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ORIGINAL ARTICLE

International multicenter retrospective study on pleomorphic rhabdomyosarcoma (P-RMS), a PUSH platform study: outcome of primary localized disease

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Background: The purpose of this study was to report the outcome of primary localized pleomorphic rhabdomyosarcoma (P-RMS).

Patients and methods: Patients with primary localized P-RMS, aged >40 years, and surgically treated with curative intent from January 2013 to December 2023 were enrolled from 25 institutions across 12 countries. Pathological inclusion criteria were predefined by expert pathologists per established World Health Organization guidelines. Primary endpoint was overall survival (OS). Secondary endpoints were disease-free survival (DFS), crude cumulative incidence (CCI) of local recurrence (LR), CCI of distant metastases (DM), post-relapse OS, and post-metastasis OS.

Results: A total of 93 patients were eligible and included in the present study. At a median follow-up of 39.8 months (interquartile range 22.83-85.69 months), 32/93 (34%) patients died and 53/93 (57%) recurred. The corresponding 5-year OS and DFS were 57.7% [95% confidence interval (CI) 46.7% to 71.2%] and 35.8% (95% CI 26.3% to 48.9%), respectively. Younger age, R0 surgical margins, and administration of radiotherapy were positive prognostic factors in multivariable analysis for DFS. LR and DM were developed in 14/93 (15%) and 39/93 (42%) patients, respectively. The corresponding 3-year CCI-LR and DM were 16% (95% CI 8.9% to 25%) and 44% (95% CI 33% to 55%). Post-metastasis median OS was 14.3 months (95% CI 9.4 months-not reached).

Conclusions: While P-RMS is known to be an aggressive histologic sarcoma subtype, one-third of patients with primary localized disease may be cured. The contribution of chemotherapy and radiotherapy to the cure rate remains unclear. Post-metastatic outcomes mirror those observed in other sarcomas.

Key words: sarcoma, pleomorphic rhabdomyosarcoma, localized disease, prognostic factors, survival

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INTRODUCTION

Pleomorphic rhabdomyosarcoma (P-RMS) is an ultra-rare sarcoma, with an incidence of 0.545 cases per million per year.[1-3] It is currently categorized by the World Health Organization (WHO) classification as a separate entity from pediatric RMS (i.e. embryonal or alveolar RMS), with distinct clinical behavior and outcomes. It mainly affects individuals in their sixth to seventh decades of life, typically arises in the deep soft tissues of the extremities, and displays aggressive behavior.[4] Almost all P-RMS cases show strong, diffuse desmin expression. Nuclear expression of myogenin (Myf4) is variable and nuclear expression of MYOD1 is rarely observed.[2]

The outcome of adult patients with P-RMS is poor, with a 5-year overall survival (OS) ranging between 20% and 40%.[5-10] Surgery, often combined with radiotherapy (RT), is considered the standard treatment for localized disease, as with other soft tissue sarcomas.[8,9,11,12] Despite bearing the 'rhabdomyosarcoma' name, however, there is no consensus on the optimal systemic treatment approach. P-RMS has been associated with poor response to conventional chemotherapy (ChT), especially when compared with alveolar or embryonal RMS.[5,6,13,14] The role of (neo) adjuvant ChT in P-RMS is poorly understood, and its use varies significantly across countries and patient age. Notably, no prospective clinical studies have been conducted specifically on this sarcoma subtype.

In this global retrospective study conducted within the 'Pushing Ultra-rare Sarcomas towards Hope (PUSH)' initiative—a global collaborative effort involving sarcoma reference centers worldwide, dedicated to advancing knowledge of the natural history of ultra-rare sarcomas and fostering the development of new treatments—we sought to describe the natural history and identify prognostic factors in patients with primary localized P-RMS.

PATIENTS AND METHODS

This international retrospective multicenter study was conducted within the PUSH consortium. All consecutive patients aged >40 years with primary localized P-RMS, who underwent curative-intent surgery from January 2013 to December 2023 at participating institutions, were retrospectively identified. The selected age threshold is aimed to identify an adult population to avoid overlap with pediatric-type RMS with anaplasia.

Collected data included patient gender, age at diagnosis, tumor site, details of (neo)adjuvant locoregional/systemic treatments, type of surgery, and margin status. Inclusion criteria are detailed in the study synopsis (Supplementary Data, available at https://doi.org/10.1016/j.esmoop.2025.106044).

A written informed consent for treatment was obtained from each patient as required by local regulation. Approval of the retrospective study was obtained from the institutional review board of each participating institution.

Eligible patients were required to have a locally established, pathologically confirmed diagnosis of P-RMS. Diagnostic criteria were predefined in the study protocol and agreed upon by expert sarcoma pathologists serving on the steering committee. The criteria included a high-grade pleomorphic malignant tumor with abundant eosinophilic cytoplasm, diffuse desmin expression, and nuclear expression of rhabdomyoblastic differentiation markers (myogenin and/or MYOD1), typically present in a minority of neoplastic cells. According to the protocol, local diagnoses had to be reviewed at participating centers, and when the predefined criteria were not fully documented, additional immunohistochemical analyses had to be carried out to complete the required characterization. The decision to administer (neo)adjuvant ChT and/or RT was made by local expert sarcoma teams and varied across institutions, typically guided by clinical assessment of relapse risk.

Statistical analysis

Patient, disease, and treatment characteristics were summarized using standard descriptive statistics.

The primary endpoint was OS. Secondary endpoints included disease-free survival (DFS), crude cumulative incidence (CCI) of local recurrence (LR), CCI of distant metastases (DM), post-relapse OS (pr-OS), and post-metastases OS (pm-OS).

OS was defined as the time from diagnosis to death from any cause. DFS was defined as the time from diagnosis to either relapse or death, whichever occurred first. The times for CCI-LR and CCI-DM were calculated from diagnosis to the occurrence of the respective relapse. Competing risks methodology was applied to estimate the cumulative incidence of LR and DM, treating death without event and the alternate relapse type as competing events. pr-OS was defined as the time from any relapse to death from any cause; pm-OS was defined as the time from DM to death from any cause. Patients without the event of interest were censored at the last known follow-up (FU).

Survival outcomes (OS, DFS, pr-OS, and pm-OS) were estimated with the Kaplan—Meier method and compared with the log-rank test. Cumulative incidence functions were used to estimate the incidence of LR and DM and were compared using Gray's test. Cox proportional hazards models were used to evaluate associations between OS and potential prognostic variables. Fine and Gray subdistribution hazard models were used to analyze the association between prognostic factors and the risk of LR or DM.

RESULTS

Patient and tumor characteristics

In total, 100 patients with primary localized P-RMS surgically treated with curative intent from 25 institutions between January 2013 and December 2023 were retrospectively identified. Of these, 93 were eligible for the present analysis. Seven patients were excluded: two were <40 years of age, four did not meet the pathological criteria, and one had

inadequate FU. All patients had the complete data required by the study protocol. Representative morphological and immunohistochemical features of P-RMS are shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.106044.

Baseline and treatment characteristics of the whole series are reported in Table 1.

Thirty-seven of 93 patients (40%) received ChT, mostly in the neoadjuvant setting (28/37, 76%), with 24/28 (86%) treated using anthracycline-based regimens. All 28 patients treated with neoadjuvant ChT were assessable for response: 12/28 (43%) achieved partial response and 2/28 (7%) had complete response (overall response rate 50%). Fifty-five of 93 patients (67%) received RT, 32/55 in a preoperative setting and 23/55 in a post-operative setting. A time-dependent model to evaluate the effect of response on LR and DM could not be implemented. Regarding DM, however, 4/14 (29%) events occurred in responder patients and 9/14 (64%) in non-responder patients.

The median FU was 39.8 months [interquartile range (IQR) 22.83-85.69 months].

Table 1. Patient characteristics

P-RMS	*N* = 93
Age at surgery (years), median (IQR)	60 (52-72)
Male/female (%)	62 (67)/31(33)
Tumor size (mm)	80 (49-120)
Primary site (%)	
Extremities	63 (68)
Other	11 (12)
Chest	10 (11)
Abdomen/retroperitoneum	9 (9)
Treatments of primary disease	
Surgery (%)	
No	0 (0)
Yes	93 (100)
R0	75 (86)
R1	12 (14)
R2	0 (0)
Missing	6
Radiotherapy (%)	
No	37 (40)
Yes	55 (60)
Preoperative	32 (58)
Post-operative	23 (42)
Missing	1
Chemotherapy (%)	
No	55 (60)
Yes	37 (40)
Neoadjuvant	28 (30)
Anthracycline and ifosfamide	17 (61)
Vincristine, anthracycline, ifosfamide	3 (10)
Vincristine, anthracycline, cyclophosphamide	2 (2)
Other anthracycline-based regimens	4 (14)
Etoposide and ifosfamide	1 (3)
Other regimens	3 (10)
Adjuvant	9 (10)
Missing	1
Status at last follow-up (%)	
Alive, no evidence of disease	46 (50)
Alive, with evidence of disease	13 (14)
Dead	32 (34)
Lost to follow-up	2 (2)

IQR, interquartile range; P-RMS, pleomorphic rhabdomyosarcoma.

Survival

Thirty-two of 93 (34%) patients died of disease. The corresponding 3- and 5-year OS rates were 60.6% [95% confidence interval (CI) 50.2% to 73.1%] and 57.7% (95% CI 46.7% to 71.2%), respectively (Figure 1). For OS, 30/32 events occurred before 40 months; the other 2 events of OS occurred at 53 and 90 months. Younger age at surgery ($P = 0.034$) and administration of RT ($P = 0.019$) were significantly associated with better OS in univariable analysis (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.106044).

Fifty-three of 93 (57%) patients recurred. The corresponding 3- and 5-year DFS rates were 40.6% (95% CI 31.4% to 52.5%) and 35.8% (95% CI 26.3% to 48.9%), respectively (Figure 2). The median time to recurrence for those who recurred was 4.31 months (IQR 2.86-7.66 months). For DFS, 52/55 events occurred before 40 months; the other 3 events of DFS occurred at 46 (DM), 59 (LR), and 140 months (DM). Younger age at surgery ($P = 0.024$), R0 surgical margins ($P = 0.040$), and administration of RT ($P < 0.001$) were significantly associated with better DFS in univariable analysis. In multivariable analysis, younger age at surgery [hazard ratio (HR) 1.03, CI 1.01-1.05, $P = 0.009$], R0 surgical margins (HR 2.51, CI 1.23-5.13, $P = 0.021$), and RT (HR 0.26, CI 0.14-0.48, $P < 0.001$) remained significant (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.106044).

Local recurrence

LR occurred in 14/93 (15%) patients. The median time to LR was 4.84 months (IQR 3.36-6.46 months) and 12/14 events of LR occurred within 12 months. The 3-year CCI-LR was 16% (CI 8.9% to 25%). CCI-LR curves of LR are shown in Figure 3.

Administration of RT ($P = 0.002$) was significantly associated with lower CCI-LR in univariable analysis (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.106044).

Distant metastases

DM occurred in 39/93 (42%) patients. The median time to DM was 3.98 months (IQR 2.86-7.80 months). The 3-year CCI-DM was 44% (CI 33% to 55%). CCI-DM curves of DM are shown in Figure 4.

No prognostic factors related to CCI-DM in univariable analysis were identified (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.106044).

Post-relapse overall survival

Median pr-OS was 18.32 months (IQR 12.53-47.37 months), with a 2-year pr-OS estimate of 34.9% (95% CI 22.5% to 54.2%). Only younger age at surgery ($P = 0.043$) was significantly related to better pr-OS in univariable analysis (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.106044). The Kaplan–Meier curve is shown in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.106044.

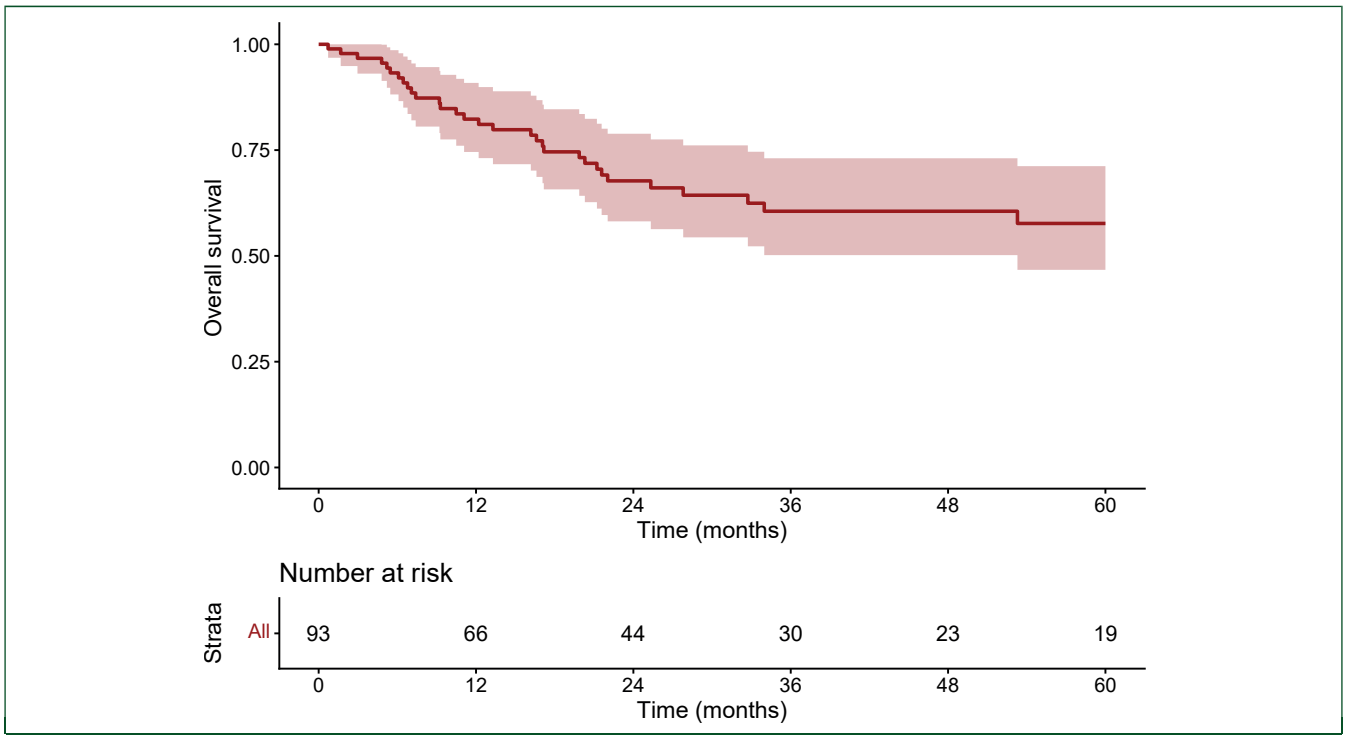

Figure 1. **Overall survival curves of primary localized pleomorphic rhabdomyosarcoma.**

Post-metastases overall survival

Median pm-OS was 14.34 months (IQR 9.41 months-not reached), with a 2-year pm-OS estimate of 30.6% (CI 17.3% to 54.1%). No prognostic factors were identified (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.106044). The Kaplan–Meier curve is shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.106044.

DISCUSSION

This international, multicenter, retrospective study reports the largest cohort to date of adult patients with primary localized P-

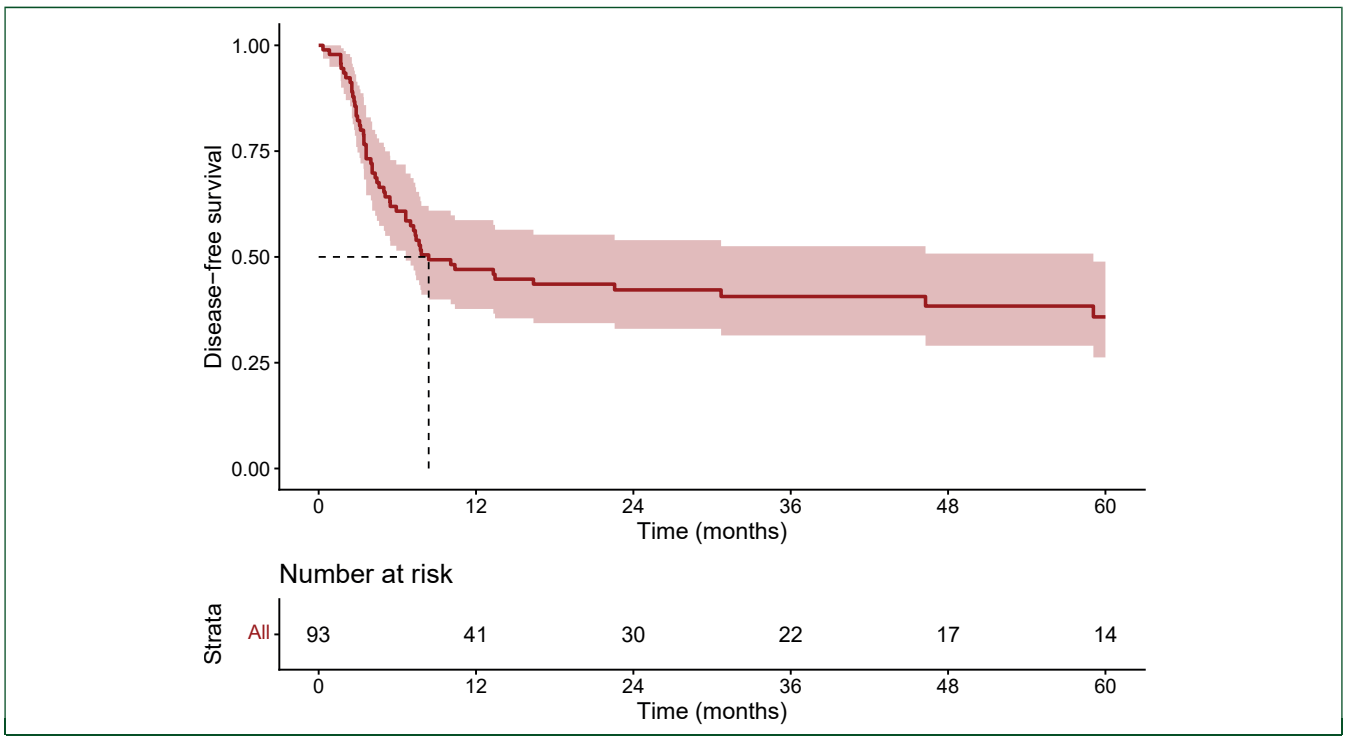

Figure 2. **Disease-free survival curves of primary localized pleomorphic rhabdomyosarcoma.**

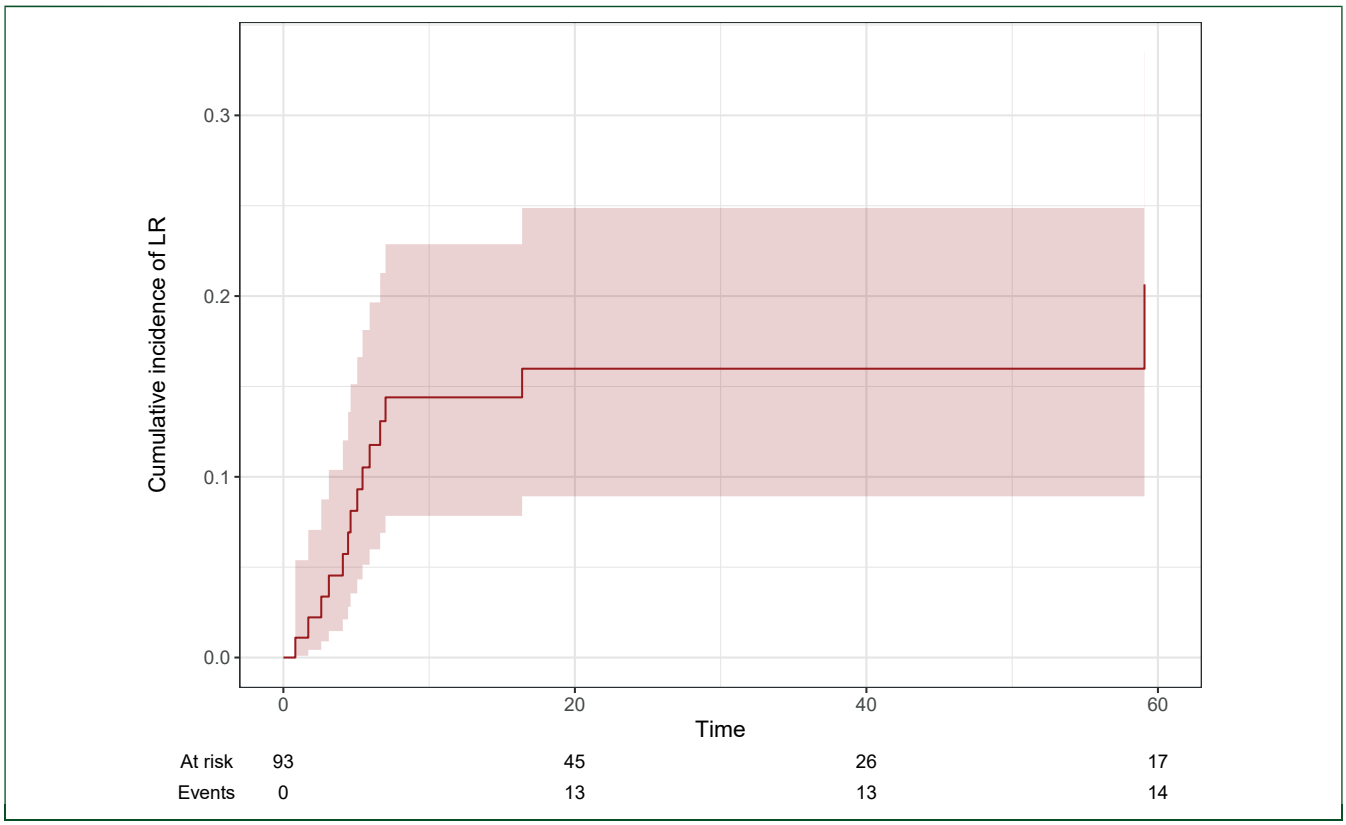

Figure 3. **Crude cumulative incidence (CCI) of local recurrence (LR).**

RMS. Patients were treated at multiple sarcoma reference centers worldwide over a contemporary 10-year time span. In this series of 93 patients, up to 40% were disease-free at 5 years and potentially cured. The impact of ChT and RT on the cure rate remains unclear. Post-metastatic outcomes mirrored those observed in other sarcomas.[15-17]

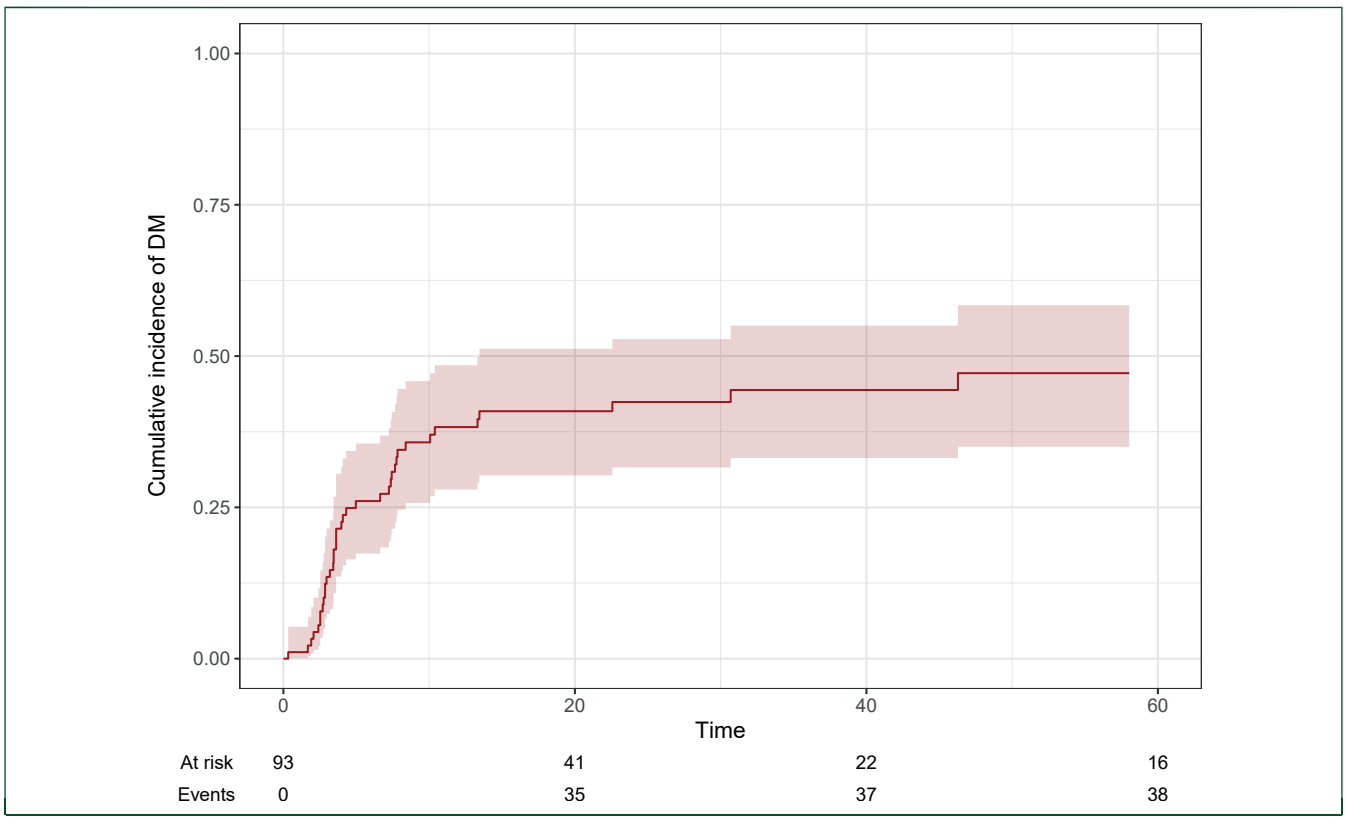

Figure 4. **Crude cumulative incidence (CCI) of distant metastases (DM).**

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This was a retrospective study, with all the inherent limitations. The relatively short median FU (40 months) may limit the robustness of conclusions regarding long-term disease control. However, most events occurred early after surgery, well before the median FU: for DFS, 52/55 events occurred before 40 months; for OS, 30/32 events occurred before 40 months. The limited number of patients receiving (neo)adjuvant ChT restricts the ability to draw firm conclusions about its impact on survival. Additionally, institutional variability in treatment strategies also complicates the identification of optimal systemic regimens.

Nevertheless, this study represents the largest series of adult P-RMS patients to date. Previously, only case reports and two major series were available.[5,6] Through this global effort, we homogenized the cohort by selecting pathologically confirmed cases managed for localized disease by expert sarcoma teams (Supplementary Data, available at https://doi.org/10.1016/j.esmoop.2025.106044). It is worth highlighting that, as expected, given the extreme rarity of this disease (i.e. ∼0.545 cases per million population per year) and its more precise definition only in recent years, the contribution of 25 institutions and a 10-year time span were required to collect ∼100 cases meeting the predefined pathological inclusion criteria to ensure diagnostic accuracy.

The genomic profile of P-RMS is non-specific and not considered beneficial for molecular diagnosis, as it does not show recurrent molecular alterations.[18] According to the literature, most P-RMS exhibit a complex genomic landscape, with copy number variations and alterations in tumor suppressor genes (*TP53*, *RB1*), similar to other genomically complex sarcomas in the differential diagnosis, such as undifferentiated pleomorphic sarcoma.[18-20] On this background and given its retrospective nature, our study did not collect molecular data. However, the investigation of these aspects and their prognostic value is planned in the observational prospective study on this neoplasm, already scheduled within the PUSH consortium.

Consistent with previous studies,[6] P-RMS occurs in patients with a median age of 60 years and exhibits quite aggressive behavior. In our series, the 5-year OS was 58%, and two-thirds of patients had disease recurrence. Conversely, Noujaim et al.[6] reported a 5-year OS of 30%. Their cohort included more than two-thirds of patients diagnosed after the age of 65 years (median age 72 years), and only 6% received (neo)adjuvant ChT. These differences in OS between the two series may reflect variations in baseline patient characteristics. We might also speculate that this difference could also be partly related to the use of ChT in localized disease, although only a prospective study could clarify this issue. These unresolved questions, left by all retrospective series published to date, will also be addressed in the prospective observational study on this histology within the PUSH initiative, as already mentioned.

The risk of early LR is common and consistent with that seen in other high-grade sarcomas, indeed nearly 50% of patients experienced recurrence within 12 months. When combined with complete resection, RT improved local control. Therefore, a multimodal treatment approach should be considered whenever appropriate, as previously reported.[7,8,12]

RT was administered in 60% of our patients, both in pre- and post-operative settings, and was significantly associated with improved DFS. The association was likely related to an improved local control, rather than an impact on the metastatic risk, given the inherent nature of this treatment modality. However, the number of events and patients was limited, and no definitive conclusions can be drawn.

ChT was administered in 40% of patients, predominantly in the neoadjuvant setting with anthracycline-based regimens. Although ChT was not significantly associated with improved survival, a 50% partial response rate suggests a higher chemosensitivity compared with previously published data and soft tissue sarcoma in general, and responder patients seem to have a better prognosis. Of note, in the metastatic series of adult P-RMS (data under submission), anthracycline-based regimens demonstrated notable activity (ORR 50%) and may therefore also be considered in a (neo)adjuvant setting to improve outcomes. By contrast, Noujaim et al. reported poor responses to conventional ChT, with only 1 of 14 patients achieving a partial response using multiagent ChT typically used in pediatric RMS. However, patients in that series were treated with highly heterogeneous regimens, limiting the ability to draw definitive conclusions. A prospective observational study within the PUSH initiative is being launched and will be instrumental in prospectively evaluating the role of systemic therapy in localized P-RMS.

Despite complete surgical resection, associated with RT in many cases, DM was common. Indeed, around half of our patients experienced DM within 5 years. This aligns with the behavior of other high-grade sarcomas and previously reported data,[6] where median time to DM was ∼5 months.

In conclusion, this study enhances our understanding of the natural history of this ultra-rare, aggressive sarcoma. It highlights the value of global collaboration across multiple institutions and countries in advancing research on ultra-rare diseases. Our findings suggest that localized P-RMS behaves similarly to high-grade sarcomas, indeed RT improves local control, and (neo) adjuvant ChT may be beneficial. Prospective studies are warranted to validate these observations, and one such prospective observational study is already launched within the PUSH framework.

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DISCLOSURE

Outside this work: AN: consulting or advisory role: Deciphera, Agenus; GM has received financial support for advisory board participation: PharmaMar, Clovis Oncology, GlaxoSmithKline (GSK)/Tesaro, Lilly, Pfizer, Boehringer Ingelheim, Deciphera, Eisai; lectures: Roche, AstraZeneca, GSK/Tesaro, Clovis Oncology, Medicamenta, EISAI, PharmaMar, Bayer, Lilly, IPSEN, Merck Sharp & Dome (MSD), Inhibrx Biosciences Inc.; and congress attendance: Roche, PharmaMar, GSK/Tesaro, MSD, Medicamenta, Pfizer, Angelini, Novartis, Merck, Lilly, Eisai; GGB: advisory role: PharmaMar, Eli Lilly, GSK, MSD, Eisai; consulting fees: Eli Lilly, PharmaMar, AboutEvents; honoraria: PharmaMar, Eli Lilly, GSK, MSD, Eisai, Istituto Gentili; travel grants: Novartis, PharmaMar, Eli Lilly; AB: consulting or advisory role: Eli Lilly, Roche, GSK, Eisai, PharmaMar, Boehringer Ingelheim, Deciphera; honoraria: GSK and PharmaMar; travel grants: Ipsen and PharmaMar; JVMGB: consulting or advisory role: Tracon Pharmaceuticals, Boehringer Ingelheim; RM: honoraria: Boehringer; SS: honoraria, consultancy, or advisory role: Aadi, Agenus, Astex Pharmaceuticals, Bavarian Nordic, Bayer, Boehringer, Daiichi Sankyo, Gentili, Glaxo, Ikena, Immunome, Merck Serono, NEC OncoImmunity, Novartis, PharmaMar, Pharma Essentia, Rain Therapeutics, Regeneron, Servier; institutional financial interests: Advenchen, Bayer, Blueprint, Boehringer, Daiichi Sankyo, Deciphera, Eisai, Epizyme, Eli Lilly, Foghorn, Glaxo, Hutchinson, Karyopharm, Novartis, PharmaMar, Rain Therapeutics, SpringWorks. All other authors have declared no conflicts of interest.

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