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Overview

Radiotherapy in the Management of Childhood Rhabdomyosarcoma

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Abstract

Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood, comprising over 50% of cases. It is considered to be an embryonal tumour of skeletal muscle cell origin, frequently occurring at genitourinary and head and neck sites, although it can arise throughout the body and at sites where there is no skeletal muscle. For most cases, multimodality therapy is required to achieve the best results, incorporating induction ifosfamide, vincristine and actinomycin D-based chemotherapy and local therapy (radiotherapy and/or surgery). Recent reports from the European Paediatric Soft Tissue Sarcoma Group (EpSSG) RMS 2005 study have shown significant improvements in outcomes; high-risk rhabdomyosarcoma having a 3-year event-free survival and overall survival of about 68% and 80%, respectively. The more routine use of radiotherapy is considered to be a contributing factor to these improved results, but does also often result in significant long-term sequelae for survivors. Despite an increasing number of rhabdomyosarcoma treated with advanced radiotherapy techniques, including protons, brachytherapy and rotational intensity-modulated radiotherapy, in an effort to reduce the frequency of late complications, there remain a number of unanswered questions. Future planned collaborative group studies, such as the EpSSG Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS) study, are looking to address these questions, investigating the potential benefits of preoperative radiotherapy, dose escalation and the irradiation of metastatic sites.

Key words: Paediatric; radiotherapy; rhabdomyosarcoma

Statement of Search Strategies Used and Sources of Information

PubMed from January 1990 to September 2018 using the broad search terms ‘rhabdomyosarcoma’, ‘radiotherapy’ and ‘treatment’. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Introduction

The spectre of malignant disease thankfully remains a rare occurrence in children and young people, although it provides a diverse and challenging group of tumours that are very different in their biology, behaviour and response to treatment compared with those seen in adult oncological practice. Of the vast array of paediatric solid tumours arising outside of the central nervous system, one of the most common is rhabdomyosarcoma, the predominant soft-tissue sarcoma of childhood. To put into context the rarity and the demographics of this tumour, in the UK there are less than 60 paediatric cases per year, with the peak incidence at 3 years of age [1]. Although they can occur throughout adult life, rhabdomyosarcoma is very rarely seen in those aged 25 years and over, with other types of soft-tissue sarcoma more frequently observed in adults.

Defined by its histological appearances, being similar to fetal muscles cells, rhabdomyosarcoma is an embryonal tumour of skeletal muscle cell origin thought to derive from mesenchymal precursors [2]. A key feature, and also one of the main challenges to establishing the diagnosis of rhabdomyosarcoma, is the fact that it can arise at any site within the body given the widespread distribution of these potential cells of origin, even occurring at anatomical sites where there is no skeletal muscle. Common primary sites include the pelvis, particularly genitourinary, and the head and neck. The diagnosis of children and young people with

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rhabdomyosarcoma, as with other soft-tissue sarcoma, can often be delayed, particularly when tumours arise internally. Presenting symptoms can often be non-specific, exemplified by those in the head and neck region where they can present with nasal congestion and discharge, or painless swelling.

Significant progress has been made in the management of rhabdomyosarcoma over the last four decades and, for most paediatric cases with localised disease, cure is now achieved, with a 3-year overall survival of about 80% for those with high-risk rhabdomyosarcoma, as shown in the survival curves in Figure 1. This success stems from the efforts of international collaborative research groups in Europe and USA that have driven numerous robust and meaningful clinical trials in both rhabdomyosarcoma and also non-rhabdomyosarcoma soft-tissue sarcoma. Typically, rhabdomyosarcoma are very responsive to chemotherapy and, therefore, most treatment strategies are multimodality, incorporating upfront or adjuvant chemotherapy.

Effective local therapy, with radiotherapy and in selected cases surgical resection, is an essential part of the current upfront therapeutic strategy for rhabdomyosarcoma, with the omission of radiotherapy for high-risk rhabdomyosarcoma linked to inferior outcomes. Despite this, local control remains one of the principal challenges still being faced as locoregional failure is observed in most relapsed cases.

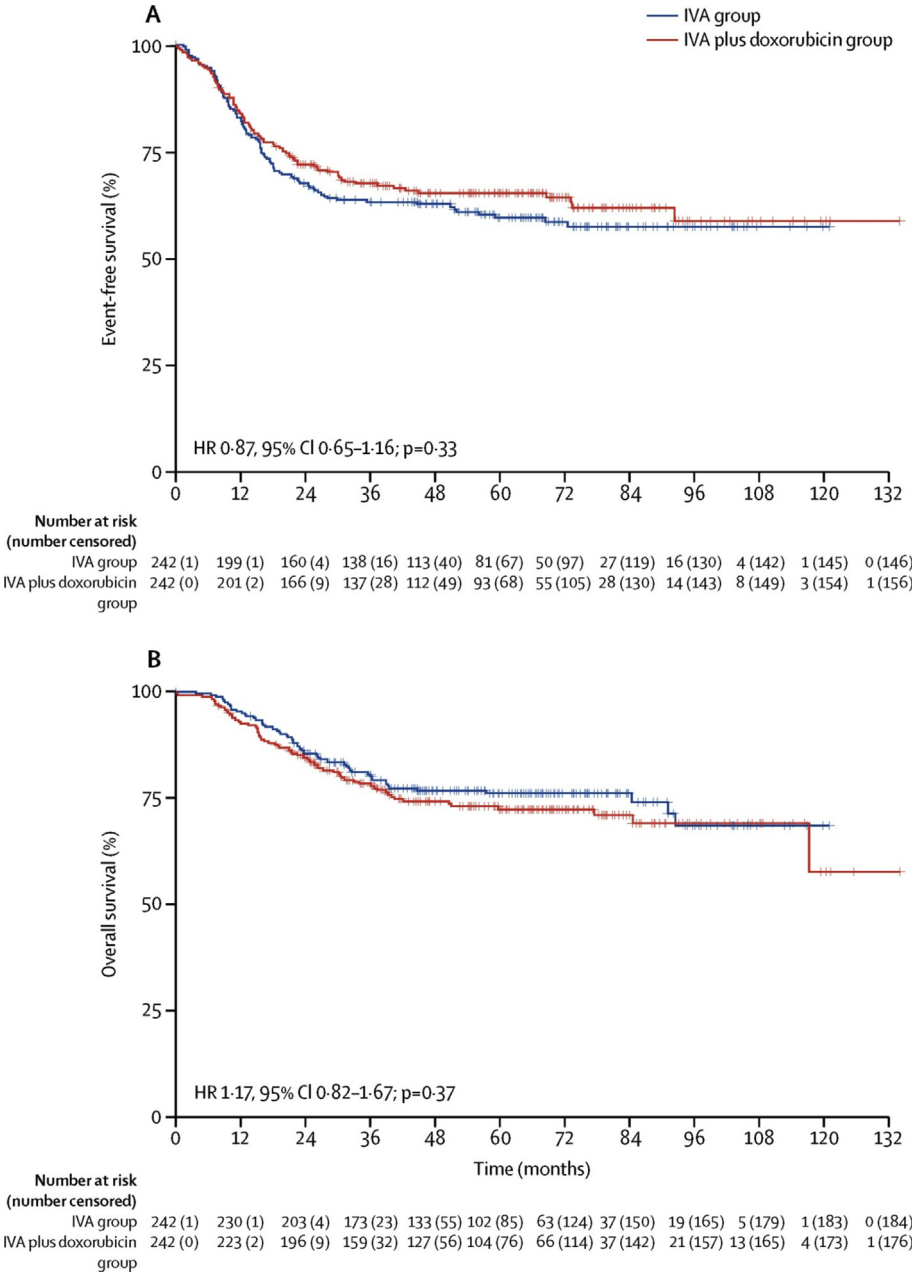

Fig 1. Kaplan–Meier plots of event-free survival (A) and overall survival (B) for patients with high-risk rhabdomyosarcoma treated in the European Paediatric Soft Tissue Sarcoma Group (EpSSG) RMS 2005 study [3].

Optimising the Treatment of Rhabdomyosarcoma

By the late 1950s, the four classical pathological categories of embryonal, alveolar, pleomorphic and botryoid rhabdomyosarcoma had been described; botryoid ('bunch of grapes' appearance) tumours being later categorised as a variant of the embryonal subtype [4]. The key distinction in recent collaborative group studies has been between embryonal and alveolar subtypes, as outcomes from the International Society of Paediatric Oncology Mixed Mesenchymal Tumours (SIOP MMT) and other collaborative group studies had showed a higher risk of relapse for those with alveolar rhabdomyosarcoma compared with the more favourable embryonal tumours. Over the last two decades there have been significant developments in the understanding of the biology of rhabdomyosarcoma and the different variants. The single most important genetic factors identified to date are the translocations that result in the PAX3 or PAX7-FOXO1 fusion genes, present in up to 80% of alveolar rhabdomyosarcoma and which are associated with a poorer prognosis; alveolar tumours without the FOXO1 fusion genes appear to have similar prognosis to embryonal rhabdomyosarcoma [5]. These findings have led to fusion gene status replacing the histopathological classification in all of the international risk stratifications used in collaborative group studies where they are now being prospectively evaluated.

The basis for current treatment strategies within the international collaborative group research studies is the stratification of rhabdomyosarcoma into different risk groupings. At the present time there remains no overarching consensus on this and different risk stratifications are being used in Europe and USA. However, there is an exciting new initiative, including representation from the European Paediatric Soft Tissue Sarcoma Group (EpSSG), Children's Oncology Group (COG), Cooperative Weichteil Sarcoma (CWS), AIEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica) and SIOP MMT research groups looking to address this issue, entitled the International Soft-tissue Sarcoma Consortium (INSTRuCT). It uses patient data from previously reported studies entered into a common database in a similar initiative to that undertaken for the International Neuroblastoma Risk Group staging system project.

Currently, the stratification for rhabdomyosarcoma used in Europe (Figure 2), by both the EpSSG and CWS groups, incorporates the following factors that have been shown to have an impact on prognosis: Intergroup Rhabdomyosarcoma Study (IRS) post-surgical stage (I, II or III), age greater than 10 years, large tumours with a diameter greater than or equal to 5 cm, in addition to the specific tumour pathological and biological subtype, and the location of the primary tumour. For localised rhabdomyosarcoma, four risk groups have been defined with low-, standard-, high- and very high-risk categories. More recently, *PAX3/7-FOXO1* fusion gene positivity, found in 70–80% of alveolar rhabdomyosarcoma, has been shown to be associated with worse outcomes for those with very high-risk disease in the RMS 2005 study, with a 5-year event-free survival (EFS) of 43% compared with 74% for fusion negative; it is currently proposed to combine these fusion-positive, node-positive patients together with metastatic patients to create a new very high-risk category for future studies in Europe [7].

These risk groupings not only provide prognostic information, but are also used to determine the intensity of the treatment required. Those with low-risk disease, where an upfront complete resection of the tumour is undertaken, are treated with eight cycles of lower intensity vincristine and actinomycin D (VA), whereas all other rhabdomyosarcoma receive nine cycles of chemotherapy. Standard-risk disease is treated with an initial four cycles of ifosfamide, vincristine and actinomycin D (IVA) then VA for subsequent cycles; for high-risk cases the recommendation is for nine cycles of IVA. Despite numerous studies exploring alternative and intensified chemotherapy schedules, IVA still remains the standard of care chemotherapy treatment for rhabdomyosarcoma in Europe. For patients with renal compromise, cyclophosphamide is usually used in place of ifosfamide, together with vincristine and actinomycin D (VAC); this schedule is also the backbone of the upfront chemotherapy used in the COG studies in North America, although recent studies have explored it in combination with temsirolimus or in an alternating schedule with vincristine and irinotecan (VAC/VI).

Given that rhabdomyosarcoma are known to be chemosensitive tumours, there has been a great deal of interest in adopting alternative chemotherapy strategies. The first randomisation of the recent RMS 2005 study investigated the addition of doxorubicin to the first four cycles of chemotherapy in the IVADo/IVA schedule, comparing this with the standard nine cycles of IVA alone. Although there was an overall improvement in 3-year EFS, up to 68%, interestingly this was seen in both arms of the study and there was no observed benefit from the addition of doxorubicin [3]. The results from this study highlight the benefits of randomised studies to provide truly robust efficacy data, and also the potential incorrect assumptions that could arise from single-arm studies using only historical controls. IVADo/IVA remains the nominal standard for very high-risk (node-positive alveolar/fusion-positive rhabdomyosarcoma) and metastatic patients, as no randomisation was carried out in these groups, although this is a point of ongoing debate [7,8].

Despite the induction chemotherapy randomisation in RMS 2005 having a negative primary outcome, it did show that there have been significant improvements in the outcomes for rhabdomyosarcoma over the last two decades. One of the probable factors contributing to this improvement in EFS is the more routine use of radiotherapy that was introduced to the European treatment strategy for the EpSSG RMS 2005 study. Achieving local control with first-line treatment is critical to producing the best outcomes for rhabdomyosarcoma, as data from historical trials have shown the outcome for patients with relapsed disease to be very poor, especially those relapsing within 18 months of diagnosis, presenting with large tumours, or relapsing after

Risk group	Site[a]	Group	Nodal Stage	Histology[b]	Age & Size[c]
Low	A	I	N0	ERMS	F
Standard	A	I	N0	ERMS	U
	F	II, III	N0	ERMS	A
	U	II, III	N0	ERMS	F
High	U	II, III	N0	ERMS	U
	A	II, III	N1	ERMS	A
	A	I, II, III	N0	ARMS	A
Very High	A	I, II, III	N1	ARMS	A

A: Any

F: Favourable

U: Unfavourable

[a] Favourable site refers to orbit, non-parameningeal head and neck (H&N) sites, and non-bladder/non-prostate GU sites; Unfavourable site refers to extremities, parameningeal sites, bladder and prostate.

[b] Favourable pathology refers to all embryonal, spindle cells, botryoid RMS; Unfavourable pathology refers to all alveolar RMS (including the solid-alveolar variant).

[c] Favourable age *and* size refer to <10 years and ≤ 5cm; Unfavourable age and size refer to ≥10 years *and* > 5cm.

Fig 2. European risk stratification schema for localised rhabdomyosarcoma (adapted from [6]).

radiotherapy [9]. In addition to the important roles of surgery and radiotherapy, there is also a growing body of evidence that the intensity of induction chemotherapy, as part of the full multimodality treatment, is also an important factor for local control. This has been shown in a number of studies from the USA, where higher levels of local failure were observed when lower doses of cyclophosphamide were used, as part of their standard VAC chemotherapy-based schedule [10–12].

The second randomisation in the RMS 2005 study also investigated modifications in systemic therapy for rhabdomyosarcoma, looking at whether the addition of a more metronomic type of maintenance chemotherapy with vinorelbine and cyclophosphamide for 6 months improves outcome for patients with high-risk disease. The results from this were presented at American Society of Clinical Oncology Annual Meeting (ASCO) in 2018 and, interestingly, although the improvement in EFS did not quite reach significance, there was a highly significant improvement in overall survival, a secondary end point for the study [13]. The results from this randomisation are practice changing and maintenance chemotherapy has now become the standard of care for these patients with high-risk disease in future EpSSG studies.

Local Therapy for Rhabdomyosarcoma

Local therapy is a key pillar of the multimodality curative treatment of rhabdomyosarcoma, although there has been variation between collaborative groups in the type of therapy and the timing of its use. In Europe, radiotherapy was traditionally withheld wherever possible in an effort to minimise potential late effects, accepting a higher risk of relapse and the possible need for radiotherapy as part of salvage therapy; in North America, radiotherapy was used

far more systematically. The surgical strategies have differed too, with a greater proportion of cases having delayed primary excision in European studies, particularly bladder-prostate rhabdomyosarcoma, a site where surgery can potentially be undertaken in combination with brachytherapy for selected cases.

More recently there has been a change in the radiotherapy strategy used in Europe following analyses from the SIOP MMT 84, 89 and 95 trials, which supported the increased use of radiotherapy for rhabdomyosarcoma in an effort to further improve outcomes. This led to the adoption of this strategy when the pan European RMS 2005 study was devised under the umbrella of the EpSSG [14]. In total, 85% of patients in the EpSSG RMS 2005 study with localised high-risk rhabdomyosarcoma went on to receive radiotherapy as part of their initial therapy; this is conceivably a major factor in the improved outcomes that the trial reported. At the outset of the RMS 2005 study, the expected 3-year EFS was 50–55% for high-risk cases, on the basis of results from previous studies, but a significant improvement of around 10% was seen; the very high-risk patients also saw an improvement in 3-year EFS from the predicted 39% up to 56% [3,7]. Despite these improvements in outcomes, local failure continues to be observed in most relapse cases, showing that there remains a need for further improvements.

In the management of these generally very chemotherapy-sensitive tumours, the optimal timing for local therapy continues to be frequently debated. The European approach for most cases with localised disease is to evaluate the response after the third cycle of induction chemotherapy, then look to start local therapy (delayed surgical excision of the primary tumour and/or radical radiotherapy) at week 13, approximating to the fifth cycle of chemotherapy. Previously, the approach in the USA differed to this, particularly for high-risk parameningeal rhabdomyosarcoma, where there was an intention to start radiotherapy at day 0, until a retrospective analysis from the Intergroup Rhabdomyosarcoma Study (IRS)-IV and D9803 studies revealed no difference in outcomes between patients starting radiotherapy at day 0 or at week 12; this has led to a change in practice and alignment with the timings used by the EpSSG [15]. For highly selected patients, local therapy may even be delayed beyond week 13, if it is felt that further response to chemotherapy may facilitate complex surgical resection or brachytherapy.

The optimal timings of local therapy differ for metastatic disease, given the potential benefits of additional chemotherapy in treating metastatic sites. Therefore, it is standard practice in Europe to re-evaluate response after the sixth cycle of chemotherapy, and for local therapy to start at about week 22. Cases with extensive metastatic disease may require their metastatic radiotherapy to be divided into two separate treatments to limit the associated bone marrow and other acute toxicities. In North America, where the practice is to deliver radiotherapy for metastatic rhabdomyosarcoma at week 20, the COG's recommendation, particularly for extensive metastatic disease, is that certain metastatic sites are prioritised for radiotherapy, with an option to consider further radiotherapy to other metastatic sites at week 47.

Scheduling of Adjuvant Radiotherapy

When considering the role for radiotherapy given in the adjuvant setting, there remain a number of outstanding questions still to be resolved. Adjuvant radiotherapy for rhabdomyosarcoma has traditionally been delivered after surgical resection, yet preoperative radiotherapy has a number of potential advantages for soft-tissue sarcomas, including: (i) improved accuracy, given that the intact tumour target volume is easier to define, (ii) reduced exposure of normal tissue to high doses of radiotherapy as the residual tumour acts as a form of 'spacer', and (iii) potentially even a reduction in the risk of second tumours given that a significant proportion of the irradiated tissue will ultimately be removed surgically. There is also radiobiological rationale, as preoperatively the tumour and surrounding tissues are less hypoxic (and therefore potentially more radioresistant), compared with the postoperative state [16].

Increasingly, preoperative radiotherapy is being used for the treatment of adult sarcoma, especially in the extremities, retroperitoneal, pelvic and spinal regions. Preoperative radiotherapy is being investigated in a number of paediatric non-rhabdomyosarcoma soft-tissue sarcoma studies, including NCT01344018 and NCT02180867, but has not yet been fully evaluated in rhabdomyosarcoma. To date, the only published experience using preoperative radiotherapy is from a small cohort of 17 children with bladder-prostate rhabdomyosarcoma in the German CWS96 study, which encouragingly reported a 5-year EFS of 82% [17]. In an effort to establish whether similar benefits to those seen in adult-type soft-tissue sarcoma with preoperative radiotherapy can be achieved for rhabdomyosarcoma, there is a randomised question comparing preoperative radiotherapy with postoperative radiotherapy in the planned EpSSG Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS) study.

The Role for Advanced Radiotherapy Techniques

When selecting the appropriate technique for the delivery of radiotherapy for rhabdomyosarcoma, one must take into consideration a multitude of factors, determining the optimal solution for the specific tumour site, extent of disease and age of the patient. In addition to maximising local control and the chance of cure, it is essential to understand the potential late toxicity of treatment. The impact of radiotherapy on the quality of life for survivors can be profound, especially when very young children are treated, as radiotherapy significantly impairs the growth of bone and other normal tissues.

In a study evaluating the late effects of radiotherapy in survivors of childhood head and neck rhabdomyosarcoma,

one or more severe or disabling consequence was reported by 63% of patients [18]. With these high rates of significant and potentially lifelong toxicities it is essential that every effort is made to minimise these risks. Internationally, an ever increasing number of children with localised rhabdomyosarcoma are being treated with proton therapy or, where this is deemed not to be appropriate, using other highly conformal techniques, such as rotational intensity-modulated radiotherapy, with the aim of reducing late toxicities in later life. With both intensity-modulated proton therapy and intensity-modulated radiotherapy there is the potential to utilise simultaneous integrated boost strategies (Figure 3) to further improve conformity and the sparing of adjacent organs at risk. Although this is not widely used, it can be considered in centres with experience of such treatments and where robust quality assurance and recording of outcomes is undertaken.

Another treatment option that is increasingly being used for rhabdomyosarcoma is brachytherapy, which many consider to be the ultimate highly conformal radiotherapy technique and one that can achieve the lowest exposure of normal tissues to irradiation. However, this is only appropriate for highly selected paediatric cases, often those with the more favourable botryoid variant of embryonal rhabdomyosarcoma and arising in the genitourinary region (vagina, uterus, bladder/prostate and perineum sites), and less commonly for selected head and neck sites. Most brachytherapy treatments for rhabdomyosarcoma are undertaken after complete or partial tumour resection, utilising modern image guidance and afterloading pulsed dose rate or high dose rate systems, but it can also be delivered as a primary treatment without surgery. A number of published single-centre series have reported encouragingly low levels of late effects and improved quality of life in survivors treated with brachytherapy [18–20]. Given the rarity of suitable tumours and the complexity of the delivery of these highly specialised treatments in children, it is recommended that brachytherapy for rhabdomyosarcoma is undertaken only at specialist national or international referral centres.

Optimal Radiotherapy Dosing

Since the first international collaborative group studies in the 1970s, there has been a gradual evolution and refinement of the radiotherapy dosing strategies, yet some uncertainties still remain. In the SIOP MMT studies, it was recommended to deliver 45 Gy, plus additional boosts of either 5 Gy for microscopic residual or 10 Gy for macroscopic residual disease [14]. However, a wide range of radiotherapy doses have been used, ranging from 36 Gy up to 55.8 Gy, using 1.5–1.8 Gy per fraction daily. To date only the COG IRSIV study has asked a randomised radiotherapy question for rhabdomyosarcoma when it compared hyperfractionated radiotherapy (HFRT), at a dose of 59.4 Gy in 54 fractions of 1.1 Gy delivered twice daily, with 50.4 Gy conventionally fractionated using 1.8 Gy given once daily. The results from the IRSIV study showed no difference in local control, which may suggest that there had not been true dose escalation of radiotherapy [21]. In addition, the acute toxicity observed with HFRT was greater than that with conventionally fractionated radiotherapy and as a result HFRT has not been widely adopted.

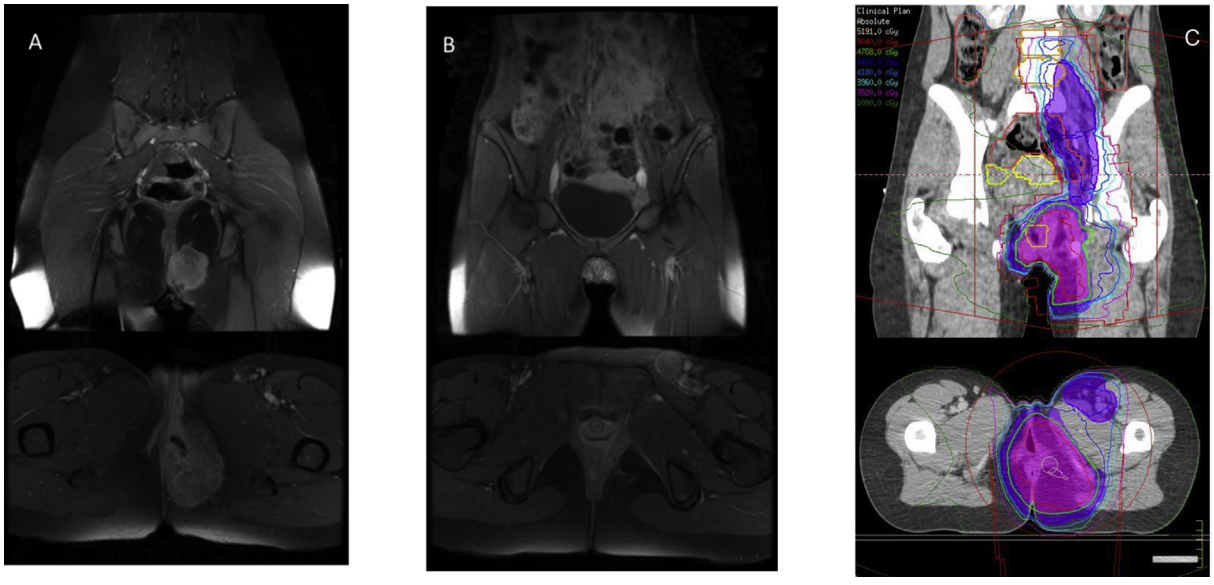

Fig 3. Rotational intensity-modulated radiotherapy using a simultaneous integrated boost technique for perineal alveolar rhabdomyosarcoma. (A) Coronal and axial T1w + c magnetic resonance imaging (MRI) showing perineal primary tumour; (B) coronal and axial T1w + c MRI showing left external iliac and left inguinal lymphadenopathy; (C) coronal and axial images from single 6 MV Volumetric Modulated Arc Therapy (VMAT) arc plan, delivering 50.4 Gy (1.8 Gy per fraction) to the perineal primary and 44 Gy (1.57 Gy per fraction) to involved lymph nodes, both in 28 daily fractions.

In view of the higher local failure risk observed in specific subgroups of rhabdomyosarcoma, there remains the potential to improve local control with dose escalation of conventionally fractionated definitive radiotherapy up to 59.4 Gy; this is now being investigated in studies being run by the COG and EpSSG. On the basis of data from the D9803 study, the COG have suggested dose-escalating radiotherapy for all patients with large tumours over 5 cm in size [22]. By comparison, in the planned EpSSG FaR-RMS study, there are randomisations of dose-escalated versus conventional dose radiotherapy for patients receiving definitive (59.4 Gy versus 50.4 Gy) or adjuvant radiotherapy (50.4 Gy versus 41.4 Gy) for tumours at unfavourable sites, or adult patients over the age of 18 years. The results from these studies should determine the true benefits for increasing the radiotherapy dose.

Irradiation of Metastatic Sites

There are conflicting data regarding the optimal local therapy for metastatic rhabdomyosarcoma and whether radiotherapy to metastatic sites truly influences outcomes. The current international standard of care recommends the systematic irradiation of all metastatic sites that can feasibly be treated; however, this does mean that it is open to some interpretation from the treating clinician. This recommendation sits in contrast to adult soft-tissue sarcoma guidelines, where routine irradiation of metastatic sites is not recommended for all cases. There are concerns regarding patients with extensive metastatic disease, where there is often a very poor prognosis, as metastatic radiotherapy has the potential to adversely impact on their quality of life and can produce significant myelosuppression, restricting the ability to deliver chemotherapy effectively.

Questions remain as to whether there are specific subgroups of patients who may benefit from metastatic radiotherapy more than others, particularly as the prognosis with metastatic disease is very variable and dependant on the burden of disease and the sites involved. Patients with lung metastases only, about 28% of metastatic rhabdomyosarcoma cases, are known to have a relatively superior outcome, with long-term survival in excess of 40%; a retrospective review of cases treated in the CWS studies showed that those achieving a pulmonary complete response by week 7–10 of induction chemotherapy had a 5-year overall survival of 68% compared with 36% ($P = 0.004$) for those not achieving this [23]. Whole lung radiotherapy at a dose of 15 Gy in 10 fractions is the current standard of care for patients with pulmonary metastases, and seems to improve pulmonary local control, although its impact on overall survival is still debated [24]. Attempts to distil out the relevant prognostic factors associated with survival in metastatic rhabdomyosarcoma include a pooled analysis of data from both US and European co-operative groups, which was published by Oberlin *et al.* in 2008 [25]. In this analysis, the four key prognostic factors identified were age (<1 year or ≥10 years), 'unfavourable' primary site (extremity, other, unidentified), bone or bone marrow involvement and having ≥3 metastatic sites. There was a significant difference in 3-year EFS between patients with <2 risk factors (44%), in comparison with those with ≥2 factors (14%). These criteria have the potential to be harnessed to aid the stratification of treatment for metastatic disease, including metastatic radiotherapy.

The wide variation in the delivery of radiotherapy to metastatic sites is highlighted in data published from the BERNIE study investigating the addition of bevacizumab to IVADo chemotherapy in metastatic paediatric soft-tissue sarcoma. From 102 patients with rhabdomyosarcoma there were 31 who had radiotherapy to all sites of disease, 49 who had radiotherapy only to selected sites and 22 patients who received no radiotherapy at all [26]. In this analysis, the overall survival was improved for those receiving radiotherapy, although selection bias will undoubtedly be a confounding factor, as those with limited metastatic disease will have been more likely to receive radiation compared with those with bone marrow involvement and, importantly, there was no radiotherapy quality assurance undertaken in the study. Although in the BERNIE study doses of 30 Gy in 10–20 fractions to metastatic sites were recommended, there are data from some single-centre studies that suggest delivering doses of >40 Gy can achieve levels of local control in excess of 90%, supporting the merits of following the dosing guidance for primary tumours and delivering 41.4 Gy in 23 fractions, or even up to 50.4 Gy in 28 fractions where there remains gross macroscopic disease [27]. These doses are not deliverable when wide-field radiotherapy is required, such as whole lung where 15 Gy is recommended, or whole abdomino-pelvic radiotherapy for peritoneal disease where there are data to support giving 24 Gy; a lower dose per fraction of 1.5 Gy is advised for such treatments [28]. Stereotactic ablative body radiotherapy schedules are not yet being used widely for children with limited or metastatic disease, although more data may support its use.

Conclusion

Radiotherapy remains a cornerstone of the multimodality treatment of paediatric rhabdomyosarcoma and has undoubtedly contributed to the improved outcomes reported in the recent EpSSG RMS 2005 study. However, local failure is still present in most cases of relapse and there is a need to better understand the interplay between induction chemotherapy and local therapy. Questions remain about the ideal scheduling of adjuvant radiotherapy, the potential benefits of dose escalation and the role for radiotherapy to metastatic sites, especially for those with unfavourable metastatic disease. The planned EpSSG FaR-RMS study, incorporating prospective radiotherapy quality assurance, and other future collaborative group rhabdomyosarcoma studies can hopefully address these.

Conflict of interest

The authors declare no conflict of interest.

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