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REVIEW

A systematic review of combined surgery and brachytherapy approaches for children and young people with relapsed and refractory rhabdomyosarcoma (Local-REFoRMS)

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Abstract

Approximately one third of children with rhabdomyosarcoma relapse or have refractory disease. Treatment approaches include a combination of systemic therapies and local therapies, directed at tumour site(s). This review was conducted to evaluate the effectiveness and safety of the combination of surgery and brachytherapy as local therapy for treating children and young people with relapsed/refractory rhabdomyosarcoma. This review identified studies based on a previous systematic review looking at the treatments for children and young people under 18 years old with relapsed/refractory rhabdomyosarcoma. Studies conducted after 2000 were included. Survival outcomes, relapse rates, adverse events and functional outcomes were extracted. From 16,965 records identified in the baseline systematic review, 205 included the words 'AMORE' or 'brachytherapy', and were screened for eligibility in this substudy. Thirteen studies met the inclusion criteria for Local-REFoRMS, including over 55 relapsed and refractory rhabdomyosarcoma patients. Most studies were retrospective cohort studies conducted within Europe. Most patients had embryonal disease within the head and neck or bladder/prostate regions, and received local therapy for first relapse. Approximately one quarter of patients relapsed following surgery and brachytherapy, with local relapses occurring more than metastatic relapse. Adverse events and functional outcomes were infrequently reported, but related to the site of surgery and brachytherapy. Study quality was limited by inconsistent reporting and potential selection bias. Outcomes following surgery and brachytherapy for a selected group of relapsed and refractory rhabdomyosarcoma show reasonable benefits, but reporting was often unclear and based on small sample sizes.

KEYWORDS
brachytherapy, childhood cancer, refractory, relapse, rhabdomyosarcoma, surgery

Abbreviations: AE(s), adverse event(s); AMORE, ablative surgery, mould technique with afterloading brachytherapy and surgical reconstruction; LRR, local relapse rate; MRR, metastatic relapse rate; OS, overall survival; PFS, progression-free survival; R&R, relapsed and refractory; RMS, rhabdomyosarcoma.

1 | INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, accounting for approximately 50% of these[1] and 4.5% of all childhood cancers.[2] Despite advances in multimodal therapy, around one-third of children and young people with RMS experience relapsed and refractory (R&R) disease.[3] Patients with low-risk disease at first diagnosis (favourable histopathological type/location/localised disease/response to treatment) have a good prognosis (70%–90% overall survival [OS]).[4] R&R RMS is associated with poorer outcomes (12%–41% 4-year post-relapse survival, 5-year OS reported as low as 2%) and increased treatment-related morbidity.[5]

Initial treatment approaches to RMS involve surgery, chemotherapy, and in many cases radiotherapy.[6] Although prognosis is best for fully resectable disease, 50% of patients have gross residual disease after surgery.[7] In the setting of relapse or uncontrolled disease, further surgery and re-irradiation with external beam approaches is not always feasible due to fears of mutilation or excessive damage to healthy tissue. In these instances, curative treatment options are limited, and whilst extensive, mutilating procedures may be considered by some, a more conservative salvage treatment is often desired.

One such example is the AMORE protocol (ablative surgery, mould technique with afterloading brachytherapy and surgical reconstruction), which has been shown to have comparable efficacy and better adverse effects compared to conventional external beam radiation therapy (EBRT) as a first-line treatment,[8,9] and has been studied as a potential salvage strategy in the treatment of R&R RMS. Similar strategies that involve surgery and brachytherapy have also been studied for this role.

The primary objective of this systematic review was to critically analyse the existing literature pertaining to the efficacy and safety of combining surgery and brachytherapy in the management of R&R paediatric RMS. Furthermore, we aimed to examine the impact of various prognostic factors on treatment response, survival outcomes and long-term sequelae. By synthesising the available evidence, this systematic review will contribute to the existing body of knowledge and support clinicians in making informed decisions regarding local therapies for R&R RMS in children and young people.

This review was developed as an additional project based on the baseline REFoRMS systematic review that evaluated early-phase studies for children and young people with R&R RMS.[10] The REFoRMS parent group who were key advisors in the original study stressed the importance of establishing the effectiveness of local therapy in this context, but as local therapy is not typically evaluated using early-phase studies, these were not included in the previous review. We established that there were multiple studies of surgery/brachytherapy combinations within the dataset, with minimal exploration of other local therapy options. Therefore, this substudy was proposed to evaluate the specific use of surgery and brachytherapy combined for treating children and young people with R&R RMS.

BOX 1: Study inclusion criteria

Population: Patients with relapsed or refractory rhabdomyosarcoma aged 0–17 years. Studies including patients with other conditions/ages were eligible for inclusion, provided the data relating to the population of interest could be extracted separately or at least 50% met the eligibility criteria.

Intervention: Any treatment regimen combining surgical approaches with brachytherapy with the intention of disease control, whether palliative or curative.

Comparator: Any other intervention, placebo or standard of care. Studies without a comparator group were also eligible.

Outcome: Survival outcomes (e.g., OS), response rates (e.g., local relapse rates [LRR]), adverse events (AEs), quality-of-life outcomes, burden of therapy outcomes (e.g., inpatient stays, travel burden) and cost-effectiveness measures.

Study design: Any case series, cohort study or observational study. Any randomised control trials and early-phase trials. Retrospective and prospective studies were eligible. Published after 2000 in any language and no geographical limitations.

2 | METHODS

The systematic review is reported in accordance with PRISMA guidelines,[11] and was prospectively registered on PROSPERO (CRD42022367405).[12]

2.1 | Searches

The search was generated based on the original library of 16,965 records from the baseline REFoRMS review[10] (see baseline REFoRMS review report for full details of search), which was then specifically searched for the words 'AMORE' and 'brachytherapy'. Any records with either word were then treated as the Local-REFoRMS pool (205 records in total) to be screened.

At both title and abstract and full-text stages, all records were independently screened by two reviewers (Euan Ballantyne, Connor Evans, Lucy Shepherd, Jessica E. Morgan) using Rayyan.[13] Disagreements were resolved through team discussions.

2.2 | Eligibility criteria

The study inclusion criteria, including efficacy, safety and other outcomes of interest, are presented in Box 1. In summary, studies investigating the combination of surgery and brachytherapy in children and young people aged 0–17 years with R&R RMS, published since 2000,

were eligible. The main differences between the study eligibility criteria of Local-REFoRMS and that of the baseline REFoRMS review[10] are that the intervention had to assess the combination of surgery and brachytherapy for local control, and study design eligibility criteria were broader with the inclusion of case series including retrospective and centre experience studies. Further study eligibility criteria can be found in the protocol.[12]

2.3 | Data extraction and quality assessment

Data extraction and quality assessment were completed by one researcher (Euan Ballantyne) and checked by another (Connor Evans or Jessica E. Morgan). Disagreements were resolved through team discussions. Demographic data were extracted for all participants unless data were available for R&R RMS patients specifically; AEs data were extracted for all participants regardless of disease; clinical outcomes were extracted for R&R RMS patients only. The data extraction form is provided within Supporting Material. A modified version of the Downs and Black checklist[14] was used for quality assessment, as in the baseline REFoRMS review.[10] In addition to the modifications to the Downs and Black checklist made in the baseline REFoRMS review, Question 13 ('Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of patients receive?') of the tool was modified so that the treatment staff and facilities were deemed representative if it was likely to be available via a direct referral pathway. Authors of full-text publications were contacted via email to clarify whether studies were eligible for inclusion if the information presented was unclear (e.g., if the study included RMS patients but it was not clear if the patients had relapsed or refractory disease).

2.4 | Analysis

The data were narratively synthesised with tabular outputs. Included interventions were clinically heterogeneous, thus meta-analysis was precluded. As with the baseline review, findings are presented in order of importance to the parent advisory group.[10]

3 | RESULTS

3.1 | Study selection

From the 16,965 records identified in the baseline review, 205 references were identified as potentially relevant for the Local-REFoRMS pool. Following title and abstract screening, 70 records were identified for full-text screening, including 50 full-text papers, 19 conference abstracts and one clinical trial registry record. The clinical trial registry record was eventually excluded as the study was identified as withdrawn, and therefore no meaningful data were available for this review.[15] After full-text screening, 13 studies were included in the review (10 full texts[16–25] and three conference abstracts[26–28]). The authors of 11 studies were contacted for further information; none replied and consequently these studies were excluded. A full list of excluded studies following full-text screening can be found in Table S1. The flowsheet for included studies is presented in Figure 1.

3.2 | Quality assessment

All 13 studies[16–28] were single-arm studies assessed using a 17-item modified Downs and Black checklist[14] (Figure 2). All studies reported their aims and the intervention of interest clearly, as well as incorporating representative treatments based on the available referral pathways. Power calculations were not reported, but this is expected given the majority of studies were retrospective cohort studies, which included all patients fulfilling the eligibility criteria during the study period. In all studies, we were unable to determine how representative participants were of the population they were recruited from, particularly given the highly selective nature of the included procedures, and thus there may be a risk of selection bias within the dataset. In general, studies reported results clearly, but random variability was reported less frequently and not all studies clearly assessed the safety of surgery and brachytherapy. Further details for the quality of each individual study can be found in Table S2.

3.3 | Demographics

Across 13 studies, at least 55 patients with R&R RMS were included (see Supporting Information S3).[16–28] All studies reported a single cohort of patients, with no comparative group studies. Importantly, five patients reported across two studies[16,18] were also reported in a later study.[17] These patients have only been included in the review once. An additional patient within these studies may have also been reported twice, as the demographic details of these patients are very similar but not an exact match (differences in the demographic characteristics reported meant this was difficult to determine). We have therefore included both reports that highlighted this potential duplicate within our reporting. See Table S4 for duplicate patient reporting information.

Ten studies recruited RMS patients only (77%),[16–22,24,26,27] eight of which included both newly diagnosed and R&R RMS patients.[16,18,20–22,24,26,27] The majority of studies were conducted within Europe (n = 9; 69%),[16–22,27,28] predominantly in two centres in France[20–22] and the Netherlands.[16–18] Patients included in the studies were treated between 1971 and 2015.

The age of participants was reported in all 13 studies, either for the whole population (n = 7)[21–24,26–28] or for R&R RMS patients (n = 6).[16–20,25] Of those reporting age for R&R RMS patients, most (n = 5, 83%) reported a median age under 10 years.[16,17,19,20,25] Two studies included a minority of patients over the age of 18 years whose data could not be separated from that of the younger patients.[19,23]

Data on sex/gender were reported in 12 studies (92%), either for the whole population (n = 1),[28] or for RMS patients specifically (n = 11)[16–22,24–27] of which three included newly

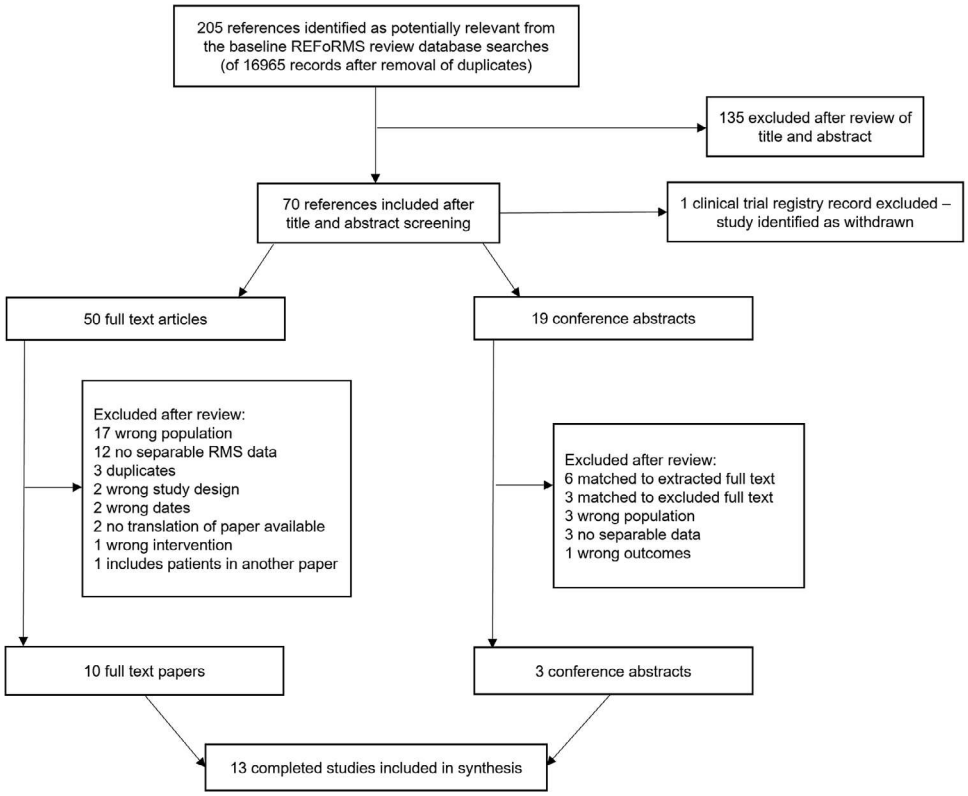

FIGURE 1 Flowsheet of included studies.

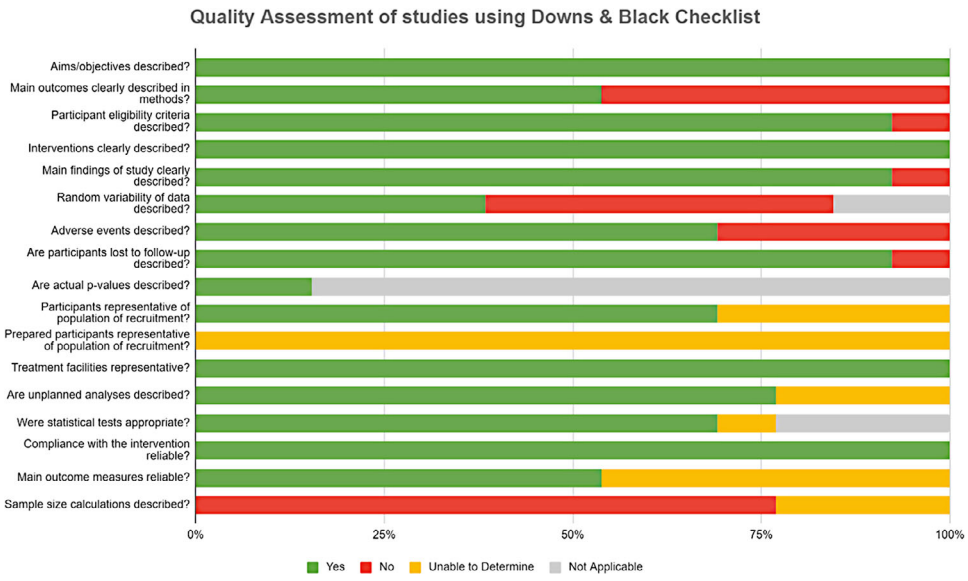

FIGURE 2 Quality assessment of included studies.

diagnosed patients.[21,24,27] Nine studies used sex as the descriptor,[16,17,20–22,24,26–28] while three studies used gender.[18,19,25] No study defined either term. Where both male and female participants with R&R RMS were reported, the ratio was 31:15 (67% male).

Across all studies, race and ethnicity were not reported. Fusion status was reported in one study, where 3% of the whole study population was positive for PAX3/7-FOX01 gene.[21]

Across five studies, histopathology was reported for R&R RMS patients ($n = 42$), with 37 and five patients with embryonal and alveolar RMS, respectively.[16–20] Site of primary tumour was reported in 11 (85%) studies for R&R RMS patients ($n = 52$).[16–22,25–28] Primary sites included orbit ($n = 22$),[17–19] head and neck ($n = 16$, nine parameningeal, seven non-parameningeal),[16–18] nasolabial fold ($n = 4$),[20] bladder/prostate ($n = 9$)[21,22,26–28] and pelvis ($n = 1$).[25]

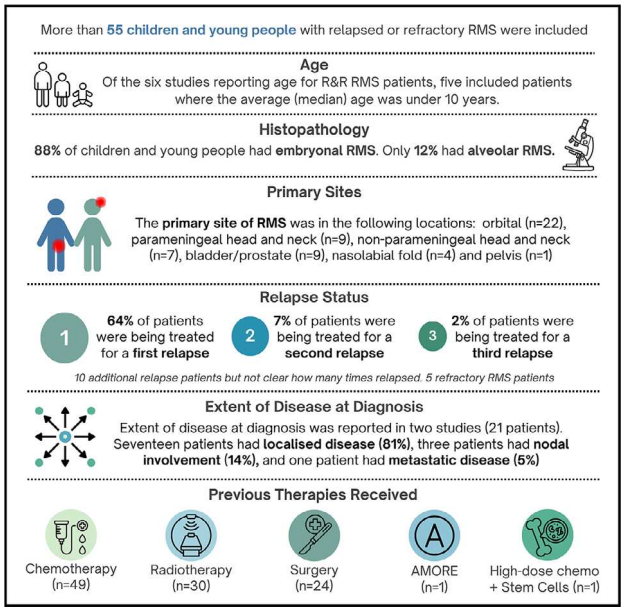

FIGURE 3 Summary infographic of population characteristics for eligible R&R (relapsed and refractory) RMS (rhabdomyosarcoma) patients.

Twelve studies reported patients' R&R status (n = 55),[16–22,24–28] whilst one study included R&R RMS patients, but the exact number was unclear.[23] Thirty-five patients were treated for first relapse,[16–20,25,26] four for second relapse,[16,17] one for third relapse,[17] 10 for undifferentiated relapse (number of relapses not specified)[20,21,24,27,28] and five for refractory RMS.[19] Seven studies reported the number of prior lines of therapy for the R&R RMS patients, with the median reported as one in all cases (and maximum three).[16–20,25,26]

Previous treatments were reported in 11 studies. Ten were specific for R&R RMS patients,[16–22,24–26] and one study reported prior treatments for the whole population but the number of R&R RMS was unclear.[23] These reported that 49 R&R RMS patients (out of 53) had been given chemotherapy previously,[16–21,24–26] one had been given high-dose chemotherapy with stem-cell rescue,[17] 30 had received radiotherapy,[16,17,19,20,24–26] 24 had surgery[16,17,19,20,22,25,26] and one had received AMORE previously.[17]

Extent of disease at diagnosis was reported for R&R RMS patients in two studies, wherein 17 patients had localised disease, three had nodal involvement and one had metastatic disease.[17,20]

No studies reported the time from end of first-line treatment to relapse/progression.

A summary of the population demographics can be found in Figure 3.

3.4 | Survival

All included studies report outcome data for at least one patient with R&R RMS (see Table 1). The number of evaluable R&R RMS patients was not clear for one study.[23] The majority of studies (n = 9, 69%) reported outcome data for five or fewer eligible patients.[18,20–22,24–28]

3.4.1 | Progression-free survival

Six studies (46%) provided outcomes on progression-free survival (PFS).[16–18,20,25,26] Three studies reported 5-year PFS, which ranged from 57% to 85.5%.[16–18] One study, including only one patient, reported 100% PFS at 1 year.[22] Three studies reported median PFS ranging from 3 months to 20.65 years.[18,20,25]

3.4.2 | Overall survival

Ten studies (77%) reported OS.[16–20,22,23,25–27] Four studies reported 5-year OS, which ranged from 42% to 82% (note these are different studies to those reporting 5-year PFS).[16,17,19,23] One study, including only one patient, reported 100% OS at 1 year.[22] Three studies reported median OS ranging from 6 months to 20.65 years.[18,20,25]

3.5 | Relapse rate

At least 15 (of at least 55 evaluable) R&R RMS patients relapsed following surgery and brachytherapy (see Table 1). Where histology was reported, the majority of these relapses related to embryonal RMS patients (n = 11, 85%),[17–20] which is consistent with the included population. The majority of these relapsed patients subsequently died from disease (11/13 patients where data available, 85%).[16,17,19,20]

3.5.1 | Local relapse rate

LRR was reported in 11 studies (85%), ranging from 0% to 100%.[16–25,27] There were 12 local relapses in 52 patients (23%) reported across 10 studies[17–20,24,25] (one study did not report the number of relapses but did provide the LRR[23]). Both local and metastatic relapses were more frequent amongst patients with head and neck RMS compared to patients with bladder/prostate RMS.

3.5.2 | Metastatic relapse rate

Metastatic relapse rate (MRR) was reported in 10 studies (77%), ranging from 0% to 100%.[16,17,19–22,24–27] There were six metastatic relapses in 49 patients (12%) reported across 10 studies.[16,17,19,25] Importantly, the study with 100% LRR/MRR[25] was for only one R&R RMS patient so the effectiveness (or lack of) for this intervention should be cautiously interpreted.

3.6 | Adverse events/functional outcomes

Data relating to AEs and functional outcomes were available for over 150 evaluable children and young people across all studies (not R&R RMS specific). Two studies failed to provide any AE data.[26,28] The data

TABLE 1 Outcome data of included studies.

Author, year	Number of evaluable R&R RMS patients	Number of patients who relapsed after the intervention	Relapse rate		Survival			Comments
			Local	Metastatic	LFS	PFS	OS	
Blank, 2009	5 First relapse, 1 second relapse	1	0%	16.7%[a]	NR	82% at 5 years (for 11 patients in Group B including 2 with residual disease)[b]	82% at 5 years (for 11 patients in Group B including 2 with residual disease)[b]	1 Distant recurrence after 6 months 2 Patients died (0.8 and 9.9 years of follow-up): 1 of distal metastases only, and one of a second primary tumour fibrosarcoma, respectively. 3 Patients had no evidence of disease at the end of follow-up (13.1, 6.0, 9.2 years after treatment). 1 Patient was alive at 1.6 years after treatment (patient from abroad without recent follow-up data)
Vaarwerk, 2019[b]	13 First relapse, 3 second relapse, 1 third relapse	7	29.4%[a]	17.6%[a]	65%[a] at 5 years	57%[a] at 5 years	57%[a] at 5 years	1 Patient had local and metastatic relapse At last follow-up, 9 patients had no evidence of disease and 8 patients had died
Blank, 2010	5 First relapse	1	20%[a]	NR	80%[a] at 2 years	Median 3.9 years [0.6–17.1 years][a] 85.5% at 5 years[b]	Median 14.7 years [3.3–17.1 years][a]	1 RMS patient relapsed 0.6 year after receiving brachytherapy. Their first treatment following this relapse was chemo + EBRT. They relapsed again and received exenteration and second brachytherapy, and was without tumour activity at the point of analysis in August 2008
Strege, 2009	5 First relapse, 5 refractory	3	30%	10%	NR	NR	62% (±18%) at 5 years	3 Patients relapsed, 1 had a local and metastatic relapse. At last clinical status, 5 patients had no evidence of disease, 4 patients had died of disease (including 2 of the relapse patients) and 1 patient was alive with disease (relapse patient)
Mazeron, 2014	4 First relapse	1	25%	0%	Median 20.65 years[a] [1–33 years]	Median 20.65 years[a] [1–33 years]	Median 20.65 years[a] [3.3–33 years]	

(Continues)

TABLE 1 (Continued)

Author, year	Number of evaluable R&R RMS patients	Number of patients who relapsed after the intervention	Relapse rate		Survival			Comments
			Local	Metastatic	LFS	PFS	OS	
Chargari, 2017	4 Relapsed (undifferentiated)	0	0%	0%	NR	NR	NR	All four patients had a complete response to relapse treatment (100%)
Martelli, 2009	1 Relapsed (undifferentiated)	0	0%	0%	100% at 1 year[a]	100% at 1 year[a]	100% at 1 year[a]	1 Complete response for relapsed RMS patient (100%) EFS: 100%[a] at 1 year
Gana, 2011	2 First relapse	Unclear	Unclear	0%	NR	NR	See comment	At an average follow-up of 6 years (1–12.5 years), there is a 100% survival rate. 1 Local relapse after treatment but not clear if this patient had relapse RMS
Stenman, 2014	1 Relapse (undifferentiated)	Unclear	NR	NR	NR	NR	NR	This patient died of disease
Gaze, 2012	1 Relapse (undifferentiated)	0	0%[a]	0%[a]	NR	NR	See comment	All remain free of disease at a median of 22 months (range 12–38 months)
Folkert, 2014	36 RMS (unclear how many R&R)	Unclear	58.3%[a]	NR	41.7% at 5 years [95% CI: 15.9%–67.5%]	NR	42% at 5 years [95% CI: 13.8%–70.2%]	EFS: 30% at 5 years [95% CI: 4.4%–55.6%] Calculated from Supporting Info
Hentz, 2014	3 Relapsed (undifferentiated)	At least 1	At least 1	0%	NR	NR	NR	1 Patient with recurrent paraspinal RMS had a local relapse noted 1.5 years after treatment
Yao, 2015	1 First relapse	1	100%[a]	100%[a]	3 months	3 months	6 months	1 Progressive disease

Abbreviations: CI, confidence interval; EBRT, external beam radiation therapy; EFS, event-free survival; LFS, local failure-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival; RMS, rhabdomyosarcoma; R&R, relapsed and refractory.

[a]Data have been calculated for eligible R&R RMS patients specifically.

[b]Includes duplicate patients as described in Table S3.

that were presented varied significantly in how well it was reported, with many studies lacking to explain how toxicities were assessed and graded, making these data difficult to synthesise. Generally, AEs were infrequently experienced. Functional outcomes related to the specific areas the brachytherapy and surgery was being given (e.g., cosmetic/facial outcomes in patients with orbital RMS), and were more frequently reported. Data pertaining to AEs and functional outcomes can be found in Table S5.

No study reported on patient experience or formal quality-of-life measures.

4 | DISCUSSION

The Local-REFoRMS systematic review provides an overview of studies evaluating the use of surgery and brachytherapy for children and young people with R&R RMS. We identified 13 studies, including at least 55 children and young people with R&R RMS who were treated with local therapy, mostly directed at orbital and non-orbital head and neck disease as well as bladder/prostate RMS. The patient population was mostly those with embryonal disease at first local relapse, and thus represents a cohort with better prognosis that the wider R&R RMS population. The majority of studies were conducted in Europe, predominantly in two centres in France or the Netherlands. Overall, the quality of reporting from these studies was good; however, there were some inconsistencies between text and figures within papers and not all data were expressed clearly, which produced difficulties in the process of data analysis. The results of our systematic review suggest that surgery and brachytherapy may be an effective treatment for a highly selected subset of R&R RMS patients. However, the quality of evidence is low, as all studies were retrospective cohort studies with small sample sizes.

Our analysis revealed several important demographic factors among the patient populations included in these studies. The majority of patients were treated in Europe, with a wide range of treatment dates spanning over several decades, from 1971 to 2015.

Age is a critical factor in RMS,[3] and our findings demonstrated variability in the age distribution of patients across different cohorts. Notably, five studies reported a median age under 10 years for R&R RMS patients, consistent with that expected of embryonal disease. However, it is important to acknowledge that a small subset of patients over the age of 18 years was included in some studies, making age stratification and analysis essential in future research. There was a predominance of male patients in the RMS cohorts. This observation aligns with existing literature suggesting a slight male predominance in RMS incidence.[29,30] Race and ethnicity data were notably absent across all studies. Although not thought to possess significant prognostic value in primary RMS,[31] its absence here is limiting to our understanding of the impact of these demographic factors on R&R RMS outcomes and equitable access to specialist therapies.

Fusion status, a molecular marker with prognostic significance in RMS, was reported in only one study cohort.[21] This is unsurprising given the time periods in which these patients were treated (from as early as 1971) whereby this analysis was not readily available. The low rate of fusion-positive disease in this study is consistent with the high percentage of embryonal histology recorded in these cohorts. Nonetheless, given the current clinical relevance of fusion status, its inclusion in future studies is crucial, especially given the increase in more precision medicine studies being conducted to treat patients with personalised protocols based on specific biomarkers and mutations.[32]

While the majority of studies reported outcomes for a limited number of patients, the reported 5-year PFS ranged from 57% to 85.5% and 5-year OS ranged from 42% to 82%. This wide range of reported outcomes is likely due to the small sample sizes, varied included populations and heterogeneity of the studies. Approximately one quarter of patients relapsed following surgery and brachytherapy with a relatively higher number of local relapses compared to metastatic relapses. Relapse rate was generally higher for patients with head and neck RMS compared to patients with bladder/prostate RMS. This demonstrates that surgery and brachytherapy provided reasonable local control for this selected group of patients, but that effective systemic treatments for those with R&R RMS are also required.

In comparison to the baseline REFoRMS review,[10] this review included more first relapse patients who were generally less extensively treated prior to surgery and brachytherapy. Despite most patients previously receiving chemotherapy as part of first-line treatment in this study, there were more R&R patients also receiving radiotherapy and surgery at first treatment in comparison to patients in the baseline review.[10] This suggests that further surgery, and brachytherapy in particular, may be a viable treatment option for children who have experienced radiotherapy previously and who relapse in specific anatomical locations. Given previous findings that prior radiotherapy is associated with poorer outcomes following relapse, the effective use of AMORE in this population is notable.[33]

Finally, it is important to note that the studies included in this review represent a selected population. Where reported, most of the population included in this review had embryonal disease (88%), were younger (83% of studies had a median age of less than 10 years for R&R patients), had disease in a favourable location, and were being treated for a first relapse (64%). These factors are associated with better survival outcomes at relapse, and therefore caution should be taken when interpreting the outcomes to patients whose disease characteristics are associated with less favourable outcomes.[3,33,34]

As with the baseline REFoRMS review, there were challenges with data extraction and quality assessment due to poor or incomplete reporting of studies. It is important to acknowledge that this review used a search pool based on a search strategy developed by an information specialist within our previous systematic review.[10] This means that an independent systematic review search dedicated to answering this review question was not conducted. However, the baseline REFoRMS search included all studies of relapse and refractory sarcoma (without limiting to early-phase studies), and thus should have captured all relevant studies for this secondary review.

The evidence base for these interventions is limited by both small numbers and the methodologies used. Retrospective cohort studies carry a risk of selection bias and reporting bias, and the lack of

any comparator makes it difficult to draw firm conclusions on the effectiveness of this approach as opposed to other options.

Combined surgery and brachytherapy approaches clearly warrant further exploration in this population, with high quality efficacy studies, reported according to key patient demographics (including age, tumour site, fusion status, time to relapse) and with clear reporting of the systemic therapies used alongside these local approaches. Studies of patient experience, quality of life and cost-effectiveness are required to inform clinical practice. In addition, studies considering the effectiveness of surgery and brachytherapy techniques at first-line treatment may be warranted.

Local therapy approaches involving surgery and brachytherapy for children and young people with R&R RMS may provide reasonable local control, though the evidence is limited by small numbers and study quality. Most evidence is in those with embryonal (fusion negative) disease in favourable sites at first localised relapse. Further evaluation using prospective research is strongly recommended.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the published studies included in the systematic review, reference numbers 16–28.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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