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ORIGINAL PAPER

# Rhabdomyosarcoma in adults: analysis of treatment modalities in a prospective single-center series

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## Abstract

Rhabdomyosarcoma (RMS) is rare in adults and it is generally characterized by poor outcome. In a previous retrospective study, we demonstrated a better prognosis in adults treated with multimodality approach resembling pediatric protocols. Thereafter, we developed specific recommendations based on the principles adopted in pediatric oncology. The present analysis reports the results in a subsequent prospective series. The study included 95 consecutive patients (age 18–77 years) treated from 2002 to 2015 for embryonal and alveolar RMS. As in the previous series, patients were stratified by the appropriateness of their treatment according to therapeutic guidelines for childhood RMS. The 5-year event-free survival (EFS) and overall survival (OS) rates were 33.6% and 40.3%, respectively. The 5-year EFS was 40.8% for patients with the highest treatment score, and 15% for those with lower score, while OS was 44.4% and 24.5%, respectively. The developing of specific recommendations enabled an increase in the number of patients treated with intensive multimodal treatment resembling pediatric strategy (69.7% vs. 39.1% in the retrospective series). This study reinforced the idea that adherence to the principles of pediatric protocols, improves adult RMS outcomes. However, treating adults with pediatric-type strategy is not enough to achieve the results obtained in children. Issues in compliance and a more aggressive biology of adult RMS might have a role in the different outcome according to age. Improving the collaboration between pediatric and adult oncologists in promoting specific clinical and biological research is crucial to improve the outcome for this patient population.

**Keywords** Rhabdomyosarcoma · Adults · Multimodal treatment · Treatment score · Childhood tumors in adults · Soft tissue sarcoma

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## Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue tumor of pediatric age. It is classically distinguished in two variants - i.e., the embryonal and the alveolar RMS [1] – while the so-called pleomorphic RMS should be seen as a pleomorphic sarcoma with myogenic rhabdomyoblastic differentiation, so a specific entity more similar to adult non-RMS soft tissue sarcomas than to other RMS [2]. Though it is a very aggressive malignancy, the 5-year overall survival (OS) rates for children and adolescents with RMS are currently around 70% thanks to treatments based on collaborative international multi-institutional protocols. The resulting approach to treatment is a multidisciplinary (a combination of intensive chemotherapy, surgery, and radiotherapy) and risk-adapted strategy (different prognostic factors are used to stratify the intensity of treatment) [3, 4]. In contrast, RMS occurs very infrequently in adults (less than 1% of all adult malignancies are soft tissue sarcomas, and RMS accounts for only 3% of them) [1], and its prognosis is distinctly unsatisfactory (with a 5-year OS between 20% and 40%) [5–11]. Judging from various published series, the poor outcome for adults with pediatric-type RMS may be due to a less favorable clinical presentation, e.g., a higher incidence of the alveolar histotype or a higher frequency of large and metastatic tumors [5–11].

In 2003, our group reported on a retrospective single-center analysis conducted on 171 adults (aged 18 years or older) who were treated for RMS between 1975 and 2001 [12]. We analyzed the treatments administered and stratified patients by the appropriateness of each individual's treatment vis-à-vis the therapeutic guidelines for childhood RMS. The study confirmed the poor prognosis for adult patients (survival at 5 years was less than 40%). It also demonstrated that only 39% of the patients had been treated consistently with pediatric protocols, and that these patients had a significantly better outcome than the others. In other words, the study suggested that the difference in outcome for adults and children with RMS might be due, at least in part, to the former not receiving adequate multimodality treatments, as adopted in pediatric protocols. Hence the idea that adult patients might fare better if their treatments more closely resembled those adopted in children.

Since the publication of those results, our Institute has adopted various measures to improve the quality of treatment for adult patients with RMS by: a) increasing the cooperation between pediatric oncologists and adult sarcoma experts; b) managing all adult RMS cases on the strength of a multidisciplinary discussion attended by both pediatric and adult medical oncologists; c) developing specific recommendations for the treatment of adult RMS, based on the principles adopted by pediatric protocols; d) including young adult patients in ongoing pediatric trials whenever possible, since the pediatric oncology unit at our center is part of the European pediatric Soft tissue sarcoma Study Group (EpSSG), whose protocols were open to patients up to 21 years old; and e) prospectively registering all adult RMS cases in our institutional database.

The present paper reports the clinical findings and results of treatment in a subsequent prospective series of adult cases with pediatric-type RMS (treated between January 2002 and December 2015).

## Materials and methods

The study concerns a prospective series of 118 consecutive adult RMS patients treated between January 2002 and December 2015 at the Istituto Nazionale dei Tumori (INT) in Milan. The criteria for inclusion in the study were: 1) age ≥ 18 years; 2) a histologically-proven diagnosis of alveolar, embryonal (including the botryoid and spindle cell variants), or not otherwise specified (NOS) RMS (patients with pleomorphic RMS were excluded); 3) no previous treatment other than primary surgery; 4) details available on patients' clinical data, treatments, and outcome; and 5) written consent to treatments and data collection (i.e., inclusion of data in the institutional database). Patient's enrollment in EpSSG trials or other clinical studies was considered a reason for exclusion. On these grounds, 12 cases were excluded from the analysis because the patients were enrolled in the EpSSG trials, and another 11 because their data were incomplete.

### Clinical grouping

The disease was assessed and staged according to pediatric oncology criteria. Local extent was measured on computerized tomography (CT) and/or magnetic resonance imaging (MRI), distant localizations were identified on chest-abdominal CT scans, whole-body scans, and bone marrow aspirates and/or biopsies. The disease was staged according to the clinical tumor-nodes-metastases (TNM) system as T1 or T2, depending on local invasiveness, and as TA or TB, depending on tumor diameter ≤ or > 5 cm) [13]. It was also staged according to the post-surgical Intergroup Rhabdomyosarcoma Study (IRS) system, depending on the amount and extent of residual tumor after initial surgery, i.e., group I – complete resection (corresponding to R0 resection), group II - microscopic residual disease (R1 resection), group III - macroscopic residual disease (R2 resection) or biopsy, and group IV - metastases at onset [14]. Tumor sites were classified as favorable (orbit, genito-urinary non-bladder/prostate,

head-neck) or unfavorable (parameningeal, extremities, bladder/prostate, other sites).

## Treatment

The treatment recommendations involved a multidisciplinary approach that included surgery, chemotherapy, and radiotherapy. Initial surgical resection was only suggested if clear histological margins were considered possible; if not, biopsy had to be considered as the first approach. Delayed surgery was recommended, after chemotherapy (and ideally after 3-4 courses). Radiotherapy (with a conventional fractionation, and doses from 50 to 60 Gy) was suggested in all cases of alveolar and NOS RMS, and for embryonal RMS incompletely resected at diagnosis. When indicated, it was suggested that radiotherapy be delivered within 12–14 weeks of the surgical procedure.

Chemotherapy was recommended for all patients. It consisted of a multidrug treatment, alternating the ifosfamide, vincristine, and actinomycin-D (IVA) regimen with ifosfamide, vincristine, and adriamycin (IVAd), or ifosfamide, vincristine, and etoposide (IVE). The suggested doses were: ifosfamide 3 g/m$^2$ × 2 days, vincristine 1.5 mg/m$^2$ (max 2 mg) x 1 day, actinomycin-D 1.5 mg/m$^2$ (max 2 mg) x 1 day, adriamycin 40 mg/m$^2$ x 2 days, etoposide 200 mg/m$^2$ x 2 days. Chemotherapy was to be delivered in 9 courses (administered every 3 weeks).

In patients with measurable disease, response to chemotherapy was assessed after 3 cycles according to RECIST criteria [15, 16]. For the present analysis, we examined changes to the chemotherapy program (vis-à-vis the plan established at the start of the treatment) in terms of dose reduction, omission of drugs, or delayed administration. Grossly, delayed administration was assessed by comparing the actual duration of the whole chemotherapy program with its scheduled length (9 cycles delivered every 3 weeks amounted to 24 weeks).

We also retrospectively applied the treatment scoring system that we had used in our previous series (1975–2001) [12]. This system scored each patient on three aspects concerning the adequacy of their: local treatment (surgery/radiotherapy); chemotherapy; and treatment as a whole (the product of the other two scores) (Table 1).

**Table 1** Description of the treatment score

| | |
|---|---|
| Local treatment | |
| Score 1 | Complete or incomplete surgery (S) + adequate radiotherapy (RT) (dose > 50 Gy, within 12–14 weeks) |
| Score 0.8 | After inadequate S, RT with a delay in excess of 4 months |
| Score 0.6 | After inadequate S, RT at a total dose lower than 45 Gy |
| Score 0 | After inadequate S, no RT |
| Chemotherapy | |
| Score 1 | IFO/CTX + ADR/ACTD (± VCR) for 8 cycles or more |
| Score 0.4–0.6 | Chemotherapy without IFO/CTX, or lasting 2, 4, 6 cycles |
| Score 0 | No chemotherapy |

## Statistical methods

All data were collected and categorized using Microsoft Excel® version 2007, and all statistical analyses were run using the SPSS® statistical software, version 15.0.

Event-free survival (EFS) and overall survival (OS) were calculated according to the Kaplan–Meier method [17], from diagnosis to relapse/progression, and from diagnosis to death, respectively. The survival curves for the patient subgroups were compared by means of a univariate analysis, using the log-rank test (significant $p$-value < 0.05) [18] to describe the potential value of various prognostic factors. Then a multivariate analysis was conducted using Cox's proportional hazards regression method (with a backward selection of covariates revealing a $p$-value of at least 0.05 at univariate analysis) to establish the independent prognostic significance of the factors considered [19].

# Results

Overall, 95 patients (age 18–77 years, median 27) were considered for the analysis. Table 2 shows their clinical characteristics. There were 66 patients with localized disease at diagnosis, and 29 with metastatic disease. The most common histological subtype was alveolar RMS (52 cases). The most common primary tumor location was the head and neck region (52 cases, 43 of them involving parameningeal sites). Most patients had advanced disease at onset: 76.8% had locally invasive disease (T2); 62.1% had tumors larger than 5 cm in size; 46.3% had lymph node involvement (N1); and 30.5% had metastatic disease at onset (M1). The metastases most commonly affected: bone (51.7% of metastatic cases); bone marrow (34.5%); lungs (31.1%); and distant lymph nodes (31.1%); and two or more sites were involved in 51.7% of patients.

## Treatment modalities

The institutional therapeutic approach was recommended to all patients. Briefly, 42.1% of patients underwent surgery (R0 resection in 31 cases, 18 at diagnosis, and 13 after chemotherapy), radiotherapy was administered to 76.8% of the sample, and chemotherapy to 93.6%.

**Table 2** Clinical characteristics of the overall sample ($n=95$)

| Patients' characteristics ($N=95$) | Localized | Metastatic | Total |
|---|---|---|---|
| Gender | | | |
| Male | 41 (62.1%) | 19 (65.5%) | 60 (63.2%) |
| Female | 25 (37.9%) | 10 (34.5%) | 35 (36.8%) |
| Age | | | |
| 19–30 years | 33 (50%) | 22 (75.9%) | 55 (57.9%) |
| 31–60 years | 29 (43.9%) | 7 (24.1%) | 36 (37.9%) |
| > 60 years | 4 (6.1%) | 0 (0.0%) | 4 (4.2%) |
| Disease extent (M) | | | |
| Localized | – | – | 66 (69.5%) |
| Metastatic | – | – | 29 (30.5%) |
| Primary site | | | |
| Parameningeal (PM) | 30 (45.5%) | 13 (44.8%) | 43 (45.2%) |
| GU not bladder or prostate | 13 (19.7%) | 4 (13.8%) | 17 (17.9%) |
| Abdomen-pelvis | 7 (10.5%) | 5 (17.2%) | 12 (12.6%) |
| GU bladder or prostate | 5 (7.6%) | 4 (13.8%) | 9 (9.5%) |
| Head-neck not PM | 9 (13.7%) | 0 (0.0%) | 9 (9.5%) |
| Extremities | 2 (3.0%) | 3 (10.4%) | 5 (5.3%) |
| Histology | | | |
| Alveolar | 32 (48.5%) | 20 (69.0%) | 52 (54.7%) |
| Embryonal | 17 (25.8%) | 9 (31.0%) | 26 (27.4%) |
| Botryoid *(embryonal)* | 9 (13.6%) | 0 (0.0%) | 9 (9.4%) |
| Spindle cell *(embryonal)* | 6 (9.1%) | 0 (0.0%) | 6 (6.3%) |
| NOS | 2 (3.0%) | 0 (0.0%) | 2 (2.2%) |
| Local invasiveness (T) | | | |
| T1A | 13 (19.7%) | 2 (6.9%) | 15 (15.8%) |
| T1B | 6 (9.1%) | 1 (3.5%) | 7 (7.4%) |
| T2A | 18 (27.3%) | 3 (10.3%) | 21 (22.1%) |
| T2B | 29 (43.9%) | 23 (79.3%) | 52 (54.7%) |
| Nodal involvement (N) | | | |
| N0 | 48 (72.7%) | 3 (10.3%) | 51 (53.7%) |
| N1 | 18 (27.3%) | 26 (89.7%) | 44 (46.3%) |
| IRS groups | | | |
| I | 18 (27.3%) | 0 (0.0%) | 18 (19%) |
| II | 5 (7.6%) | 0 (0.0%) | 5 (5.3%) |
| III | 43 (65.1%) | 0 (0.0%) | 43 (45.2%) |
| IV | 0 (0.0%) | 29 (100%) | 29 (30.5%) |

The scheduled chemotherapy was modified in 42 cases. In most of them, the changes concerned dose reductions or the omission of single drugs due to toxicity, which involved: peripheral or central neurological toxicity related to vincristine and ifosfamide, respectively (in 42.8% of cases); myelosuppression (in 69%); or mucositis (28.6%).

One patient chose to discontinue the treatment after 4 cycles for personal (not clinical) reasons. Chemotherapy was not administered to 6 patients: two because they had metastatic disease and were only given supportive care due to the rapid progression of their disease and clinical deterioration;

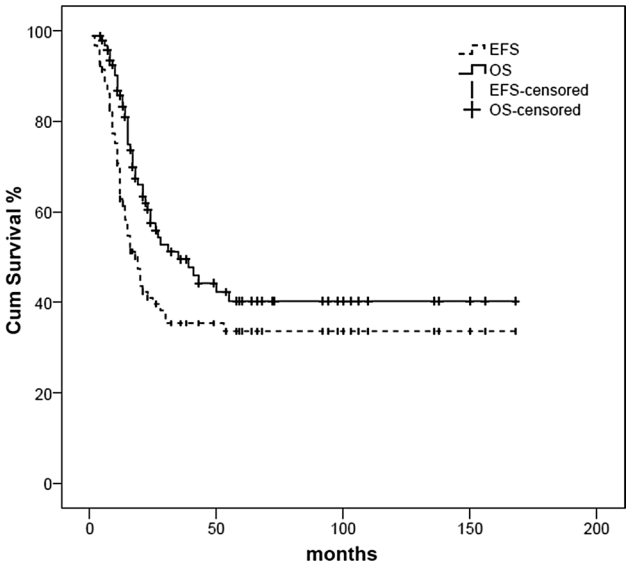


**Fig. 1** EFS and OS rates for the overall sample

two due to advanced age (77 years) and/or co-morbidities (severe heart disease); and two patients refused the adjuvant treatment.

Delays in the scheduled treatment were recorded in 50 out of 88 cases who completed the chemotherapy (56.8%): 12 patients (13.6%) experienced a < 10% extension of their treatment plan, 20 (22.7%) an extension of 10–20%, 11 (12.5%) an extension of 20–30%, and 7 (7.9%) an extension > 30%. The reasons for these delays in the delivery of the chemotherapy were: toxicities in 56% of cases; logistic and organizational problems in 34%; and other causes in 10% (an unexpectedly slow recovery after surgery, other co-morbidities).

Applying our treatment score, a score of 1 (= treatment in line with pediatric principles) was awarded for local treatments in 82 patients (86.3%), for systemic treatments in 76 patients (80%), and for overall treatment in 70 patients (73.7%).

## Treatment outcome

Response to chemotherapy was evaluable in 71 patients: a complete response was seen in 9 cases (12.7%), a partial response in 50 (70.4%), stable disease in 9 (12.7%), and disease progression in 3 (4.2%). The overall response rate was 83.1%.

The median EFS and OS rates were 19 months and 35 months, respectively. With a median follow-up of 60 months (range 5–173), the 5-year EFS and OS rates were 33.6% and 40.3%, respectively (Fig. 1). In patients with localized tumor, the 5-year EFS and OS rates were 43.8%

**Table 3** Median event-free survival (EFS) and overall survival (OS) rates, and log-rank test for univariate analysis by patients' characteristics (NR = value "not reached" judging from the reported follow-up)

| Patients' characteristics ($N=95$) | No of patients | 5-year EFS (%) | p-value (log-rank) | 5-year OS (%) | *p*-value (log-rank) |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 60 | 32.4 | 0.950 | 40.8 | 0.929 |
| Female | 35 | 36.6 | | 37.1 | |
| Age | | | | | |
| 19–30 years | 55 | 31.7 | 0.889 | 37.2 | 0.287 |
| > 30 years | 40 | 37.8 | | 41.7 | |
| Disease extent (M) | | | | | |
| Localized | 66 | 43.8 | < 0.0001 | 51.8 | < 0.0001 |
| Metastatic | 29 | 10.6 | | 12.7 | |
| Primary site | | | | | |
| Favorable | 26 | 62.6 | 0.002 | 62.7 | 0.005 |
| Unfavorable | 69 | 22.6 | | 31.3 | |
| Histology | | | | | |
| Alveolar | 52 | 23.9 | 0.022 | 27.4 | 0.04 |
| Non-alveolar | 43 | 46.7 | | 58.8 | |
| Local invasiveness (T) | | | | | |
| T1 | 22 | 57.4 | 0.002 | 67.7 | 0.008 |
| T2 | 73 | 25.4 | | 32.2 | |
| Primary lesion size | | | | | |
| ≤ 5 cm (A) | 36 | 50.1 | 0.041 | 55.9 | 0.018 |
| > 5 cm (B) | 59 | 22.6 | | 30.0 | |
| Nodal involvement (N) | | | | | |
| N0 | 51 | 53.5 | < 0.0001 | 64.8 | < 0.0001 |
| N1 | 44 | 11.8 | | 13.8 | |
| IRS groups | | | | | |
| I–II | 23 | 67.0 | < 0.0001 | 69.5 | < 0.0001 |
| III | 43 | 31.1 | | 42.0 | |
| IV | 29 | 10.6 | | 12.7 | |

and 51.8%, respectively; and in patients with metastatic disease, they were 10.6% and 12.7%.

As shown in Table 3 (univariate analysis), statistically significant differences emerged in both the EFS and the OS rates in relation to: presence of metastases; tumor histology; primary site; tumor invasiveness; tumor size; nodal involvement; and IRS stage. On Cox's multivariate regression analysis, two factors remained significantly related to OS, i.e., the absence of distant metastases (hazard ratio [HR] 0.46; *p*-value 0.028), and the absence of regional lymph node involvement (HR 0.39; *p*-value 0.036). Favorable primary sites correlated with a better OS, but without reaching statistical significance (HR 0.39; *p*-value 0.094).

For descriptive purposes, we also calculated the survival rates by the treatments administered. The 5-year OS rates were 54.1% versus 36.9% (*p*-value 0.437) for patients whose treatment schedules were extended by < 10% versus > 10%, and they were 40.9% as opposed to 44.9% (*p*-value 0.801) for patients who did or did not need a dose reduction or the omission of a single chemotherapeutic agent.

Table 4 shows the survival rates vis-à-vis our pediatric treatment score. As concern the treatment overall, the 5-year EFS rate was 40.8% for patients scoring 1, and 15% for those scoring < 1 (*p*-value < 0.0001), while the 5-year OS rate was 44.4% and 24.5%, respectively, (*p*-value 0.127) (Fig. 2). The OS rate was significantly associated with a score of 1 when we only considered patients with localized disease, i.e., it was 58.8% in patients scoring 1 versus 30.3% in those scoring < 1 (p-value 0.044).

## Discussion

This study describes a prospective series of embryonal and alveolar RMS arising in adults and treated at a referral center for soft tissue sarcomas. The overall outcome in this series was considerably worse than in pediatric series (5-year OS 40.3%).

Our analysis confirmed that one of the reasons for the unsatisfactory prognosis in adult RMS patients is an

**Table 4** Univariate analysis of EFS and OS in the overall sample and in patients with localized disease, by treatment score (NR = value "not reached" judging from the reported follow-up)

| | No of patients | 5-year EFS (%) | p-value (log-rank) | 5-year OS (%) | *p*-value (log-rank) |
|---|---|---|---|---|---|
| *Overall sample* | 95 | | | | |
| Chemotherapy score | | | | | |
| 0–0.8 | 19 | 14.0 | 0.003 | 31.5 | 0.147 |
| 1 | 76 | 38.9 | | 43.2 | |
| Local treatment score | | | | | |
| 0–0.8 | 13 | 15.4 | 0.001 | 17.1 | 0.175 |
| 1 | 82 | 37.0 | | 42.8 | |
| Combined score | | | | | |
| 0–0.8 | 25 | 15.0 | < 0.0001 | 24.5 | 0.127 |
| 1 | 70 | 40.8 | | 44.4 | |
| *Localized disease* | 66 | | | | |
| Chemotherapy score | | | | | |
| 0–0.8 | 15 | 17.8 | 0.002 | 39.5 | 0.042 |
| 1 | 51 | 52.1 | | 56.7 | |
| Local treatment score | | | | | |
| 0 | 11 | 18.2 | 0.001 | 20.2 | 0.113 |
| 0.8–1 | 55 | 49.6 | | 56.0 | |
| Combined score | | | | | |
| 0 | 20 | 18.8 | <0.0001 | 30.3 | 0.044 |
| 0.8–1 | 46 | 55.6 | | 58.8 | |

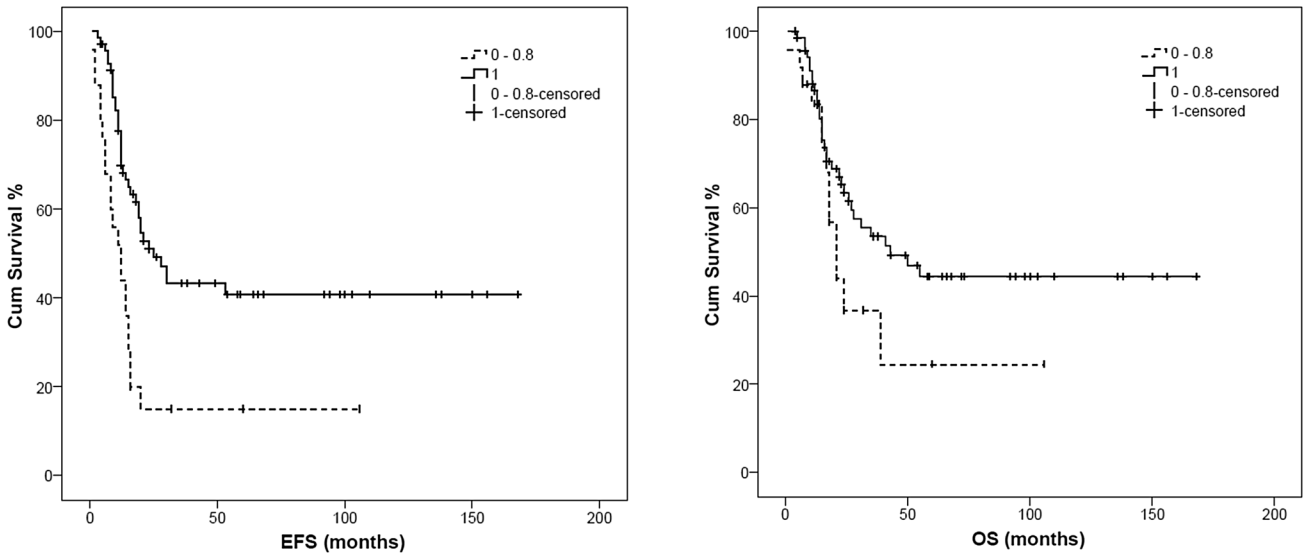


**Fig. 2** EFS and OS rates for the overall sample, by treatment score

unfavorable clinical presentation. Compared with children, adults are more likely to have the alveolar histotype (as in 54.7% of our adult series as opposed to 30.1% in a series of pediatric cases seen at the same institution [20]), regional lymph node involvement (46.3% vs. 26.9%), and distant metastases at diagnosis (30.4% vs. 20.4%). It is worth noting that the clinical features of the adult patients with metastases were also particularly aggressive: in our series, the bone and bone marrow were involved in many cases (51.7% and 34.5% of the metastatic cases, respectively), with lung metastases rather less frequent (31.1%), whereas the largest published series of children with metastatic RMS had metastases involving the lung in 47%, bone marrow in 38%, and bone in 34% of cases [21].

Given the findings in our previous series, this study reinforced the impression that the quality of the treatment

administered, in terms of its adherence to the principles adopted in pediatric protocols, may influence patient outcomes. Patients treated in line with our pediatric strategy (i.e., those with a treatment score of 1) had a better outcome than the others. In particular, among the patients with localized disease, those scoring 1 achieved a 5-year OS of 58.8%, while for the others it was 30.3% ($p$-value 0.044).

The measures adopted at our institute (i.e., a multidisciplinary team involving both adult and pediatric oncologists, specific therapeutic recommendations, prospective registration of patients in an institutional database) enabled an increase in the number of adult patients treated according to our strategy for managing pediatric RMS. In fact, the proportion of patients with localized tumor scoring 1 rose from 39.1% in the previous retrospective series [12] to 69.7% in the present prospective series. On the other hand, 26.3% of our patients (and 30.3% of those with localized RMS) did not receive the whole treatment compliant with pediatric principles. There were several reasons for this, including some patients' decision to refuse or abandon the proposed treatments, their advanced age or co-morbidities, but it was reportedly mainly due to chemotherapy-related toxicity. This implied delays in the provision of the planned treatments in many cases (56.8%). These findings confirm that adults may tolerate intensive treatments less well than children (e.g., they experience more vincristine-associated neurotoxicity) [22, 23].

Though we succeeded in increasing the number of adult cases treated according to the pediatric strategy, the adult patients' survival remained unsatisfactory. We recorded only a slight improvement in 5-year OS, from 45.7% in the 1975–2001 series [12] to 51.8% in the present series (considering patients with localized disease). This means that adopting therapeutic strategies derived from pediatric protocols can improve the prognosis for adult RMS patients, but not enough to achieve the results obtained in children.

In previously-published studies [5–11], various authors have said that adults with RMS tended to receive highly heterogeneous and sometimes ineffective treatments, and that this - together with the rarity of the disease, the dispersion of cases, and the lack of specific protocols - negatively influenced their prognosis. The results in our prospective series of patients (which were managed making a great effort to provide homogeneous treatments derived from pediatric experience) suggest that the poor outcome of adult RMS is likely to be multifactorial, however. Inadequate treatment is certainly an issue, but simply adopting pediatric-type treatment protocols may not achieve the therapeutic results currently seen in children. It could be that part of the prognostic gap between children and adults is attributable to biological differences in RMS arising in different age groups. Our knowledge about the complex genomic landscape of pediatric RMS is constantly increasing [24–27], but there is still a shortage of information (and a lack of studies) on RMS in adults.

Improving the collaboration between pediatric and adult oncologists in promoting specific (clinical and biological) research on adult RMS is a key factor, but this needs to be done not only at single institutions, but on an international scale, involving both the pediatric and the adult sarcoma expert communities. Some steps in this direction have already been taken: the next EpSSG protocol on RMS will have an upper age cut-off of 50 years in order to include adult oncology centers. On one hand, however, it remains to be seen whether adult patients and medical oncology centers can be involved in a large cooperative project developed by the pediatric community (with treatments tailored for pediatric patients), also considering that adult patients' complete adherence to pediatric protocols has been shown to be problematic. As an alternative, it might be better to develop specific international protocols tailored for adults with RMS.

In conclusion, our study showed that adults with pediatric-type RMS had a better chance of being cured when treated according to pediatric protocols, although these adult patients' prognosis remained much worse than is generally seen in children with RMS. We consequently believe that adult RMS patients should always be considered at higher risk, not only if they have metastatic disease (in which case the prognosis is still extremely poor), but also if they have localized disease. Adult age per se should be seen as an important prognostic factor. A more appropriate use of standard therapies may improve their outcome to some degree, but new therapeutic strategies are needed for adult patients with RMS. Identifying new molecular targets (by gaining a better understanding of the biology of the disease), and devising new tailored treatment approaches will be crucial to improving the outcome for this patient population.

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**Data availability** All the data of patients and material used for this analysis are collected and available in the paper archive and in the electronic database of our Institution: Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian 1, 20133, Milan, Italy. The datasets generated during the current study is available from the corresponding author on reasonable request.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest to disclose.

**Ethical approval** This study was performed in accordance with the Declaration of Helsinki. The project was approved by the Research Ethical Committee of the Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy (code 150053 of the Italian National Observatory on Clini-

cal Trials). All the patients signed a written informed consent for their involvement in the project and for the use of their personal data.

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