosarcoma who were included in the EpSSG rhabdomyosarcoma 2005 study (because electronic case report forms included more details on treatment administration and toxicity in high-risk participants who were randomly assigned). Toxicity was evaluated according to the US National Cancer Institute Common Toxicity Criteria (version 3).[28]

Statistical analysis

For statistical analysis, continuous variables were summarised as medians and IQRs, and categorical variables were reported as counts and percentages. χ^2 tests or Fisher's exact test (depending on frequencies) were computed to investigate the differences in distribution of clinical characteristics and type of event by the two age groups. 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 (<15 years, 15–21 years), histology (favorable, unfavorable), tumour primary site (favorable, unfavorable), stage of disease (localised, metastatic), IRS group (I, II, III, IV), T-invasiveness (T1, T2), tumour size (≤5 cm, >5 cm), and loco-regional nodes involvement (N0, N1). 5-year event-free survival and 5-year overall survival with 95% CIs were calculated using the Greenwood method. All the prognostic factors were considered for their effect on event-free survival and overall survival by use of Cox univariable models to assess hazard ratios (HR) throughout the follow-up. A p-value of less than 0·05 was considered significant. Multivariable analysis was done for event-free survival and overall survival including variables with p less than 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 non-proportional factors and patients with unevaluable primary tumour sizes, unknown T-invasiveness, or unknown nodal involvement, 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 analysis, data interpretation, or writing of the report.

Results

Overall, 2278 patients were registered, 1900 from the EpSSG rhabdomyosarcoma 2005 study and 378 from the EpSSG MTS 2008 study. After excluding those not meeting eligibility criteria, those who lacked data or histological confirmation of rhabdomyosarcoma, and those aged 21–25 years, 1719 patients (1523 aged <15 years and 196 aged 15–21 years) from the EpSSG rhabdomyosarcoma 2005 study and 258 patients (197 aged <15 years and 61 aged 15–21 years) from the EpSSG MTS 2008 study were included in our analysis (figure 1). No imbalances were found regarding patient enrolment by year of study.

Of 1720 children, 712 (41·4%) were female and 1008 (58·6%) were male; of 257 adolescents and young adults, 79 (30·7%) were female and 178 (69·3%) were male. Adolescents and young adults were more likely than were children to have metastatic tumours (61 [23·7%] of 257 *vs* 197 [11·5%] of 1720; p<0·0001), unfavourable histological subtypes (119 [46·3%] *vs* 451 [26·2%]; p<0·0001), a tumour larger than 5 cm (177 [68·9%] *vs* 891 [51·8%]; p<0·0001), and regional lymph node involvement (109 [42·4%] *vs* 339 [19·7%]; p<0·0001; table 1). By contrast, children more often had tumours arising at unfavourable sites including parameningeal, bladder and prostate, extremities, and other sites (1136 [66·0%] of 1720 *vs* 132 [51·4%] of 257; p<0·0001). A high proportion (102 [39·7%] of 257) of adolescent and young adult patients had tumours in paratesticular and vaginal or uterus sites.

Outcome data were available for all 1977 patients. Median follow-up was 71·0 months (range 1·9–167·7; IQR 51·1–99·5). For all patients, the 5-year event-free survival was 65·9% (95% CI 63·7–67·9) and the overall survival was and 75·1% (73·1–77·0). For patients with localised rhabdomyosarcoma, the 5-year event-free survival was 70·7% (95% CI 68·4–72·8) and the overall survival was 80·5% (78·5–82·4), compared with event-free survival of 33·2% (27·3–39·2) and overall survival of 37·0% (30·4–43·7) for patients with metastatic disease.

Adolescent and young adult patients had significantly worse survival than did children. Overall, the 5-year event-free survival was 52·6% (95% CI 46·3–58·6) in adolescents and young adults and 67·8% (65·5–70·0) in children (p<0·0001), and the 5-year overall survival was 57·1% (50·4–63·1) in adolescents and young adults and 77·9% (75·8–79·8) in children (p<0·0001; figure 2).

(Continued from previous page)

	Younger than age 15 years (n=1720)	Age 15–21 years (n=257)	Total (n=1977)	p value*
Nodal involvement				
N0	1370 (79·7%)	145 (56·4%)	1515 (76·6%)	<0·0001
N1	339 (19·7%)	109 (42·4%)	448 (22·7%)	..
Unknown or unspecified	11 (0·6%)	3 (1·2%)	14 (0·7%)	..
Median follow-up, months				
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)	..

Data are n (%) or median (IQR) unless otherwise specified. The five patients with tumour primary site unknown, the 18 with unknown invasiveness, the 27 with tumour size not available, and the 14 with unspecified nodal involvement were excluded from analysis but included in percentage calculations for a descriptive purpose. T1=tumour localised to the organ or tissue of origin. T2=tumour extending beyond the tissue or organ of origin. N0=no evidence of loco-regional lymph node involvement. N1=evidence of loco-regional lymph node involvement. *p values generated from the χ^2 test investigate the differences in the distribution by each clinical characteristic and age groups, p<0·05 indicates statistical significance. †Favourable disease includes embryonal botryoid, and spindle cell rhabdomyosarcomas; unfavourable disease includes alveolar, mixed embryonal or alveolar, and solid alveolar rhabdomyosarcomas, and rhabomyosarcomas that were not otherwise specified. ‡Favourable site: orbit; head and neck, no parameningeal; genito-urinary, no bladder and prostate; unfavourable site: head and neck, parameningeal; genito-urinary, bladder and prostate; extremities; other sites; unknown. §Intergroup Rhabdomyosarcoma Study Group I: primary complete resection (R0 surgery); group II: microscopic residual disease (R1 surgery) or primary complete resection but N1; group III: macroscopic residual disease (R2 surgery or biopsy); group IV: metastatic disease.

Table 1: **Clinical characteristics of the patients eligible for the two protocols rhabdomyosarcoma 2005 and MTS 2008, according to age categories**

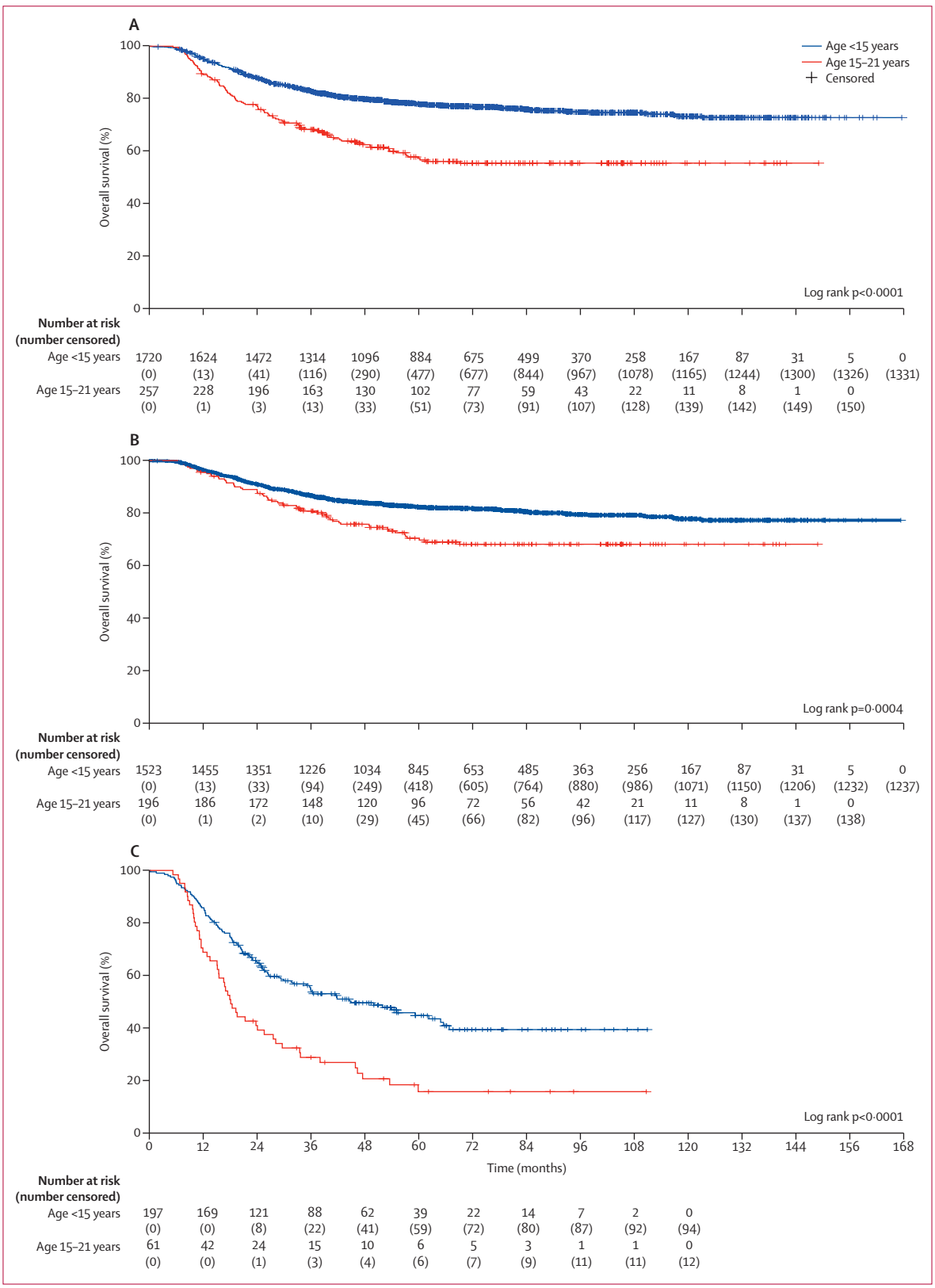

Figure 2: **Overall survival according to age group in all patients (A), in patients with localised rhabdomyosarcoma (B), and in patients with metastatic rhabdomyosarcoma (C)**

	N	5-year event-free survival (95%CI)		p value	5-year overall survival (95%CI)		p value
		Younger than age 15 years	Age 15–21 years		Younger than age 15 years	Age 15–21 years	
Overall							
Combined 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 rhabdomyosarcoma	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 rhabdomyosarcoma	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
Unfavourable histotypes							
Combined series	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 rhabdomyosarcoma	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 rhabdomyosarcoma	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)	0·0010
Favourable histotypes							
Combined series	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 rhabdomyosarcoma	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 rhabdomyosarcoma	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

Favourable histotypes include embryonal, botryoid, and spindle cell rhabdomyosarcomas; unfavourable histotypes include alveolar, mixed embryonal or alveolar, and solid alveolar rhabdomyosarcomas, and rhabomyosarcomas that were not otherwise specified.

Table 2: **5-year event-free survival and overall survival for different histology subgroups, by age category**

	EpSSG rhabdomyosarcoma 2005 study				EpSSG MTS 2008 study			
	Younger than age 15 years (n=437)	Age 15–21 years (n=73)	Total (n=510)	p value	Younger than age 15 years (n=119)	Age 15–21 years (n=50)	Total (n=169)	p value
Local failure	257 (58·8%)	27 (37·0%)	284 (55·7%)	0·0020	22 (18·5%)	3 (6·0%)	25 (14·8%)	0·038
Regional failure	40 (9·2%)	13 (17·8%)	53 (10·4%)	..	5 (4·2%)	0	5 (3·0%)	..
Metastatic failure	111 (25·4%)	29 (39·7%)	140 (27·5%)	..	88 (73·9%)	44 (88·0%)	132 (78·1%)	..
Unknown site of progression	0	0	0	..	1 (0·8%)	0	1 (0·6%)	..
Other events	29 (6·6%)	4 (5·5%)	33 (6·4%)	..	3 (2·5%)	3 (6·0%)	6 (3·6%)	..

Data are n (%) unless otherwise indicated. P values were calculated using Fisher's exact test, which compares the distribution of event types by age group, excluding the unknown site of progression category. The patient with unknown site of progressive disease has been excluded. Local failure is defined as local progression or local relapse. Regional failure is defined as regional lymph nodal relapse with or without concomitant local failure. Metastatic failure is defined as metastatic progression or relapse with or without local or regional failure. Other events include refusal of therapy, protocol discontinuation due to toxicity, second tumour, death due to other causes. EpSSG=the European paediatric Soft tissue sarcoma Study Group.

Table 3: **Type of events by age categorisation, according to the EpSSG rhabdomyosarcoma 2005 study and EpSSG MTS 2008 study**

Univariable analysis for the whole cohort, and by localised and metastatic disease, and multivariable analyses for event-free survival and overall survival is shown in the appendix (pp 3–9). The Cox regression model confirmed the inferior prognosis of patients aged 15–21 years, with hazard ratios of 1·48 (95% CI 1·20–1·83; p=0·0002) for poorer event-free survival and 1·73 (1·37–2·19; p<0·0001) for poorer overall survival.

Event-free survival and overall survival remained significantly different when outcomes for patients with non-metastatic and metastatic disease were analysed separately (figure 2). In patients with localised rhabdomyosarcoma, 5-year overall survival was 69·7% (95% CI 62·4–75·9) in adolescents and young adults and 81·9% (95% CI 79·8–83·8) in children (p=0·0004). In patients with metastatic rhabdomyosarcoma, 5-year overall survival was 15·8% (95% CI 7·3–27·1) in adolescents and young adults and 44·7% (36·8–52·3) in children (p<0·0001). There were significant differences in survival by histological subgroups between the two age groups, except for those with localised favourable histotypes (table 2).

Overall, 679 (34·3%) of 1977 patients developed an event and 496 (25·1%) died. The distribution of first events comparing adolescent and young adult patients with children in the two studies is presented in table 3. Although a relatively high proportion of local failure was recorded in children, regional and metastatic failures were more frequent in patients aged 15–21 years. Specifically in the rhabdomyosarcoma 2005 study, metastatic failure comprised 39·7% (29 of 73) of the events in the adolescent and young adults group, and 25·4% (111 of 437) in children (a χ^2 test resulted in a p value of 0·011).

Modifications of the chemotherapy programme were reported in 174 (20·7%) of 839 evaluable cases, including 13 (15·3%) of 85 adolescents and young adults and 161 (21·4%) of 754 children, with a difference of 6·0%

	IVA			IVADo		
	Younger than age 15 years (n=420)	Age 15–21 years (n=42)	p value	Younger than age 15 years (n=273)	Age 15–21 years (n=34)	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
Neutrophils	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	0·99	6 (2·2%)	0	0·99
Hepatotoxicity	3 (0·7%)	0	0·99	3 (1·1%)	0	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	0	0	..	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

Data are n (%) unless otherwise specified. p values were calculated using Fisher's exact test. IVA=ifosfamide, vincristine, actinomycin-D. IVADo=ifosfamide, vincristine, actinomycin-D, doxorubicin.

Table 4: **Grades 3–4 toxicity in patients with localised high-risk rhabdomyosarcoma enrolled in the randomised trial and treated in the IVA and in the IVADo groups, according to the age categories**

(95% CI 3·5–12·9). Tumour response evaluation was available for 689 patients with localised high-risk rhabdomyosarcoma. Response to chemotherapy was reported in 49 (84·4%) of 58 adolescents and young adults (seven with complete remission and 42 with partial remission) and in 564 (89·3%) of 631 children (32 with complete remission and 532 with partial remission). Radiotherapy was given to 72 (84·7%) of 85 adolescents and young adults and to 609 (80·4%) of 757 children. Considering only patients classified as IRS group III, delayed surgery was performed in 33 (51·6%) of 64 adolescents and young adults and in 357 (53·9%) of 662 children.

The acute grade 3–4 toxicities in patients with non-metastatic high-grade rhabdomyosarcoma enrolled in rhabdomyosarcoma 2005 who were randomly assigned to treatment with IVA or IVADo chemotherapy are presented in table 4. Haematological toxicity was more frequently reported for children than for adolescent and young adult patients. Infection associated with IVA and IVADo chemotherapy occurred in 14 (33·3%) of 42 adolescent and young adult patients treated with IVA and in 19 (55·9%) of 34 adolescent and young adult patients treated with IVADo, and in 279 (66·4%) of 420 children treated with IVA and 232 (85·0%) of 273 children treated with IVADo (p<0·0001).

Discussion

This study aimed to compare clinical findings, treatments, and outcome of rhabdomyosarcoma in adolescent and young adult patients (aged 15–21 years) with children (<15 years) enrolled in two prospective EpSSG clinical protocols.

The inferior outcome of adolescents and young adults with rhabdomyosarcoma has been previously 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.[9,10,20–23,29,30] Compared with children, adolescent and young adult patients often experience decentralised care and are not often enrolled into clinical trials. Adult patients do not generally have access to paediatric rhabdomyosarcoma protocols and cooperative prospective studies specifically dedicated to adult rhabdomyosarcoma have not been developed.[9,16] Limited inclusion of adolescent patients into rhabdomyosarcoma 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 during 2008–15. The study showed that adolescents were less represented in EpSSG protocols, even though the trials recruited patients up to 21 years of age; while 77% of the patients aged 0–14 years were included in EpSSG protocols, the percentage dropped to 64% for adolescents (15–19 years).[22]

The current study focused on those patients with rhabdomyosarcoma enrolled into EpSSG trials, therefore eliminating the potential effect on survival of the lower recruitment of adolescents into clinical trials. Primarily, our study confirmed that adolescent and young adult patients with rhabdomyosarcoma had significantly worse outcomes than did children. The 5-year overall survival was 57·1% in adolescent and young adult patients and 77·9% in children, and multivariable analysis confirmed that age 15–21 years was associated with poor overall survival. Outcomes remained significantly worse for adolescent and young adult patients when different subgroups were analysed, except for patients with non-metastatic favourable histotypes, who achieved similar results to children with the inclusion in a paediatric trial. The unfavourable clinical presentation of older patients when compared with children has been reported as an important factor explaining the poorer outcomes.[3,13–16] Our study confirmed that adolescent and young adult patients with rhabdomyosarcoma were more likely than were 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 aged 15–21 years, this was most frequently metastatic relapse. Speculation of the reasons for the high frequency of distant and lymph nodal metastases at onset, as well as on the significantly higher proportion of adolescent and

young adult patients developing metastatic relapse, remains difficult; however, these findings might potentially be seen as indirect markers of intrinsic tumour aggressiveness of rhabdomyosarcoma arising in adolescent and young adult patients. Patient age needs to be further investigated as a continuous variable to potentially determine whether a cut-off different from age 15 years could better identify the point at which outcomes for younger and older patients diverge.

A further aim of our study was to compare the treatment administered and treatment toxicity in adolescent and young adult patients with children. Studies have reported that adult patients with rhabdomyosarcoma have often not received treatment considered standard of care in paediatric patients.[13,16,23,29,30] This is because intensive treatments designed for children might be less well tolerated in older patients,[16] and the lack of experience of adult oncology teams in applying the key concepts of rhabdomyosarcoma therapy might hinder the possibility of adult patients receiving treatment in line with paediatric strategies.[13,21,23] Different studies suggested that the lower adherence to the principles adopted in paediatric protocols influenced patient outcomes.[13,16,23,29,30] In our study, we did not observe major toxicity and major protocol modifications in adolescent and young adult patients compared with children. We considered the possibility that adolescent and young adult patients might not truthfully report their compliance to the oral maintenance therapy, and therefore our study protocol required local researchers to ensure compliance of their patients several times during the therapy. Our analysis found that modifications of the chemotherapy programme were reported in 15·3% of patients aged 15–21 years and 21·3% of patients younger than age 15 years, and grade 3–4 haematological toxicity and infection were observed more frequently in children than in adolescent and young adult patients. These findings suggest that adolescent and young adult patients, at least up to 21 years old, can be treated with intensive therapies originally designed for children, with no major tolerability issues. Whether this strategy might also be applicable to older adults remains unknown (the upper age limit of the cohort at 21 years old was a major limitation of our study). Pharmacokinetic and pharmacodynamic studies are needed to investigate chemotherapy toxicity according to age, with the possible goal of optimising treatment protocol for different age groups (eg, more intensive treatments for adolescent and young adult patients).

In conclusion, our study of adolescent and young adult patients with rhabdomyosarcoma treated within paediatric clinical trials showed better results than those reported in epidemiological studies: the 5-year overall survival of 57·1% for patients aged 15–21 years (treated between 2005 and 2016) compared favourably with the 5-year overall survival of 39·6% for patients aged 15–19 years reported in the EUROCARE-5 study (2000–07).[17] This finding supports the strategy of the current EpSSG rhabdomyosarcoma study (ie, the Frontline and Relapsed Rhabdomyosarcoma [FarRMS] study, opened in 2020) to include adult patients without an upper age limit. The inclusion of adolescent and young adult patients in paediatric trials to receive therapy derived from paediatric protocols is feasible and can improve the prognosis of this age group of patients with rhabdomyosarcoma. However, our study showed that treatment results remained significantly worse in adolescents and young adults when compared with children, even when they are treated in the same way. A tailored treatment strategy might 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 might suggest that in older patients, more aggressive tumour biology could play an important role in the different outcomes. Increasing numbers of somatic mutations,[31] a high frequency of MYOD1-mutant tumours,[32] and differences in microenvironmental signal modulation might occur as children grow.[18] An integrated and comprehensive approach including the genomic aspects, along with professional cooperation of both paediatric and adult sarcoma experts, will be essential to to improve our knowledge of tumorigenesis in adolescent and young adult patients with rhabdomyosarcoma , including a better understanding of age-related biological factors, which will potentially help to identify targeted treatments to further improve outcomes.

Contributors

AF, GB, and JHMM were responsible for study conception and design and writing the original draft of the manuscript. All authors were involved in the literature search, data collection, data interpretation, writing review, and editing of the manuscript. AF, BC, MC, RAS, GB, and JHMM did the data analysis. AF and BC verified the underlying data. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

JCC has acted as a consultant and advisor for Bayer. All other authors declare no competing interests.

Data sharing statement

Individual participant data are not publicly available since this requirement was not anticipated in the study protocol. The protocols can be requested through the European paediatric Soft tissue sarcoma Study Group website.

For the **European paediatric Soft tissue sarcoma Study Group website** see https://www.epssgassociation.it/en/

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