Relapse after nonmetastatic rhabdomyosarcoma: Salvage rates and prognostic variables

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Abstract

Background: Patients with relapsing rhabdomyosarcoma (RMS) pose a therapeutic challenge, and the survival rate is reportedly poor. We describe a retrospective series of relapsing RMS patients treated at a referral center for pediatric sarcoma, investigating the pattern of relapse, salvage rates, and factors correlating with final outcomes.

Methods: The analysis concerned 105 patients < 21 years old treated from 1985 to 2020 with initially localized RMS at first relapse. For risk-adapted stratification purposes, patient outcomes were examined using univariable and multivariable analyses based on patients' clinical features at first diagnosis, first-line treatments, clinical findings at first relapse, and second-line treatments.

Results: First relapses occurred 0.08–4.8 years (median 1 year) following initial diagnosis and were local/locoregional in 59% of cases. Treatment at first relapse included chemotherapy in all but two cases, radiotherapy in 38, and surgery in 21. Median event-free survival (EFS) after first relapse was 4 months, while 5-year EFS was 16.3%; median overall survival (OS) was 9 months, while 5-year OS was 16.7%. Several variables influenced survival rates. Considering only clinical findings and treatment at relapse, Cox’s multivariable analysis showed that OS correlated significantly with time to relapse, radiotherapy administered at relapse, response to chemotherapy, and whether a second remission was achieved.

Conclusion: Survival following first relapse of patients with localized RMS at initial diagnosis is poor. The variables found to influence survival can be utilized in a risk-adapted model to estimate the chances of salvage to guide decisions for second-line treatments.

KEYWORDS
prognostic factors, relapse, rhabdomyosarcoma, salvage rate, second-line therapy, stratification
1 | INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of pediatric age, with around 400 cases being diagnosed each year in patients aged 0–19 years in Europe, and 55 in Italy.1–2 RMS is a highly malignant tumor, locally aggressive and with a strong propensity to metastasize,3 but intensive risk-adapted multimodal therapies developed in recent decades have brought significant improvements in long-term survival rates.4–6 Nonetheless, around 30% of patients with localized tumors (and 70% of those initially presenting with metastatic disease) still suffer tumor progression or relapse.4–11

Localized tumors (and 70% of those initially presenting with metastatic sarcomas (NRSTS)).20 The following variables were investigated for a study conducted on relapsing nonrhabdomyosarcoma soft tissue tumor.

In order to focus on the pattern of relapse in a more homogeneous group of patients presenting initially with only localized disease,3 but intensive risk-adapted multimodal therapies developed in recent decades have brought significant improvements in long-term survival rates.4–6 Nonetheless, around 30% of patients with localized tumors (and 70% of those initially presenting with metastatic disease) still suffer tumor progression or relapse.4–11

Relapsing RMS patients pose therapeutic challenge: outcomes following a first relapse are reportedly poor; there is no internationally agreed standard of care; and new effective treatments are urgently needed.12 Several variables may influence the chances of survival after RMS relapse, and it is important to consider them when deciding on second-line treatment options.4–11

The present report concerns a series of RMS patients treated at a referral center for pediatric sarcoma, who relapsed after presenting initially with nonmetastatic disease. The aim here was to describe the pattern and timing of these relapses, the salvage rates, and any clinical or treatment-related variables (at first diagnosis and at the time of relapse) that might influence patients’ outcomes. A further aim of the study was to propose a risk-adapted patient stratification to facilitate the planning of salvage therapy.

2 | MATERIALS AND METHODS

Patients were selected retrospectively from the clinical database of the Pediatric Oncology Unit at the Istituto Nazionale Tumori in Milan (Italy). Study inclusion criteria were a histological diagnosis of RMS; age under 21 years at the time of first diagnosis; initial diagnosis between 1985 and 2020; nonmetastatic disease at first diagnosis; tumor relapse or progression after first therapy; details available on clinical findings, treatment modalities, and outcomes; and written consent to participate in the study. Institutional review board approval was obtained before the data were collected.

The histological diagnosis was established by pathologists at our institution before starting treatment. Cases were classified as alveolar RMS, embryonal RMS, or not-otherwise-specified (NOS) RMS. Patients with metastatic disease at diagnosis were excluded from the present study in order to focus on the pattern of relapse in a more homogeneous group of patients presenting initially with only localized tumor.

The method adopted for the present study was the same as in a study conducted on relapsing nonrhabdomyosarcoma soft tissue sarcomas (NRSTS).20 The following variables were investigated for each patient:

a. Clinical findings at first diagnosis: sex; age; histological subtype; tumor site (favorable sites: head–neck nonparameningeal, orbit, genitourinary non-bladder/prostate; unfavorable sites: parameningeal, genitourinary bladder/prostate, extremities, other sites); tumor size (diameter ≤5 or >5 cm); presence or absence of regional lymph node metastases; surgical stage according to the Intergroup Rhabdomyosarcoma Study (IRS) grouping system (group I: complete resection at first surgery; group II: microscopic residual disease; group III: macroscopic residual disease).4–11

b. First-line treatment modalities: surgery, classified on the grounds of the histological margins (considering both first surgical procedures and any surgery delayed until after primary chemotherapy) as: R0: complete resection with microscopically free margins, R1: marginal resection with suspected microscopic residues, R2: intralesional resection with macroscopic residues; radiotherapy; type of chemotherapy with two drugs (vincristine and actinomycin-D [VA]), three (ifosfamide, vincristine, and actinomycin-D [IVA], or vincristine, actinomycin-D, and cyclophosphamide [VAC], or more than three (vincristine, actinomycin-D, cyclophosphamide, and Adriamycin [VACA], vincristine, actinomycin-D, ifosfamide, and Adriamycin [VAIA], carboplatin, epi-doxorubicin, vincristine, actinomycin-D, ifosfamide, and etoposide [CEVAIE], or ifosfamide, vincristine, actinomycin-D, and doxorubicin [VAoDo]): response to chemotherapy (assessed after three cycles) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.022;

c. Clinical findings at the time of first relapse: local or metastatic relapse (including nodal metastases), time to recurrence (the interval between first diagnosis and recurrence, arbitrarily defined as early or late when less or more than 12 months, respectively), site and number of metastases;

d. Second-line treatment modalities: surgery, radiotherapy, chemotherapy, and response to chemotherapy (assessed after three cycles of second-line therapy); achievement of a second remission with second-line therapy, defined as the absence of disease after surgery, or complete tumor remission after chemotherapy and/or radiotherapy, persisting for at least 6 months.

2.1 | Statistical analysis

Primary end-points were survival rates after relapse, calculated from the time of the first disease progression/recurrence to the latest uneventful follow-up, further disease progression or relapse, or death due to any cause for event-free survival (EFS), and to death or latest contact with patients who were still alive for overall survival (OS). The different clinical and therapeutic variables were investigated using univariable and multivariable analyses to ascertain their potential role as prognostic factors. In the univariable analysis, survival after relapse was estimated with the Kaplan–Meier method;23 and the log-rank test was used to compare the survival curves for patient subgroups.24 The multivariable analysis was developed using Cox’s proportional hazards regression method to establish the independent prognostic significance of the variables considered.25 A backward variable...
### TABLE 1  Patients’ characteristics and treatments at first diagnosis and at time of first relapse

| Clinical findings at diagnosis       | Patients | %  |
|-------------------------------------|----------|----|
| **Sex**                             |          |    |
| Female                              | 41       | 39.0 |
| Male                                | 64       | 61.0 |
| **Age**                             |          |    |
| <10 years                           | 37       | 35.2 |
| ≥10 years                           | 68       | 64.8 |
| **Histotypes**                      |          |    |
| Embryonal                           | 68       | 64.8 |
| Alveolar                            | 31       | 29.5 |
| Not otherwise specified             | 6        | 5.7  |
| **Tumor site**                      |          |    |
| Extremities                         | 8        | 7.6  |
| Trunk                               | 3        | 2.9  |
| Intra-abdominal                     | 23       | 21.9 |
| Head–neck parameningeal            | 39       | 37.1 |
| Head–neck nonparameningeal<sup>a</sup>| 10       | 9.5  |
| Genitourinary non-bladder/prostate | 12       | 11.4 |
| Genitourinary bladder/prostate     | 10       | 9.5  |
| **Tumor size**                      |          |    |
| ≤5 cm                               | 18       | 17.1 |
| >5 cm                               | 87       | 82.9 |
| **Nodal status**                    |          |    |
| N0                                  | 73       | 69.5 |
| N1                                  | 32       | 30.5 |
| **IRS group**                       |          |    |
| I                                   | 12       | 11.4 |
| II                                  | 8        | 7.6  |
| III                                 | 85       | 81.0 |
| **First-line treatments**           |          |    |
| **Type of surgery**                 |          |    |
| R0–R1                               | 32       | 30.5 |
| R2/biopsy                           | 73       | 69.5 |
| **Radiotherapy**                    |          |    |
| No                                  | 30       | 28.6 |
| Yes                                 | 75       | 71.4 |
| **Chemotherapy**                    |          |    |
| 2–3 drugs                           | 23       | 21.9 |
| >3 drugs                            | 82       | 78.1 |
| **Response to chemotherapy**        |          |    |
| No                                  | 18       | 21.2 |
| Yes                                 | 67       | 78.8 |
| **Clinical findings at relapse**    |          |    |
| **Type of relapse**                 |          |    |
| Local                               | 45       | 42.9 |
| Regional lymph nodes                | 8        | 7.6  |
| Local and regional lymph nodes      | 9        | 8.6  |
| Distant metastases (±local relapse and regional lymph nodes) | 43 | 40.9 |
| **Time of relapse**                 |          |    |
| Early (≤12 months)                  | 53       | 50.5 |
| Late (>12 months)                   | 52       | 49.5 |
| **Second-line treatments**          |          |    |
| **Surgery**                         |          |    |
| No                                  | 84       | 80.0 |
| Yes                                 | 21       | 20.0 |
| **Radiotherapy**                    |          |    |
| No                                  | 67       | 63.8 |
| Yes                                 | 38       | 36.2 |
| **Systemic treatment**              |          |    |
| No                                  | 1        | 1.0  |
| Yes                                 | 104      | 99.0 |

(Continues)
TABLE 1 (Continued)

| Clinical findings at diagnosis          | Patients | %   |
|----------------------------------------|----------|-----|
| Response to systemic treatment          |          |     |
| No                                     | 51       | 53.7|
| Yes                                    | 44       | 46.3|
| Second remission                       |          |     |
| No                                     | 77       | 73.3|
| Yes                                    | 28       | 26.7|
| Overall status                         |          |     |
| Alive in remission                     | 17       | 16.2|
| Dead                                   | 86       | 81.9|
| On treatment                           | 2        | 1.9 |

*Including orbit.

Abbreviation: IRS, Intergroup Rhabdomyosarcoma Study.

A selection procedure was applied to the covariates with a p-value of at least <.02 in the univariable analysis. The clinical and treatment factors at relapse were investigated as part of the multivariable analysis. All data analyses were run using the R statistical software (SPSS), version 15.0.

3 | RESULTS

The clinical database at our unit included 376 patients under 21 years old, treated between 1985 and 2020 for nonmetastatic RMS. From this series, we selected 105 consecutive patients (age range 6 months to 20 years, median 13 years) whose tumor progressed or relapsed. All patients fulfilling inclusion criteria were included in the study.

Table 1 shows patients’ clinical characteristics and details of the treatments administered at the time of their first diagnosis and at the time of their first relapse.

All patients received chemotherapy as part of their first-line treatment. This involved combinations of two or three drugs in 23 cases (one VA, three VAC, and 19 IVA), and more than three in 82 (50 VACA, 12 VAIA, 13 CEVAIE, and seven IVADO). In 83 patients with evaluable disease, response to chemotherapy was recorded as: 10 complete remissions, 57 partial remissions, 11 stable disease, and seven tumor progressions. First-line treatment included R0 surgery in 24 cases, R1 surgery in eight, and R2 surgery in five, while 68 patients only had a biopsy. Radiotherapy was administered to 75 patients (with doses in the range of 44.8–60 Gy).

In our series, treatment failed within 0.08–4.8 years (median 1 year) of the patients first being diagnosed. The disease progressed during upfront therapy in 26 patients, and soon after its completion in 27. Overall, there were 53 cases of tumor progression/relapse within 1 year of patients’ first diagnosis. Only 14 out of 105 patients (13%) relapsed 2 years or more after being diagnosed, and none after 5 years.

Tumor progression/relapse was local in 45 cases; it involved regional lymph nodes in eight; in nine, it affected both the local site and a regional lymph node; and distant metastases occurred in 43 cases (metastatic relapse was associated with local relapse in 15 cases, and with lymph node involvement in four cases).

3.1 | Treatment at relapse

After a patient’s RMS progressed/relapsed, treatments included systemic therapy in all but one patient (who refused any therapy), radiotherapy in 38, and surgery in 21. Radiotherapy was given to 28 patients with a locoregional relapse, and to 10 with distant recurrences (with or without locoregional disease). It was only in three cases that radiotherapy was delivered to metastatic sites (all lung metastases), while in the other 35 it involved local or regional sites of disease. Surgery was only performed on local tumors and/or regional lymph node metastases; one patient had an amputation; none had metastases surgically removed.

Various medical therapies were used in second-line systemic treatments over the study period: 17 patients had vincristine, irinotecan (VI) or vincristine, irinotecan, temozolamide (VIT); 14 had vinorelbine or vinorelbine plus oral cyclophosphamide; 14 had CEVAIE; 13 had oral etoposide; eight had topotecan-based chemotherapy; seven had a cisplatin-based regimen; various other drug combinations were administered in 10 cases; and the type of second-line systemic treatment was not specified in 20. One patient was given targeted therapy at first relapse. When response to systemic therapy could be assessed, there was at least a partial response according to the RECIST in 44 cases, and none in 51. In all, 28 patients achieved a complete remission with second-line therapy.

3.2 | Outcome

At the time of this analysis, 19 patients were alive and 86 had died of their disease. Among the patients still alive, 17 were in remission (15 in second remission and two in third remission) from 2 to 25 years (median 13 years) after their first relapse; and two patients were receiving treatment.

With a median follow-up of 15 years (range 10 months to 25 years) for the patients still alive, the median EFS after first relapse was 4 months (95% confidence interval: 2.82–5.18), and the EFS rates were 28.5% and 16.3% at 1 and 5 years, respectively. The median OS was 9 months (95% confidence interval: 7.33–10.67),
FIGURE 1  Post-relapse overall survival (OS) for the whole series
with OS rates of 36.1% and 16.7% at 1 and 5 years, respectively (Figure 1).

Table 2 shows the results of the univariable analysis, with OS rates at 5 years post relapse by patients’ characteristics. Survival did not correlate with the study period. Considering the clinical findings at the time of first diagnosis, OS was associated with primary site, tumor size, nodal status, and IRS group. OS was better for patients who had an initial R0–R1 resection, received no first-line radiotherapy, and whose chemotherapy included only two or three as opposed more numerous different drugs.

As concerns the clinical findings at the time of relapse, OS was significantly better for patients with a local or locoregional relapse, and for those with a late relapse. OS correlated with the feasibility of surgery, the administration of radiotherapy, response to systemic therapy, and the achievement of a second remission. There was evidence of a trend toward a better survival for patients whose second-line chemotherapy was VI or VIT.

Table 3 shows the results of the multivariable analysis focusing on the variables at relapse. Cox’s regression analysis was performed on 95 cases (those with data available on their response to second-line chemotherapy). Survival correlated significantly with time to relapse, radiotherapy performed at relapse, response to chemotherapy, and the achievement of a second remission persisting for at least 6 months.

These findings were used to calculate the OS based on the number of prognostic risk factors (i.e., early relapse, no radiotherapy, no response to chemotherapy, and failure to achieve a second remission). As shown in Figure 2, the estimated 5-year OS was 68.0% for patients with no risk factors (20 cases), 31.0% for patients with one of the above factors (11 cases), and 0% for patients with more than one such prognostic risk factor (64 cases) (p < .001).

4 | DISCUSSION

This study retrospectively analyzed the pattern of relapse, salvage rates, and risk factors correlating with post-relapse outcomes in a large series of pediatric patients with initially localized RMS treated at a single institution. In particular, our study analyzed in details the clinical features of the relapse itself and the post-relapse treatment.

Our analysis confirmed the known pattern of recurrence in RMS: a large proportion of patients whose disease recurred had a locoregional relapse and most relapses occurred within a relatively short time frame (50% of our cases relapsed within a year, and 87% within two). It was also clear that the chances of survival for patients with recurrent RMS have remained poor. Despite its limitations (such as a retrospective design and a lengthy study period), our study enabled us to identify several variables influencing survival. This is helpful when deciding on a risk-adapted approach and for orienting the choice of second-line treatment, as it enables us to distinguish between patients with and without realistic prospects of cure with the currently available therapeutic options.

Post-relapse survival correlated with patients’ clinical characteristics at the time of their initial diagnosis (i.e., tumor site and size, nodal involvement, and IRS group). Other studies also identified an alveolar histology as another prognostic factor. Such clinical features can be seen as indirect markers of a disease’s intrinsic aggressiveness, which remains much the same if and when it relapses. Various factors relating to upfront treatment have been reported as being associated with post-relapse outcomes, and our study confirmed as much. Survival correlated with the extent of surgical resection, the use of radiotherapy, and the type of chemotherapy delivered. The post-relapse outcome was worse in patients who had been given radiotherapy, and in those administered chemotherapy regimens that included more than three agents: this is likely to reflect a confounder effect relating to the choice of risk-directed therapy for patients considered at higher risk.

Our analysis focused particularly on the clinical features of the relapse itself. As in other reports, we found that patients who progressed while still on upfront therapy, and those who relapsed soon afterwards had worse outcomes than those who relapsed later on; and patients whose relapse involved distant metastases had worse outcomes than those whose disease relapsed locoregionally.

Different from most of the previous studies, which were not able to analyze post-relapse treatment, we also examined how relapses were treated. A unique finding in our study on univariable analysis was that survival correlated with the feasibility of surgery, the delivery of radiotherapy, response to systemic therapy, and the achievement of a second remission. No statistically significant differences emerged by type of second-line chemotherapy.

The findings regarding the feasibility of surgery and the use of radiotherapy may be biased by our selection of relapsing patients: most of the patients who underwent surgery and were given radiotherapy had favorable characteristics (e.g., locoregional relapses), and this might make it difficult to distinguish the relative effect of patient selection versus the real contribution of radiotherapy and surgery to the better outcome seen in these patients. These results would nonetheless underscore the importance of post-relapse local measures in patients with recurrent RMS, suggesting that aggressive surgery may be justified as a salvage treatment, and to be recommended whenever
TABLE 2  Post-relapse OS and log-rank test for univariable analysis by patients’ characteristics

| Category                                      | N   | Groups                          | N   | 5-year OS (%) | p-Value |
|-----------------------------------------------|-----|---------------------------------|-----|---------------|---------|
| Clinical findings at diagnosis                |     |                                 |     |               |         |
| Year of diagnosis                             | 105 | 1985–2004                       | 76  | 13.2          | .473    |
|                                               |     | 2005–2020                       | 29  | 29.3          |         |
| Sex                                           | 105 | Female                          | 41  | 23.9          | .380    |
|                                               |     | Male                            | 64  | 12.0          |         |
| Age                                           | 105 | <10 years                       | 37  | 23.4          | .322    |
|                                               |     | ≥10 years                       | 68  | 12.8          |         |
| Histological types                            | 105 | Embryonal                       | 68  | 22.6          | .446    |
|                                               |     | Alveolar                        | 31  | 6.5           |         |
|                                               |     | Not otherwise specified         | 6   | 16.7          |         |
| Tumor site<sup>a</sup>                        | 105 | Favorable                       | 22  | 40.4          | <.001   |
|                                               |     | Unfavorable                     | 83  | 10.4          |         |
| Tumor size                                    | 105 | ≤5 cm                           | 18  | 44.1          | .001    |
|                                               |     | >5 cm                           | 87  | 11.5          |         |
| Nodal status                                  | 105 | N0                              | 73  | 22.2          | .019    |
|                                               |     | N1                              | 32  | 3.8           |         |
| IRS group                                     | 105 | I                               | 12  | 58.3          | .001    |
|                                               |     | II                              | 8   | 25.0          |         |
|                                               |     | III                             | 85  | 9.8           |         |
| First-line treatments                         |     |                                 |     |               |         |
| Surgery                                       | 105 | R0–R1                           | 32  | 43.5          | <.001   |
|                                               |     | R2/biopsy                       | 73  | 4.0           |         |
| Radiotherapy                                  | 105 | No                              | 30  | 53.1          | <.001   |
|                                               |     | Yes                             | 75  | 1.5           |         |
| Chemotherapy                                  | 105 | 2–3 drugs                       | 23  | 37.5          | .013    |
|                                               |     | >3 drugs                        | 82  | 11.2          |         |
| Response to chemotherapy                      | 85  | No                              | 18  | 14.8          | .889    |
|                                               |     | Yes                             | 67  | 8.3           |         |
| Clinical findings at relapse                  |     |                                 |     |               |         |
| Type of relapse                               | 105 | Local                           | 45  | 26.9          | .020    |
|                                               |     | Locoregional<sup>b</sup>        | 17  | 23.5          |         |
|                                               |     | Metastatic (+local)             | 43  | 4.7           |         |
| Time of relapse                               | 105 | ≤12 months                      | 53  | 5.7           | <.001   |
|                                               |     | >12 months                      | 52  | 28.2          |         |
| Second-line treatments                        |     |                                 |     |               |         |
| Surgery at relapse                            | 105 | No                              | 84  | 4.8           | <.001   |
|                                               |     | Yes                             | 21  | 64.3          |         |
| Radiotherapy at relapse                       | 105 | No                              | 67  | 0.0           | <.001   |
|                                               |     | Yes                             | 38  | 43.4          |         |
| Type of chemotherapy at relapse               | 105 | Irinotecan-based regimens (VI, VIT) | 17 | 39.7 | .069 |
|                                               |     | Other regimens                  | 88  | 13.0          |         |
| Response to systemic treatment                | 95  | No                              | 51  | 0.0           | <.001   |
|                                               |     | Yes                             | 44  | 40.3          |         |
| Second remission                              | 105 | No                              | 77  | 0.0           | <.001   |
|                                               |     | Yes                             | 28  | 62.0          |         |

Abbreviations: IRS, Intergroup Rhabdomyosarcoma Study; OS, overall survival; VI, vincristine, irinotecan; VIT, vincristine, irinotecan, temozolamide.<sup>a</sup>Favorable site: head and neck nonparameningeal, genitourinary non-bladder/prostate. Unfavorable site: head and neck parameningeal, genitourinary bladder/prostate, extremities, trunk, intra-abdominal.<sup>b</sup>Regional lymph nodes with or without local relapse.
feasible. Other studies reported better outcomes for locally relapsing patients who underwent surgical resection than for those not treated surgically, but its worth noting that very aggressive, mutilating, radical surgery did not yield better outcomes than conservative surgery. Other studies found that adding radiotherapy to salvage treatments had a beneficial effect.

Other groups developed specific algorithms on the strength of their findings to estimate the likelihood of successful salvage therapy. With the same goal in mind, we combined the prognostic factors emerging from our multivariable analysis to predict the outcome for relapsing RMS patients. Our model differed from others in that we only considered the clinical and treatment variables at relapse (i.e., early relapse, radiotherapy not performed, lack of response to chemotherapy, and failure to achieve a second remission).

These findings underscore the need to standardize our clinical approach to RMS patients who relapse, and to find new, effective therapies. The management of relapsing patients should preferably include tumor biopsy (not only to confirm the diagnosis, but also, and especially, to enable the tumor’s molecular characterization); an assessment of the patient’s post-relapse prognosis; a decision on the feasibility of local control measures; a search for any available dedicated clinical trials; and a frank discussion with patients and their families about their goals.

Developing therapeutic trials specifically for relapsing RMS remains a challenge. Very few such efforts have been made in the last decade. The Children’s Oncology Group (COG) completed a randomized phase 2 study (ARST0921) that used vinorelbine–cyclophosphamide chemotherapy plus either the mammalian target of rapamycin (mTOR) inhibitor temsirolimus or the vascular endothelial growth factor (VEGF) inhibitor bevacizumab in RMS at first relapse: the study did not show significant difference in response rate between the two arms, but reported a better 6-month EFS for patients given temsirolimus (69% vs. 55%). The European paediatric Soft tissue sarcoma Study Group (EpSSG) recently reported the results of a randomized phase 2 trial testing the addition of temozolamide to VI chemotherapy: the study showed better response (44% vs. 31%) and better survival rates on the VIT arm. These two prospective trials showed a different impact of response to chemotherapy on post-relapse survival. In our retrospective series, response to second-line therapy emerged as a major prognostic factor in both univariable and multivariable analyses.

While it is clear that the first critical deed should be that of preventing relapse by improving the efficacy of front-line treatment, a multifaceted action on the part of the pediatric sarcoma community is clearly warranted to develop prospective phase I–II trials dedicated to patients with relapsing RMS. Patients with such an extremely poor prognosis should be offered experimental therapies as part of clinical trials. It is always extremely difficult to increase the availability of new drugs for pediatric patients, however. Wider international collaborative projects are needed, including protocols for systematic molecular profiling in an effort to identify new targets and lead to effective agents. The recently opened EpSSG Frontline and Relapse Rhabdomyosarcoma (FaR-RMS) study (EudraCT: 2018-000515-24) includes investigating treatments for newly diagnosed patients with localized and metastatic RMS, but also offers an opportunity to try new systemic treatment combinations, including targeted agents, in patients with relapsing RMS.

FIGURE 2 Post-relapse overall survival (OS) based on number of prognostic risk factors emerging from the multivariable analysis (early relapse, radiotherapy not performed, no response to chemotherapy, and failure to achieve a second remission).

DATA AVAILABILITY STATEMENT
The data are available on request from the authors.

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CONFLICT OF INTEREST
The authors have no potential conflicts of interest to declare.

TABLE 3 Cox’s regression for the multivariable analysis of survival by patients’ characteristics at time of relapse

| Characteristics                  | Hazard ratio | 95% CI       | p-Value |
|----------------------------------|--------------|--------------|---------|
| Local/locoregional relapse       | 0.93         | 0.58–1.49    | .756    |
| Late relapse (>12 months)        | 0.58         | 0.36–0.94    | .027    |
| Surgery at relapse               | 0.78         | 0.20–3.07    | .723    |
| Radiotherapy at relapse          | 0.46         | 0.25–0.88    | .018    |
| Response to chemotherapy at relapse | 0.29      | 0.15–0.54    | <.001   |
| Second remission achieved        | 0.16         | 0.04–0.65    | <.001   |

RISK FACTORS (N°)
- 0
- 1
- 2–3/4-censored
- 5-censored
- 1-censored

FIGURE 2 Post-relapse overall survival (OS) based on number of prognostic risk factors emerging from the multivariable analysis (early relapse, radiotherapy not performed, no response to chemotherapy, and failure to achieve a second remission).
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