Head & Neck

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Parameningeal Rhabdomyosarcoma: Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS 2005 Study

Reineke A. Schoot[1] | Pieter Taselaar[1] | Giovanni Scarzello[2] | Frederic Kolb[3] | Beatrice Coppadoro[4] | Simone ter Horst[1,5] | Henry Mandeville[6] | Andrea Ferrari[7] | Raquel Hladun[8] | Sylvie Helfre[9] | Sima Ferman[10] | Anna Kelsey[11] | Marinka L. F. Hol[1,12] | Christine Devalck[13] | Myriam Ben-Arush[14] | Daniel Orbach[15] | Julia Chisholm[16] | Meriel Jenney[17] | Veronique Minard-Colin[18] | Gianni Bisogno[4] | Johannes H. M. Merks[1,19]

[1]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands | [2]Veneto Institute of Oncology IOV—IRCCS, Padua, Italy | [3]Plastic and Reconstructive Surgery, UC San Diego, University of California, San Diego, California, USA | [4]Department of Women's and Children's Health, Hematology Oncology Division, University of Padua, Padua, Italy | [5]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands | [6]Department of Radiotherapy, the Royal Marsden NHS Foundation Trust, and the Institute of Cancer Research, Sutton, UK | [7]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy | [8]Pediatric Oncology and Hematology Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain | [9]Department of Radiation Oncology, Institut Curie, Paris, France | [10]Pediatric Oncology Department, National Cancer Institute, Rio de Janeiro, Brazil | [11]Department of Paediatric Histopathology, Royal Manchester Children's Hospital, Manchester, UK | [12]ENT Department, University Medical Center Utrecht, Utrecht, The Netherlands | [13]Departement of Hemato-Oncology, HUDERF, HUB, ULB, Brussels, Belgium | [14]Joan and Sanford Weill Pediatric Hematology Oncology and Bone Marrow Transplantation Division, Ruth Rappaport Children's Hospital, Rambam Medical Center, Haifa, Israel | [15]SIREDO Oncology Centre (Care, Innovation and Research for Children, Adolescents and Young Adults With Cancer), PSL University, Institut Curie, Paris, France | [16]Children and Young People's Unit, Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK | [17]Department of Paediatric Oncology, Children's Hospital for Wales, Cardiff, UK | [18]Department of Pediatric and Adolescent Oncology, Gustave Roussy, INSERM U1015, Université Paris-Saclay, Villejuif, France | [19]Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Correspondence: Reineke A. Schoot (r.a.schoot-3@prinsesmaximacentrum.nl)

Received: 22 May 2024 | **Revised:** 1 August 2024 | **Accepted:** 28 October 2024

Section Editor: John R de Almeida

Funding: This work was supported by Royal Marsden Cancer Charity, Alice's Arc, children's cancer charity, and NIHR Biomedical Research Centre, Royal Marsden NHS Foundation Trust/Institute of Cancer Research.

Keywords: head and neck | parameningeal | pediatric | prognostic risk factors | rhabdomyosarcoma

ABSTRACT

Background: Parameningeal (PM) site is an unfavorable characteristic in rhabdomyosarcoma (RMS). We described the treatment and outcome for patients with PM RMS and investigated the prognostic value of risk factors. We scored PM site by originating site and by highest risk extension.

Methods: Patients with PM RMS were treated within the European pediatric Soft tissue sarcoma Study Group (EpSSG) RMS 2005 study with risk-adapted, multi-modal treatment.

Reineke A. Schoot and Pieter Taselaar are contributed equally to this work.

Results: Three-hundred-eighty-one patients with PM RMS were included. Radiotherapy was administered in 359 patients (77 with surgery). After a median follow-up of 75 months, 5-year event-free survival was 60% (95% confidence interval (CI) 55%–65%), 5-year overall survival was 65% (95% CI 60%–70%).
Conclusions: The outcome for patients with PM RMS has not improved in comparison to previous historical studies, despite the more rigorous application of radiotherapy (94% of patients). Signs of meningeal involvement, PM site, and age at diagnosis remained prognostic risk factors.
Trial Registration: EudraCT number 2005-000217-35

1 | Introduction

The parameningeal (PM) localization is a known adverse prognostic factor in rhabdomyosarcoma (RMS) management [1]. The PM sites are difficult to reach by surgery, and due to its proximity to the meninges, tumor cells may more easily spread to the central nervous system (CNS). The PM localization consists of several sites, such as the pterygopalatine fossa and paranasal sinuses. This classification in PM sites has been used in the past decades by the larger collaborative groups, the North American Children's Oncology Group (COG), the European pediatric Soft tissue sarcoma Study Group (EpSSG), and the Cooperative Weichteilsarkom Study Group (CWS). In 2014, COG and EpSSG published a pooled analysis on PM RMS, described treatment and outcome [1], and defined several adverse prognostic risk factors, PM site being one of them. Their analysis revealed that within the PM category, patients with a primary tumor in the infratemporal/pterygopalatine fossa or the paranasal sinus had the poorest outcome (unfavorable sites). The other adverse prognostic risk factors were age (< 3 or > 10 years), signs of meningeal involvement (MI), and tumor size. The 10-year overall survival (OS) for patients with a PM RMS was 66%, but patients with three to four adverse prognostic risk factors had a 10-year OS of 51% compared to 81% for patients with zero or one risk factor.

Thus far, PM site and the presence of MI have not been incorporated into treatment stratifications. Furthermore, the allocation of the PM sites is a highly academic endeavor; (1) it may be difficult to decide upon the originating primary site, especially when tumors extend into different anatomical localizations, and (2) in most centers, the PM site will be collected from radiology reports by data managers, who have had no specific training on the complicated anatomy of the head and neck area.

In this manuscript, we describe the treatment and outcome for patients with PM RMS, treated within the EpSSG RMS 2005 study. Secondary aims of this study are to investigate the validity of the risk factors defined in the pooled analysis by Merks et al. with a specific focus on the prognostic value of PM sites, and to investigate whether PM tumor site should be defined by the originating site or the site with the highest risk in which the tumor is extending.

2 | Materials and Methods

The EpSSG RMS 2005 study was a prospective clinical trial that was conducted in 108 hospitals in 14 countries. Ethical approval and signed informed consent from each patient/legal representative were obtained prospectively. Patients with a newly diagnosed RMS, < 25 years old, without metastatic disease were eligible for this study. Details of the RMS 2005 study were described previously [2–4]. The primary tumor and locoregional lymph nodes were assessed using magnetic resonance imaging (MRI) or computed tomography (CT). In case of suspicious nodes, biopsy or another form of nodal sampling was recommended. PM localization is considered an unfavorable site, and consequently, the majority of patients were allocated to subgroup D (standard risk), E, F, G (high risk), or H (very high risk) (Data S1). Usually radical resection is not feasible upfront in PM RMS; but if IRS I, a patient could be allocated to subgroup A or B (Data S1). Patients with positive cerebrospinal fluid were considered metastatic and treated in the MTS 2008 study [5]. After three courses of chemotherapy, response was evaluated and categorized by volume reduction [6], and local treatment (radiotherapy with/without surgery) was planned. Surgery was considered by multidisciplinary teams in patients with residual tumor and in whom a resection was considered feasible without causing mutilation. Debulking surgery was discouraged. Radiotherapy (with or without surgery) was recommended for all patients with a PM RMS, including those patients who achieved complete remission and patients > 1 year and ≤ 3 years. For patients ≤ 1 year, individual decisions were made. Initiation of radiotherapy was recommended concomitant with the fifth chemotherapy course (week 13). For the purpose of this study, early radiotherapy was considered < week 10 and late > week 21. Radiotherapy dose was prescribed according to tumor histology, response to chemotherapy, and IRS group and varied between 36 and 50.4 Gy (with a potential boost of 5.4 Gy). In patients with skull base erosion, the radiation fields covered the initial skull base erosion. For patients with intracranial extension, the residual intracranial component that was present at restaging, before the onset of radiation, was included in the radiation field with an additional safety margin of 2 cm.

2.1 | PM Site Analysis

At the outset of the RMS 2005 study, PM sites were defined as follows: (i) middle ear, (ii) nasal cavity (NC) or paranasal sinuses, (iii) nasopharynx, (iv) infratemporal/pterygopalatine fossa or parapharyngeal area, (v) orbital tumors with PM extension [i.e., with bone erosion of the orbital roof, intracranial extension (ICE), cranial nerve palsy (CNP), or with extension to a PM space], and "other PM" (Data S1). In 2014, the results of the pooled analyses showed that patients with a PM primary in the infratemporal or pterygopalatine fossa or in the paranasal sinus had a poorer prognosis [1]. Within the RMS 2005 study, however, these PM sites were not registered separately but still registered together with more favorable PM

sites (ii; including NC, iv; including parapharyngeal area). So for purpose of the current study, we re-evaluated the radiology reports (obtained at diagnosis) of patients with a primary tumor located in (ii) the NC or paranasal sinuses and (iv) the infratemporal/pterygopalatine fossa or parapharyngeal area. The other risk factors described by Merks et al. [1] were unfavorable age, MI (ICE, cranial base bony erosion (CBBE), CNP), and large tumor size (> 5 cm). First, we re-classified PM site based upon suspected originating site. In a second assessment, all sites of extension were described and were then categorized by the site with the highest risk localization based on the pooled analysis results [1]. If it was not possible to disentangle where the tumor originated from, or if sites had comparable risk, site was classified as "combined sites." Radiology reports were obtained from the EpSSG database and scored independently by two investigators (PT, RS). Reports were translated in an online translation machine (deepl.com). Any discordances and a selection of difficult cases were discussed in a larger multidisciplinary team consisting of a pediatric sarcoma radiologist (StH) and two head and neck oncologists (LS, MH). Any sites that were incorrectly allocated in the original dataset were marked.

2.2 | Statistical Analyses

Survival probabilities were estimated using the Kaplan–Meier method and the log-rank test. Event-free survival (EFS) was calculated as the time between diagnosis and disease progression, recurrence, or death due to any cause. OS was calculated as the time between diagnosis and death due to any cause. After reclassification, we investigated the effect of localization of the originating site and the highest risk localization on EFS and OS by performing univariable and multivariable analyses. The multivariable analysis was performed using Cox's proportional hazards model, entering variables with $p < 0.25$ in the univariable analysis, such as patient age, MI, tumor size and invasiveness, and applying a stepwise selection. All statistical analyses were performed using the SAS statistical package.

3 | Results

3.1 | Patient and Treatment Characteristics

Among a total of 1733 patients with localized RMS prospectively enrolled in the EpSSG RMS 2005 study, 410 patients had a PM primary or an orbital/HNnPM primary with PM extension. We excluded 25 patients for whom no radiology reports were available. Four others were wrongly classified as PM and had a HNnPM primary instead, without any PM extension, and were excluded from further analysis. Patient and treatment characteristics of 381 patients included in this study are shown in Table 1. Forty-five patients with an HNnPM or orbital primary were considered PM based on the extension of their tumor. Median age was 5.9 years (interquartile range (IQR) 3.5–9.4 years), the majority of patients had favorable histology ($n = 290$, 76%, including 9 patients with spindle cell histology), and fusion status was negative in 65% of patients (unknown in 23%). Radiological evidence of MI was present

TABLE 1 | Patient and treatment characteristics.

	***N* = 381**	**%**
Age at diagnosis		
< 3 years	70	18
3–10 years	229	60
> 10 years	82	22
Gender		
Female	166	44
Male	215	56
Definitive histology		
Alveolar RMS	86	24
Embryonal RMS	281	73
RMS NOS	5	1
Spindle cells/leiomyomatous RMS	9	2
Fusion status		
Negative	248	65
Positive	45	12
Missing	88	23
Originating primary site		
ITF/PPF	64	17
Middle ear	48	12
NC	17	5
NC + PNS	12	3
Nasopharynx	68	18
HN/orbit with PM extension	45	12
PNS	42	11
PPS	19	5
Combined sites	15	4
Other PM	51	13
Evidence of meningeal involvement		
Cranial base bony erosion		
Yes	227	60
No	146	38
Not evaluable	8	2
Cranial nerve palsy		
Yes	130	34
No	243	64
Not evaluable	8	2
Intracranial tumor		
Yes	122	32

(Continues)

TABLE 1 | (Continued)

	N = 381	%
No	250	66
Not evaluable	9	2
Meningeal involvement		
Yes	257	68
No	115	30
Not evaluable	9	2
Cerebrospinal Fluid		
Negative	308	81
Not done	73	19
T-invasiveness		
T1	65	17
T2	315	83
Tx	1	0
Tumor size		
≤ 5 cm	152	40
> 5 cm	224	59
Size not available	5	1
Loco-reg N		
N0	291	76
N1	87	23
Nx	3	1
IRS Group		
IRS I	1	0
IRS II	12	3
IRS III	368	97
Treatment group		
Standard risk	91	24
High risk	257	67
Very high risk	33	9

Abbreviations: HN, head and neck; IRS, intergroup rhabdomyosarcoma studies; ITF, infratemporal fossa; N, lymph node; N, number; NC, nasal cavity; NOS, not otherwise specified; PM, parameningeal; PNS, paranasal sinus; PPF, pterygopalatine fossa; PPS, parapharyngeal space; RMS, rhabdomyosarcoma.

in 257 patients (67%). Several patients had multiple signs of MI; being CBBE (*N* = 227, 60%), CNP (*N* = 130, 34%), or ICE (*N* = 122, 32%). Cerebrospinal fluid was negative in 308 patients (81%) and not performed in the remaining 73 patients (19%). About 60% (*n* = 224) of patients had a primary tumor > 5 cm, and nodal disease was present in 23% (*n* = 87) of patients. Most patients were treated in the HR group (*N* = 257, 67%). In addition to the IVA backbone, 133 patients (35%) received doxorubicin. Response assessment after 3–4 cycles of chemotherapy was available in 322 out of 368 patients with IRS III disease: 22 patients (7%) had a complete remission, 198 (61%) a partial response, 69 (21%) a minor partial response, 28 (9%) stable disease, and 5 (2%) progressive disease. After completion of (neo)adjuvant chemotherapy, 118 patients (31%) received maintenance treatment; 23/118 patients of them were in the very high-risk group. Local treatment involved radiotherapy in the majority of patients (*n* = 359, 94%); details of radiotherapy were missing in two patients. A majority of patients received photon radiotherapy (*n* = 229, 64%), one-third was treated with proton radiotherapy (*n* = 103, 29%), and 11 patients (3%) received electrons, nine Cobalt 60 (3%), three brachytherapy (0.8%), and two (0.6%) mixed electrons with photons. Radiotherapy was administered early (before week 10) in 12 patients, as scheduled per protocol in 296 patients (between week 10 and week 21), and late (after week 21) in 49 patients. Median radiotherapy dose to the primary tumor was 50.4 Gy (range 50.4–54.0). In 73/357 patients (20%), radiotherapy was administered to both the primary tumor and the lymph nodes. Median dose to lymph nodes was 41.5 Gy (range 14.4–59.4). Among IRS III patients, local treatment details were available in 366/368. Local treatment consisted of radiotherapy only in 267 patients (73%), a combination of surgery and radiotherapy in 77 patients (21%), only surgery in three patients (0.8%), or no local treatment in 19 patients (5%). At the end of treatment, 182 patients (59%) achieved complete remission, and 125 (41%) had (microscopic or macroscopic) residuals.

3.2 | Reclassification

Imaging reports were reviewed for 191 patients with a primary tumor located in the (ii) the NC or paranasal sinuses (PNSs) (*n* = 85), and (iv) the infratemporal (ITF)/pterygopalatine fossa (PPF) or parapharyngeal area (*n* = 106). After a review of the imaging reports, the originating tumor site was considered different from the site reported in the database in 42/191 (22%) patients (Table 2a). This means that the originating site, originally grouped as "ITF/PPF or PPS" was reclassified as another PM site, not being ITF/PPF or PPS, and similar for "NC or PNS." In the next step, if all sites of extension were considered and sites were reclassified according to the highest risk site, 11/191 (6%) patients were classified to another site (Table 2b). As these are all PM sites, there were no consequences for the allocated risk groups and consequent treatment in RMS 2005.

3.3 | Outcomes

Median follow-up for live patients (*n* = 243) was 75 months (range 8.2–162.1). Out of 381 patients, 153 (40%) developed an event, and 140 (37%) died: 39 out of 153 patients developed progressive disease at the primary site (25%) (median time from diagnosis 7.9 months, range 1.8–21.8, including six patients with both progression at primary site and metastatic relapse), 69 (45%) had a loco-regional relapse, 32 (21%) had a metastatic relapse, 7 (5%) a combined loco-regional and metastatic relapse, 4 (3%) developed a second tumor, and 2 (1%) patients died due to nondisease related causes. From the 39 patients who developed progressive disease, 13 tumors progressed during (neo)adjuvant chemotherapy, 19 progressed within 5 months after completion of adjuvant chemotherapy,

TABLE 2A | Reclassification of primary tumor sites by originating site.

Initial allocated site	Reclassified originating site								
	ITF/PPF	Middle ear	NC	NC + PNS	Nasopharynx	HN/ orbit + PM	PNS	PPS	Combined sites
ITF/PPF + PPS ($n = 106$)	61	4	1	—	2	8	—	19	11
NC + PNS ($n = 85$)	3	—	16	12	5	4	41	—	4

Abbreviations: HN, head and neck; ITF, infratemporal fossa; NC, nasal cavity; PM, parameningeal; PNS, paranasal sinus; PPF, pterygopalatine fossa; PPS, parapharyngeal space.

2 progressed during maintenance treatment, and 5 within 5 months after completion of maintenance treatment. From the 13 patients with tumor progression during (neo)adjuvant chemotherapy, four did not respond at all and had PD at first evaluation, four had initial SD, and five tumors initially responded before progressing. The events occurred within the radiotherapy field ($n = 68$), in the radiotherapy field margin ($n = 7$), outside the radiotherapy field ($n = 44$), patients not receiving radiotherapy ($n = 18$), or in relation to radiotherapy fields was unknown ($n = 16$). In total, 45 patients developed at least one metastatic lesion. In 29 patients, metastases were located in the CNS (spinal cord, brain, cerebrum, cerebellum, meningeal dissemination), and two additional patients had positive cerebrospinal fluid at relapse.

For the complete cohort of 381 patients with PM RMS, the 5-year EFS was 60% (95% confidence interval (CI) 55%–65%), and the 5-year OS was 65% (95% CI 60%–70%) (Figure 1). Outcomes by originating PM site and by highest risk site are shown in Table 3. There was no significant difference in OS, where there was a significant difference in EFS when categorizing PM site by highest risk extension in this univariable analysis ($p = 0.0176$). The 5-year EFS (also univariable analysis) was better for patients without evidence of MI (72%, 95% CI 62%–79%) compared to patients with CNP and/or CBBE (60%, 95% CI 51%–67%), or patients with ICE and/or CNP and/or CBBE (51%, 95% CI 41–59; $p = 0.0007$). Similarly, the 5-year OS was 80% (95% CI 71%–87%) for patients without signs of MI, 62% (95% CI 53%–70%) for patients with CNP and/or CBBE, and 55% (95% CI 46%–63%) for patients with ICE and/or CNP and/or CBBE, respectively ($p = 0.0002$). In multivariable analyses, PM site by highest risk extension, age at diagnosis, signs of MI, and tumor invasiveness (T stage) were significantly associated with EFS (Table S1). Age at diagnosis and signs of MI were significantly associated with OS in multivariable analysis, while histology, PM site by highest risk extension, T stage, tumor size were not (Table S2).

4 | Discussion

Despite the application of radiotherapy in a higher percentage of patients, the outcome for the 381 patients in this cohort is similar to previous historical studies [1]. Risk factors such as MI and age at diagnosis and PM site (by highest risk extension) remained of prognostic value, and in addition, tumor invasiveness was associated with EFS. Classification of PM sites appeared to be an academic endeavor, with misclassifications in 22% of evaluated imaging reports. No sites could be identified as individual poor risk localization, potentially because of the large number of subgroups and inherent small numbers per subgroup that were identified.

No survival improvement was achieved in patients with PM RMS compared to the historical pooled analyses conducted by Merks et al. [1] (5-year OS 65% (95% CI 60%–70%) compared to 69.5% (95% CI 66.7%–72.2%) for the pooled analysis). Merks et al. showed, similar to the pooled analyses published in 1996 by Benk et al. that a more rigorous application of radiotherapy resulted in better outcome [1, 7]. The percentage of patients (94%) that received radiotherapy in the current study was similar to the percentage in the pooled cohort (92%) described by Merks et al. [1] In comparison to the European SIOP MMT cohort (SIOP-MMT89 and SIOP-MMT95) from this same pooled analyses, the percentage of patients receiving RT in the currently reported RMS 2005 study was slightly higher (94%), compared to 85% of patients from the SIOP MMT cohort. Despite this difference of 11% in radiotherapy administration, the 5-year OS rate in the historical SIOP-MMT cohort (63.3% (95% CI 58.3%–67.8%)) [1] was not much different from the more recently treated European series reported in this manuscript. There were no large differences in risk factors between the historical pooled cohort and the current manuscript with regard to tumor size/stage, age, or signs of MI, although comparisons between cohorts should be made cautiously because of methodological reasons. Moreover, one would expect that developments in imaging techniques, surgery and radiotherapy techniques, and improvement in supportive care measures might have translated into improved outcomes.

Several adjustments have been made to the treatment approach of PM RMS in the past decades. Firstly, as mentioned above, in Europe, radiotherapy is applied more rigorously in current practice. There has been much debate on the timing of radiotherapy in PM RMS. Where the North American protocols historically prescribed radiotherapy at the beginning of treatment, in the first 9 weeks (depending on protocol and risk group), the European groups prescribed radiotherapy in week 9 or later (RMS 2005 study, week 12). In 2007, Douglas, Arndt, and Hawkins [8] described a single center cohort of 26 patients with PM RMS that received delayed radiotherapy (week 12) and concluded that treatment with neo-adjuvant, intensive chemotherapy with delayed radiotherapy facilitated good local control and survival for patients with PM RMS. This finding was confirmed in 2013 by Spalding et al. [9], who compared patients with PM

TABLE 2B | Reclassification of primary tumor sites by highest risk site.

Initial allocated site	Reclassified by extending site/highest risk site									
	ITF/PPF	Middle ear	Middle ear or PPS	NC	Nasopharynx	Nasopharynx or NC	Nasopharynx or PPS	PNS	PNS or ITF/PPF	PPS	PPS or NC
ITF/PPF + PPS ($n = 106$)	68	1	3	—	1	—	1	—	21	10	1
NC + PNS ($n = 85$)	5	—	—	11	1	4	—	32	32	—	—

Abbreviations: HN, head and neck; ITF, infratemporal fossa; NC, nasal cavity; PM, parameningeal; PNS, paranasal sinus; PPF, pterygopalatine fossa; PPS, parapharyngeal space.

RMS treated within two different COG protocols: IRS-IV (radiotherapy at week 0) and D9803 (radiotherapy at week 12 for patients without ICE). Therefore, no impact is expected from the timing of radiotherapy in patients with PM RMS, and current studies across the Atlantic suggest to apply RT around weeks 12–13 (ARST1431- and FaR-RMS study).

Secondly, more conformal radiotherapy techniques have been introduced for irradiation of patients with PM RMS, aiming to reduce the radiation of surrounding healthy tissue. Historically, patients with PM RMS with signs of MI received whole brain irradiation in the early North American COG trials, but whole brain irradiation was removed from the COG protocols because it failed to improve outcome [10]. The current manuscript describes a cohort of patients treated over a time span of 10 years (2006–2016) and demonstrates the increasing application of proton therapy: one-third of patients received protons compared to two-third of patients that received photons. In addition, the treatment with photons has become more conformal over the past decades, with the introduction of better imaging techniques and methods such as intensity-modulated radiation therapy (IMRT). Several centers have described their experience with proton beam therapy in patients with PM RMS [11–13]. Although the local control rates were satisfactory in these reports, larger multicenter reports or randomized studies are lacking, investigating the effect of more precise radiotherapy techniques and margin reduction. In this study, only 7/155 (5%) of the events occurred in the radiotherapy field margin, but 68/155 (44%) within the radiotherapy field. The relatively high rate of in-field relapses raises the question of whether the administered dose was sufficient rather than a discussion with regard to the margins. Michalski et al. [14] analyzed the influence of radiation therapy parameters on outcome in children with localized PM RMS that received irradiation and concluded that doses of at least 47.5 Gy seemed to result in better local control. This seems in line with the median dose administered in the cohort described in this manuscript, with a median dose of 50.4 Gy on the primary tumor. In the currently open Frontline and Relapsed RhabdoMyoSarcoma (FaR-RMS) study, there will be two randomized questions further investigating the role of dose escalation in RMS treatment.

After a review of the radiology reports, the subgroup assignment for the originating site of the PM RMS tumors was reclassified for almost a quarter of the patients. The percentage of misclassifications was much lower (6%) if the highest risk site of tumor extension was considered. This illustrates, first of all, that disentangling where a tumor originates from is a rather academic and hypothetical exercise, if at all possible on imaging, where we have often delegated this classification to data managers. Secondly, the purpose of site allocation should be kept in mind; site is used for risk stratification. Which aspect determines patients are at increased risk of (local) treatment failure? One could hypothesize that certain sites are difficult to reach for local treatment or have a close relation to the meninges and that the presence of the tumor in these sites determines the risk of failure rather than the fact of whether the tumor originates or extends into this specific area. In two large historical studies, PM site was an independent risk factor [1, 10], but these studies were based on CRF reports, most often completed by data managers without a background in head and neck anatomy. In this study, the imaging reports were evaluated

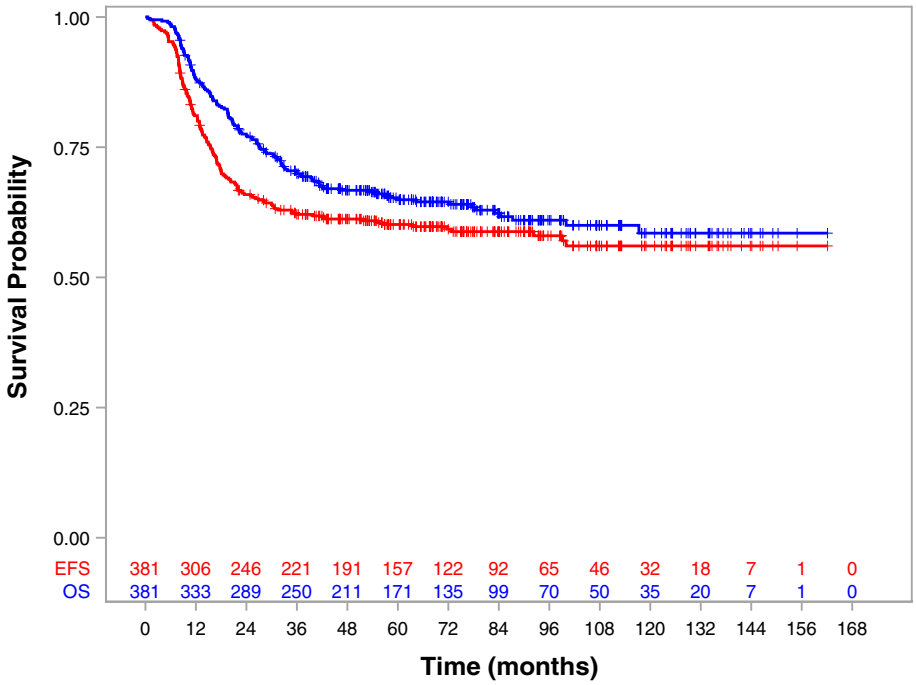

FIGURE 1 | Outcome for patients with parameningeal rhabdomyosarcoma. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 | Overall survival by a. originating and b. highest risk (including extension) subsite.

	N	Deaths	5-years OS (95% CI)	*p*	Events	5-years EFS (95% CI)	*p*
a. OS originating site					**c. EFS originating site**		
Nasopharynx	68	15	80.2 (68.3–88.0)	0.2665	15	79.4 (67.4–87.2)	0.1023
NC + PNS	12	3	73.3 (37.9–90.6)		5	65.6 (32.0–85.6)	
Middle ear	48	17	63.6 (48.0–75.6)		19	62.1 (46.8–74.2)	
NC	17	5	66.7 (37.5–84.6)		6	60.0 (31.8–79.7)	
PNS	42	17	59.1 (42.7–72.3)		17	59.5 (43.2–72.6)	
HN/orbit with PM ext	45	18	58.4 (42.2–71.5)		19	57.2 (41.4–70.2)	
ITF/PPF	64	26	60.5 (47.4–71.4)		31	54.4 (41.4–65.7)	
Combined sites	15	8	53.3 (26.3–74.4)		8	53.3 (26.3–74.4)	
Other PM	51	21	63.0 (47.8–74.9)		24	51.9 (37.2–64.7)	
PPS	19	8	73.7 (47.9–88.1)		11	38.8 (16.9–60.3)	
	N	**Deaths**	**5-years OS (95% CI)**	***p***	**Events**	**5-years EFS (95% CI)**	***p***
b. OS highest risk, including extension					**d. EFS highest risk, including extension**		
PNS	32	7	78.1 (59.5–88.9)	0.1015	8	78.1 (59.5–88.9)	0.0176
Nasopharynx	63	15	78.5 (65.8–87.0)		15	77.8 (65.3–86.1)	
Middle ear	45	16	63.5 (47.4–75.9)		18	61.9 (46.0–74.3)	
HN/orbit with PM ext	33	13	59.3 (40.4–74.1)		13	60.0 (41.2–74.5)	
PPS	10	4	70.0 (32.9–89.2)		4	58.3 (23.0–82.1)	
Combined sites	63	28	59.4 (46.0–70.5)		31	53.8 (40.8–65.2)	
ITF/PPF	73	28	62.5 (50.2–72.6)		35	52.7 (40.4–63.5)	
Other PM	51	21	63.0 (47.8–74.9)		24	51.9 (37.2–64.7)	
NC	11	6	—		7	—	

Abbreviations: HN, head and neck; ITF, infratemporal fossa; NC, nasal cavity; PM, parameningeal; PNS, paranasal sinus; PPF, pterygopalatine fossa; PPS, parapharyngeal space.

in detail by trained medical doctors. Originating PM site did not appear to be of prognostic value, but the results are very likely affected by the relatively small number of patients and the large number of subgroups. The detailed evaluation did however reveal that it is often impossible to disentangle the originating site of the primary tumor, and when taking into account the highest risk extension, there was an association with EFS both in univariable and multivariable analysis. Signs of MI, specially ICE, have shown to be associated with poorer EFS and OS, in line with previous reports [1, 10]. Concerns have been raised with regard to the number of CNS relapses in patients with ICE [11, 13], especially because very few patients with a CNS relapse can be salvaged [15]. In this study, 20% of all events were in the CNS, but signs of MI were highly prevalent and present in 67% of all patients with PM RMS and therefore may not help to discriminate patients at increased risk for CNS relapse. Interestingly, this percentage of MI was similar to the study by Raney et al. [10], who reported MI in 73% of patients treated between 1978 and 1997, despite the introduction and development of new imaging techniques in the past decades. The PM sites were defined decades ago and have been used in both European and North American RMS protocols. We advocate for a critical reconsideration of these PM sites: the allocation is prone to misclassification and the sites are not used for risk group stratification refinement in the currently used treatment protocols.

An important limitation of this study is the lack of central radiology review of the imaging. We evaluated imaging reports provided by different radiologists with different levels of expertise in head and neck RMS imaging, only for a selection of PM sites. A second limitation is the lack of prospective radiotherapy quality assurance and the evaluation of the site of relapse in relation to the administered radiotherapy fields. Lastly, the size of the cohort was not powered to analyze the prognostic relevance of PM sites. Nevertheless, the systematic assessment of imaging reports provides a valuable assessment of the challenges involved with the allocation of PM sites.

The PM location remains unfavorable for risk of local failure, and no improvement in outcome has been achieved in the past decade. This group of patients is therefore eligible for the randomized question investigating the value of radiotherapy dose escalation in the currently running FaR-RMS study. Additionally, real-time radiotherapy quality assurance has been implemented in the FaR-RMS study, aiming to improve radiotherapy planning and subsequent reduction of local failure [16]. Lastly, all patients with PM RMS will receive at least six months of maintenance chemotherapy, with a substantial number of high-risk patients that will be eligible for the randomization comparing standard (six months) versus prolonged (one year) maintenance therapy. Further studies are needed to understand which patients are more prone to local treatment failure, and CNS relapses to allow for better outcomes for this group of high-risk patients.

Author Contributions

Reineke A. Schoot: conceptualization (lead), data curation (equal), formal analysis (supporting), methodology (lead), writing – original draft (lead), writing – review and editing (lead). **Pieter Taselaar:** conceptualization (equal), formal analysis (supporting), methodology (supporting), writing – original draft (equal), writing – review and editing (equal). **Giovanni Scarzello:** conceptualization (supporting), formal analysis (supporting), methodology (supporting), writing – original draft (supporting), writing – review and editing (supporting). **Frederic Kolb:** writing – original draft (supporting), writing – review and editing (supporting). **Beatrice Coppadoro:** conceptualization (equal), data curation (lead), formal analysis (lead), methodology (equal), writing – original draft (equal), writing – review and editing (equal). **Simone ter Horst:** conceptualization (supporting), formal analysis (equal), methodology-Equal, writing – original draft (supporting), writing – review and editing (equal). **Henry Mandeville:** writing – original draft (supporting), writing – review and editing (supporting). **Andrea Ferrari:** writing – original draft-(supporting), writing – review and editing (supporting). **Raquel Hladun:** writing – original draft-(supporting), writing – review and editing (supporting). **Sylvie Helfre:** writing – original draft (supporting), writing – review and editing (supporting). **Sima Ferman:** writing – original draft (supporting), writing – review and editing (supporting). **Anna Kelsey:** writing – original draft (supporting), writing – review and editing (supporting). **Marinka L. F. Hol:** formal analysis (supporting), writing – original draft (supporting), writing – review and editing (supporting). **Christine Devalck:** writing – original draft (supporting), writing – review and editing (supporting). **Myriam Ben-Arush:** writing – original draft (supporting), writing – review and editing (supporting). **Daniel Orbach:** writing – original draft (supporting), writing – review and editing (supporting). **Julia Chisholm:** writing – original draft (supporting), writing – review and editing (supporting). **Meriel Jenney:** writing – original draft-(supporting), writing – review and editing (supporting). **Veronique Minard-Colin:** conceptualization (supporting), formal analysis (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal). **Gianni Bisogno:** conceptualization (equal), data curation (supporting), formal analysis (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal). **Johannes H. M. Merks:** conceptualization (lead), data curation (equal), formal analysis (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal).

Acknowledgments

Data management and statistical processing have been funded by Alice's Arc, children's cancer charity focusing on rhabdomyosarcoma, United Kingdom (alice-sarc.org). JCC is supported by The Giant Pledge through the Royal Marsden Cancer Charity. This work represents independent research supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London and the NIHR Birmingham Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Ethics Statement

Ethical approval from each patient/legal representative was obtained prospectively.

Consent

A signed informed consent from each patient/legal representative was obtained prospectively.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data from the RMS 2005 study have been collected in an international platform called INSTRuCT (Pediatric Cancer Data Commons consortium, https://commons.cri.uchicago.edu/, https://commons.cri.uchicago.edu/instruct/). Data requests need review and approval by INSTRuCT executive committee.

References

1. J. H. M. Merks, G. L. De Salvo, C. Bergeron, et al., "Parameningeal Rhabdomyosarcoma in Pediatric Age: Results of a Pooled Analysis From North American and European Cooperative Groups," *Annals of Oncology* 25, no. 1 (2014): 231–236.

2. G. Bisogno, M. Jenney, C. Bergeron, et al., "Addition of Dose-Intensified Doxorubicin to Standard Chemotherapy for Rhabdomyosarcoma (EpSSG RMS 2005): A Multicentre, Open-Label, Randomised Controlled, Phase 3 Trial," *Lancet Oncology* 19 (2018): 1061–1071.

3. G. Bisogno, G. L. De Salvo, C. Bergeron, et al., "Vinorelbine and Continuous Low-Dose Cyclophosphamide as Maintenance Chemotherapy in Patients With High-Risk Rhabdomyosarcoma (RMS 2005): A Multicentre, Open-Label, Randomised, Phase 3 Trial," *Lancet Oncology* 20 (2019): 1566–1575.

4. G. Bisogno, V. Minard-Colin, I. Zanetti, et al., "Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RM2005 Study," *Journal of Clinical Oncology* 41 (2023): 2342–2349, https://doi.org/10.1200/JCO.22.02093.

5. R. A. Schoot, J. C. Chisholm, M. Casanova, et al., "Metastatic Rhabdomyosarcoma: Results of the European Paediatric Soft Tissue Sarcoma Study Group MTS 2008 Study and Pooled Analysis With the Concurrent BERNIE Study," *Journal of Clinical Oncology* 40, no. 32 (2022): 3730–3740.

6. R. Van Ewijk, R. A. Schoot, M. Sparber-Sauer, et al., "European Guideline for Imaging in Paediatric and Adolescent Rhabdomyosarcoma—Joint Statement by the European Paediatric Soft Tissue Sarcoma Study Group, the Cooperative Weichteilsarkom Studiengruppe and the Oncology Task Force of the Eruopean Society of Paediatric Radiology," *Pediatric Radiology* 51, no. 10 (2021): 1940–1951.

7. V. Benk, C. Rodary, S. S. Donaldson, et al., "Parameningeal Rhabdomyosarcoma: Results of an International Workshop," *International Journal of Radiation Oncology, Biology, Physics* 36, no. 3 (1996): 533–540.

8. J. G. Douglas, C. A. S. Arndt, and D. S. Hawkins, "Delayed Radiotherapy Following Dose Intensive Chemotherapy for Parameningeal Rhabdomyosarcoma (PM-RMS) of Childhood," *European Journal of Cancer* 43 (2007): 1045–1050.

9. A. C. Spalding, D. S. Hawkins, S. S. Donaldson, et al., "The Effect of Radiation Timing on Patients With High Risk Features of Parameningeal Rhabdomyosarcoma: An Analysis of IRS-IV and D9803," *International Journal of Radiation Oncology, Biology, Physics* 87, no. 3 (2013): 512–516.

10. R. B. Raney, J. Meza, J. R. Anderson, et al., "Treatment of Children and Adolescents With Localized Parameningeal Sarcoma: Experience of the Intergroup Rhabdomyosarcoma Study Group Protocols IRS-II Through-IV, 1978-1997," *Medical and Pediatric Oncology* 38 (2002): 22–32.

11. J. A. Bradley, D. J. Indelicato, H. Uezono, et al., "Patterns of Failure in Parameningeal Alveolar Rhabdomyosarcoma," *International Journal of Radiation Oncology, Biology, Physics* 107, no. 2 (2020): 325–333.

12. M. M. Ladra, H. C. Mandeville, A. Niemierko, et al., "Local Failure in Parameningeal Rhabdomyosarcoma Correlates With Poor Response to Induction Chemotherapy," *International Journal of Radiation Oncology, Biology, Physics* 92, no. 2 (2015): 358–367.

13. E. B. Ludmir, D. R. Grosshans, M. F. McAleer, et al., "Patterns of Failure Following Proton Beam Therapy for Head and Neck Rhabdomyosarcoma," *Radiotherapy and Oncology* 134 (2019): 143–150.

14. J. M. Michalski, J. Meza, J. C. Breneman, et al., "Influence of Radiation Therapy Parameters on Outcome in Children Treated With Radiation Therapy for Localized Parameningeal Rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group Trials II Through IV," *International Journal of Radiation Oncology, Biology, Physics* 59, no. 4 (2004): 1027–1038.

15. B. De, M. D. Kinnaman, L. H. Wexler, K. Kramer, and S. L. Wolden, "Central Nervous System Relapse of Rhabdomyosarcoma," *Pediatric Blood & Cancer* 65 (2018): e26710.

16. S. M. Kelly, R. Effeney, M. N. Gaze, et al., "QUARTET: A SIOP Europe Project for Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents With Cancer," *European Journal of Cancer* 172 (2022): 209–220.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.