Is Surveillance Imaging in Pediatric Patients Treated for Localized Rhabdomyosarcoma Useful? The European Experience

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BACKGROUND: After the completion of therapy, patients with localized rhabdomyosarcoma (RMS) are subjected to intensive radiological tumor surveillance. However, the clinical benefit of this surveillance is unclear. This study retrospectively analyzed the value of off-therapy surveillance by comparing the survival of patients in whom relapse was detected by routine imaging (the imaging group) and patients in whom relapse was first suspected by symptoms (the symptom group). METHODS: This study included patients with relapsed RMS after the completion of therapy for localized RMS who were treated in large pediatric oncology hospitals in France, the United Kingdom, Italy, and the Netherlands and who were enrolled in the International Society of Paediatric Oncology Malignant Mesenchymal Tumor 95 (1995-2004) study, the Italian Paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma 96 (1996-2004) study, or the European Paediatric Soft Tissue Sarcoma Study Group Rhabdomyosarcoma 2005 (2005-2013) study. The survival times after relapse were compared with a log-rank test between patients in the imaging group and patients in the symptom group. RESULTS: In total, 199 patients with relapsed RMS were included: 78 patients (39.2%) in the imaging group and 121 patients (60.8%) in the symptom group. The median follow-up time after relapse was 7.4 years (interquartile range, 3.9-11.5 years) for survivors (n = 86); the 3-year postrelapse survival rate was 50% (95% confidence interval [CI], 38%-61%) for the imaging group and 46% (95% CI, 37%-55%) for the symptom group (P = .7). CONCLUSIONS: Although systematic routine imaging is the standard of care after RMS therapy, the majority of relapses were detected as a result of clinical symptoms. This study found no survival advantage for patients whose relapse was detected before the emergence of clinical symptoms. These results show that the value of off-therapy surveillance is controversial, particularly because repeated imaging may also entail potential harm.

KEYWORDS: radiology, rhabdomyosarcoma, surveillance imaging, survival.

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INTRODUCTION
Pediatric patients treated for rhabdomyosarcoma (RMS) are subjected to intensive surveillance after therapy because up to one-third of patients with localized disease at the initial diagnosis experience tumor relapse. The majority of these relapses are locoregional, and the lungs are the most affected metastatic site. Three-year survival after relapse is approximately 37%, and it is associated with several factors such as histology, the initial tumor site, the pattern of relapse (local or metastatic), and prior radiotherapy.

The recommended surveillance after treatment, according to the European Paediatric Soft Tissue Sarcoma Study Group Rhabdomyosarcoma 2005 (EpSSG-RMS 2005) protocol, includes a clinical examination together with a magnetic resonance imaging (MRI) or computed tomography (CT) scan of the primary tumor site and a chest x-ray, which should be performed every 3 months in the first year and every 4 months in the second and third years after treatment. The recommended surveillance is once a year in the fourth and fifth years after treatment.

However, no available evidence shows that current surveillance recommendations lead to earlier detection of relapse and, therefore, to improved survival for patients with relapsed RMS. Furthermore, repetitive imaging is associated with substantial costs, could add additional radiation exposure, and often requires anesthesia. Furthermore, frequent hospital visits could potentially cause psychological distress to patients and parents.

The questionable survival benefit of current surveillance strategies and the potential adverse factors associated with surveillance emphasize the need for an assessment of the value of surveillance imaging. In this international, multicenter, retrospective study, we aimed to evaluate the value of surveillance imaging by determining the method of detection of relapse and its impact on survival in a cohort of patients treated according to consecutive European pediatric protocols.

MATERIALS AND METHODS
Included patients were treated in the International Society of Paediatric Oncology Malignant Mesenchymal Tumor 95 study, the Italian Paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma 96 study, or the EpSSG-RMS 2005 study. All studies were approved by the appropriate national review boards. Patients, guardians, or both gave informed consent to participate in the individual studies according to the research ethics requirements of the individual institutions.

Eligible patients, identified from the databases of the individual studies, suffered from relapsed RMS 0 to 5 years after they had achieved complete remission at the end of therapy (or a stable residual mass more than 6 months after the end of therapy); all had localized RMS at the initial diagnosis, were diagnosed between 1995 and December 2013, and were 0 to 18 years old at time of the initial diagnosis.

Treatment at the initial diagnosis was according to the risk stratification of the reference protocol at the time of diagnosis. Treatment generally consisted of a combination of chemotherapy with surgery and/or radiotherapy, as described previously. The local therapy approach differed per protocol. If possible, delayed surgery was performed in case of residual tumor. Patients received radiotherapy according to protocol, with specific favorable subgroups not receiving radiotherapy (according to the site, response to chemotherapy, secondary surgery, and risk group).

Treatment after relapse was dependent on the initial therapy; chemotherapy regimens were left to the discretion of the treating physician or were part of phase 2 trials. Local therapy (surgery and/or radiotherapy) was applied if feasible; in general, radiotherapy was administered to patients who did not receive radiotherapy during their initial treatment.

Tumor surveillance after the end of treatment was performed according to the applicable treatment protocol. In general, surveillance imaging comprised imaging of the primary site by ultrasound, CT, or MRI every 3 to 4 months in the first 3 years after the end of treatment. The frequency of follow-up was once or twice a year in the fourth and fifth years after the end of treatment (see Supporting Table 1).

Data were collected from patients who had been treated in 21 larger pediatric oncology centers in France, Italy, the United Kingdom, and the Netherlands. Data were collected from patient charts and radiology reports by 1 dedicated physician nationwide or by experienced pediatric oncologists (depending on the participating country), and they were recorded with a standardized case report form. The following information was collected: clinical characteristics at the initial diagnosis, therapy for the initial tumor, type of relapse, information on the method of relapse detection and the presence of clinical symptoms at the time of relapse detection, total number of imaging studies, and follow-up technique used to detect disease relapse. Furthermore, we collected data on treatment after relapse and outcome after relapse. The type of relapse was classified as locoregional (defined as...
relapse at the local site, locoregional nodal relapse, or both), metastatic, or locoregional and metastatic.

The method of relapse detection was categorized as “routine imaging with/without clinical symptoms” (shortened to “routine imaging”) or “imaging initiated because of clinical symptoms” (shortened to “clinical symptoms”). This distinction was made on the basis of patient charts and radiology reports.

**Statistical Analysis**

Analyses were performed with SPSS (version 24.0.0.1) and R (version 3.4.3). The distribution of variables at diagnosis and relapse and the treatment characteristics of patients whose relapse was detected by routine imaging and patients whose relapse was detected by clinical symptoms were compared with chi-square tests. Overall survival (OS) was calculated from the time of diagnosis of relapse to death from any cause. Outcomes for living patients were censored at the time of their last reported contact (data cutoff point: December 31, 2017). OS curves were obtained with the Kaplan-Meier method. A log-rank test was used to compare OS levels between routine imaging patients and clinical symptom patients. P values lower than .05 were considered statistically significant. The following predefined subgroups were evaluated to determine whether specific patients might benefit from surveillance: histology, tumor site, tumor size, nodal status at presentation, Intergroup Rhabdomyosarcoma Study grouping, risk group, prior radiotherapy, and treatment protocol. No statistical tests were performed for these groups because of the large number of groups and subsequently small numbers of patients per group. Patients with a pulmonary relapse were specifically described because chest radiographs are also routinely performed during surveillance after the end of treatment.

**RESULTS**

**Patient Population**

In total, 202 patients with relapsed RMS were diagnosed at the participating centers, and 199 of these patients were included in the current analyses. Three patients were excluded because the date of relapse was missing (n = 1), the method of relapse detection was missing (n = 1), or the patient was lost to follow-up (n = 1). Information on characteristics at the initial diagnosis is presented in Table 1.

The median time from the initial diagnosis to relapse was 18.5 months (interquartile range, 13.5-25.2 months) for the total cohort. Relapse was locoregional in 153

### Table 1. Characteristics of the Patients Included in This Analysis (n = 199)

| Characteristic                          | No. of Patients (%) |
|----------------------------------------|---------------------|
| Age at initial diagnosis               |                     |
| <10 y                                   | 150 (75.4)          |
| ≥10 y                                   | 49 (24.6)           |
| Sex                                     |                     |
| Male                                    | 121 (60.8)          |
| Female                                  | 78 (39.2)           |
| Primary site                            |                     |
| Orbit                                   | 34 (17.1)           |
| Head and neck                           | 18 (9.0)            |
| Parameningeal                           | 47 (23.6)           |
| GU bladder–prostate                     | 19 (9.5)            |
| GU nonbladder–prostate                  | 17 (8.5)            |
| Limbs                                   | 26 (13.1)           |
| Other                                   | 39 (19.1)           |
| Nodal status                            |                     |
| N0                                      | 162 (81.4)          |
| N1                                      | 34 (17.1)           |
| Unknown                                 | 3 (1.5)             |
| T status                                |                     |
| T1                                      | 90 (45.2)           |
| T2                                      | 98 (49.2)           |
| Unknown                                 | 11 (5.5)            |
| IRS group postsurgical stageb           |                     |
| I                                       | 14 (7.0)            |
| II                                      | 24 (12.1)           |
| III                                     | 161 (80.9)          |
| Protocol                                |                     |
| SIOP-MMT95                              | 76 (38.2)           |
| STSC-RMS96                              | 22 (11.1)           |
| EpSSG-RMS 2005                          | 101 (50.8)          |

Abbreviations: EpSSG-RMS 2005, European Paediatric Soft Tissue Sarcoma Study Group Rhabdomyosarcoma 2005; GU, genitourinary; IRS, Intergroup Rhabdomyosarcoma Study; RMS, rhabdomyosarcoma; SIOP-MMT95, International Society of Paediatric Oncology Malignant Mesenchymal Tumor 95; STSC-RMS96, Italian Paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma 96.

*a* Favorable histology includes all embryonal, spindle cell, and botryoid RMS; unfavorable histology includes all alveolar RMS, including RMS, not otherwise specified (n = 2).

*b* The IRS groups were categorized as follows: group I, primary complete resection (R0); group II, microscopic residual (R1) or primary complete resection but N1; and group III, macroscopic residual (R2).

patients (76.9%), 26 patients (13.1%) had a metastatic relapse, and 20 patients (10.1%) had a combined locoregional and metastatic relapse.

**Relapse Detection**

In 121 patients (60.8%), relapse was detected by clinical symptoms; in 22 patients (11.1%), relapse was detected by routine imaging with clinical symptoms present at the time of routine imaging; and in 56 patients (28.1%), relapse was detected by routine imaging without clinical symptoms.
The median time from the end of treatment to relapse was 8.0 months (interquartile range, 5.3-13.9 months) for patients whose relapse was detected by routine imaging (with or without clinical symptoms) and 12.0 months (interquartile range, 5.6-19.2 months) for patients whose relapse was detected by clinical symptoms ($P = .003$; Fig. 1). The latest relapse detected by routine imaging occurred 2.5 years after the end of treatment. In 17 patients (8.5%), relapse was detected within 3 months after the completion of therapy, and no scheduled follow-up imaging had yet been performed. In all other symptomatic cases, relapse was detected after patients had already undergone routine surveillance imaging per protocol. Previously identified factors associated with the outcome after relapse did not differ significantly between the 2 groups according to the method of relapse detection. However, a significant difference was observed between the 2 groups according to the treatment protocol ($P = .02$; Table 2).

The most frequently reported symptoms were a palpable mass (n = 80) and pain (n = 80). Furthermore, patients presented with a mass effect leading to obstruction (n = 20), dysuria/hematuria (n = 6), neurological symptoms (n = 5), or other symptoms (n = 30).

The total number of follow-up examinations for the total cohort consisted of 405 MRI scans, 206 ultrasounds, and 45 CT scans of the primary site as well as 601 chest x-rays and 47 chest CT scans. MRI of the primary site was the most frequent modality detecting relapse in the routine imaging group (n = 56).

**Survival After Relapse**

The 3-year OS rate after relapse for the total group was 48% (95% confidence interval [CI], 40%-55%); the 3-year OS rates were 50% (95% CI, 38%-61%) for routine imaging patients and 46% (95% CI, 37%-55%) for clinical symptom patients ($P = .7$; Fig. 2). The median follow-up time after relapse was 7.4 years (interquartile range, 3.9-11.5 years) for survivors (n = 86). Among patients who had not received prior radiotherapy, the 3-year OS rate was 72% (95% CI, 55%-90%) for routine imaging patients and 63% (95% CI, 50%-76%) for clinical symptom patients ($P = .7$).
TABLE 2. Distribution of Characteristics Associated With Survival Based on the Mode of Relapse Detection

| Characteristic | Routine Imaging (n = 78), No. (%) | Clinical Symptoms (n = 121), No. (%) | P<sup>a</sup> |
|---------------|----------------------------------|-------------------------------------|--------|
| Histology<sup>b</sup> |                                  |                                     | .36    |
| Favorable     | 57 (73)                          | 81 (67)                             |        |
| Unfavorable   | 21 (27)                          | 40 (33)                             |        |
| Tumor size    |                                  |                                     | .19    |
| ≤5 cm         | 31 (40)                          | 59 (49)                             |        |
| >5 cm         | 43 (55)                          | 55 (45)                             |        |
| Unknown       | 4 (5)                            | 7 (6)                               |        |
| Primary site  |                                  |                                     | .16    |
| Orbit         | 9 (12)                           | 25 (21)                             |        |
| Head and neck | 6 (8)                            | 12 (10)                             |        |
| Parameningeal | 19 (24)                          | 28 (23)                             |        |
| GU bladder-prostate | 9 (12) | 10 (8) |        |
| GU nonbladder-prostate | 11 (14) | 6 (5) |        |
| Limbs         | 12 (15)                          | 14 (12)                             |        |
| Other         | 12 (15)                          | 26 (21)                             |        |
| IRS group postsurgical stage<sup>c</sup> |                                  |                                     | .54    |
| I             | 4 (5)                            | 10 (8)                              |        |
| II            | 8 (10)                           | 16 (13)                             |        |
| III           | 66 (85)                          | 95 (79)                             |        |
| Nodal status  |                                  |                                     | .94    |
| N0            | 63 (81)                          | 99 (82)                             |        |
| N1            | 13 (17)                          | 21 (17)                             |        |
| Nx            | 2 (3)                            | 1 (1)                               |        |
| Type of recurrence |                                  |                                     | .74    |
| Local         | 59 (76)                          | 94 (78)                             |        |
| Metastatic with/without local | 19 (24) | 27 (22) |        |
| Prior radiotherapy |                                  |                                     | .17    |
| No            | 26 (33)                          | 52 (43)                             |        |
| Yes           | 52 (67)                          | 69 (57)                             |        |
| Time to relapse<sup>d</sup> |                                  |                                     | .57    |
| <1.5 y        | 44 (56)                          | 60 (50)                             |        |
| ≥1.5 y        | 38 (44)                          | 61 (50)                             |        |
| Treatment protocol |                                  |                                     | .02    |
| SIOP-MMT95    | 24 (31)                          | 52 (43)                             |        |
| STSC-RMS96    | 5 (6)                            | 17 (14)                             |        |
| EpSSG-RMS2005 | 49 (63)                          | 53 (43)                             |        |

Abbreviations: EpSSG-RMS 2005, European Paediatric Soft Tissue Sarcoma Study Group Rhabdomyosarcoma 2005; GU, genitourinary; IRS, Intergroup Rhabdomyosarcoma Study; RMS, rhabdomyosarcoma; SIOP-MMT95, International Society of Paediatric Oncology Malignant Mesenchymal Tumor 95; STSC-RMS96, Italian Paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma 96.

Bold indicates P value < .05.

<sup>a</sup>Favorable histology includes all embryonal, spindle cell, and botryoid RMS; unfavorable histology includes all alveolar RMS, including RMS, not otherwise specified (n = 2).

<sup>b</sup> The IRS groups were categorized as follows: group I, primary complete resection (R0); group II, microscopic residual (R1) or primary complete resection but N1; and group III, macroscopic residual (R2).

<sup>c</sup>Time to relapse in years after the initial diagnosis.

<sup>d</sup>time to relapse after the completion of therapy for pediatric RMS is recommended in current treatment protocols. The assumption is that surveillance imaging will lead to earlier detection of tumor relapse and subsequently to an improved prognosis after relapse. So far, no evidence is available for this assumption<sup>3,20</sup>. This study shows that the majority of patients with relapsed RMS experience clinical symptoms at the time of relapse (71.8%). We have found no evidence that the detection of a relapse before the emergence of clinical symptoms results in improved survival after relapse. As might be expected, the time to first relapse was significantly shorter for the routine imaging group than the clinical symptom group. Because the interval between surveillance imaging was gradually extended in the years after therapy, it was less likely that patients were detected by routine imaging after the first 3 years of follow-up. Nevertheless, also in the first 2 years after the end of therapy, in the majority of patients (106 of 180), relapse was detected because of clinical symptoms. Our findings are consistent with a single-center study by Lin et al<sup>9</sup> (n = 43), who compared survival for patients with relapsed RMS in whom events were detected by clinical symptoms with survival for patients in whom events were detected by routine imaging. The 3-year OS rate was 20% (n = 15) for patients whose relapse was detected by routine imaging and 11% (n = 28) for patients whose relapse was detected by clinical symptoms (P = .38). However, Lin et al included a heterogeneous group of patients, including patients with metastatic disease at the initial diagnosis and patients who relapsed during treatment.

Recent studies assessing the value of routine imaging in other soft-tissue and bone sarcomas have shown contradictory results, and this illustrates the necessity for tumor-specific studies assessing the value of surveillance imaging because its value is dependent on tumor-specific factors (eg, tumor biology and chance of survival after relapse).<sup>21-23</sup>

The current study is limited by its retrospective design. We tried to limit this bias by using a standardized case report form. Furthermore, data were collected by 1 dedicated physician nationwide or by experienced
pediatric oncologists to limit the number of data collectors and ensure required expertise. A further limitation is that we included only patients treated in larger pediatric oncology centers; this might have biased our results. However, patient and tumor characteristics were comparable to those of a large cohort of patients with relapsed RMS previously described by Chisholm et al. Because of its retrospective design and uncertainty about whether clinical symptoms that were present at the time of routine imaging would have led to additional imaging, we decided to combine this group (routine imaging with symptoms) with the group of patients whose relapse was detected by routine imaging without symptoms. Furthermore, the included patients were treated according to different protocols over almost 2 decades; treatment approaches have changed over time, and higher resolution imaging techniques have become available. This might be the reason that more patients were detected by routine imaging in the subgroup treated according to the EpSSG-RMS 2005 protocol; however, the majority of patients (51.5%) still were detected by clinical symptoms, and 64.4% of the patients had clinical symptoms at the time of relapse detection (n = 65).

Although we included almost 200 patients with relapsed RMS, the number of patients did not allow us to evaluate the value of surveillance imaging in specific subgroups (eg, patients less likely to present with clinical symptoms because of tumor localization). We cannot be certain that specific patients might benefit from early detection of relapse; the time span before clinical symptoms become apparent could be longer for tumor relapses at specific sites.

On the basis of the number of patients who did not experience a tumor relapse after achieving complete remission in the EpSSG-RMS 2005 study (79.6%), the number of patients without clinical symptoms at the time of relapse (28.1%), and the follow-up recommendations (12 scans of the primary site and 12 chest x-rays in the first 5 years after therapy), we estimated that 178 scans of the primary site and 178 chest x-rays would be needed to detect 1 patient with a relapse without clinical symptoms.

Figure 2. Overall survival after relapse (including 95% confidence intervals) according to the method of relapse detection. The P value is based on a log-rank test.
Because RMS generally occurs in young patients, a substantial proportion of patients require general anesthesia (often below the age of 8 years; 58.3% in the current analysis) to generate good-quality imaging. Besides the short-term risk associated with general anesthesia, there is an ongoing debate about the consequences of the use of general anesthesia in the developing brain. 

Worrisome as well is that there is increasing evidence of gadolinium deposition in parts of the brain after repeated administration of gadolinium contrast agents, although the clinical significance of these findings remains unclear. 

In addition, follow-up imaging also implies repetitive radiation exposure, mainly caused by chest radiographs, because local imaging is usually performed with MRI. 

Furthermore, the repetitive surveillance imaging causes stress and anxiety for patients and parents. On the basis of our analyses, it appears that the risk of these potential side effects could be reduced by reducing the number of radiological examinations.

McHugh and Roebuck previously questioned the value of surveillance imaging and stated that randomized controlled trials are needed to determine whether earlier detection of relapse by routine imaging results in improved survival. The feasibility of including pediatric patients in a trial randomizing between radiological follow-up and only clinical follow-up is questionable, and the question is whether we need a randomized trial to modify surveillance recommendations.

An argument against completely abandoning radiological follow-up is that imaging might be needed to accurately determine event-free survival according to historical standards because this would affect survival outcomes for these trials. However, we should reduce surveillance imaging to a minimal period and frequency and be guided by the actual risk of relapse per time period, the chances for a cure in case of relapse, crucial clinical trial endpoints, and the needs of patients and their parents. Although the treatment for newly diagnosed patients with RMS is based on extensive risk stratification models, the follow-up recommendations after the end of treatment are identical for all patients. Potentially, patients with a high chance of successful salvage treatment might benefit more from frequent radiological imaging than patients with a small chance of a cure after relapse; a nomogram previously developed by Chisholm et al might help to select those patients potentially benefitting from frequent surveillance. We strongly feel that we should try to achieve an international consensus on surveillance recommendations for patients treated for RMS.

In conclusion, according to the results of this study, there is no evidence showing that current surveillance regimes after therapy for patients treated for localized RMS lead to improved survival after relapse. There is a need for risk-adapted follow-up strategies to improve the efficiency of follow-up after RMS treatment, but the needs and preferences of patients and parents should also be taken into account.

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**TABLE 3. Survival Analyses Based on Initial Characteristics and Prior Treatment**

| Routine Imaging | Clinical Symptoms |
|-----------------|-------------------|
| **No.** | **3-y OS, % (95% CI)** | **No.** | **3-y OS, % (95% CI)** |
| All patients | 78 | 50 (38-61) | 121 | 46 (37-55) |
| **Histology** | | | | |
| Favorable | 57 | 55 (42-68) | 81 | 51 (40-62) |
| Unfavorable | 21 | 35 (14-57) | 40 | 35 (19-50) |
| **Primary site** | | | | |
| Orbit | 9 | 100 | 25 | 88 (75-100) |
| Head and neck | 6 | 83 (54-100) | 12 | 67 (40-93) |
| Parameningeal | 19 | 21 (3-40) | 28 | 13 (0-26) |
| GU bladder–prostate | 9 | 56 (23-88) | 10 | 20 (0-45) |
| GU nonbladder–prostate | 11 | 73 (46-99) | 6 | 80 (45-100) |
| Limbs | 12 | 25 (1-50) | 14 | 52 (23-81) |
| Other | 12 | 40 (7-73) | 26 | 27 (10-44) |
| **Tumor size** | | | | |
| ≤5 cm | 31 | 80 (65-94) | 59 | 65 (53-77) |
| >5 cm | 43 | 30 (16-44) | 55 | 28 (16-40) |
| **Nodal status** | | | | |
| NO | 63 | 58 (45-70) | 99 | 54 (44-64) |
| N1 | 13 | 23 (0-46) | 21 | 11 (0-28) |
| **IRS group postsurgical stage** | | | | |
| I | 4 | 75 (33-100) | 10 | 80 (55-100) |
| II | 8 | 38 (4-71) | 16 | 69 (46-92) |
| III | 66 | 50 (38-62) | 95 | 38 (28-48) |
| **Prior radiotherapy** | | | | |
| No | 26 | 72 (55-90) | 52 | 63 (50-76) |
| Yes | 52 | 39 (25-52) | 69 | 32 (21-44) |
| **Risk group** | | | | |
| Low risk | 0 | 90 (78-100) | 4 | 100 |
| Standard risk | 29 | 27 (13-41) | 42 | 69 (54-83) |
| High risk | 45 | 17 (0-47) | 62 | 35 (23-47) |
| Very high risk | 6 | 13 | 8 (0-15) |
| **Treatment protocol** | | | | |
| SIOP-MMT95 | 24 | 46 (26-66) | 52 | 60 (47-74) |
| STSC-RMS96 | 5 | 40 (0-83) | 17 | 47 (23-71) |
| EpSSG-RMS2005 | 49 | 53 (39-68) | 53 | 31 (18-44) |

Abbreviations: CI, confidence interval; EpSSG-RMS 2005, European Paediatric Soft Tissue Sarcoma Study Group Rhabdomyosarcoma 2005; GU, genitourinary; IRS, Intergroup Rhabdomyosarcoma Study; OS, overall survival; RMS, rhabdomyosarcoma; SIOP-MMT95, International Society of Paediatric Oncology Malignant Mesenchymal Tumor 95; STSC-RMS96, Italian Paediatric Soft Tissue Sarcoma Committee Rhabdomyosarcoma 96.

aFavorable histology includes all embryonal, spindle cell, and botryoid RMS; unfavorable histology includes all alveolar RMS, including RMS, not otherwise specified (n = 2).

bThe IRS groups were categorized as follows: group I, primary complete resection (R0); group II, microscopic residual (R1) or primary complete resection but N1; and group III, macroscopic residual (R2).

cBased on the EpSSG-RMS 2005 risk group stratification (see Supporting Table 2).
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AUTHOR CONTRIBUTIONS
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