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The Impact of Radiotherapy in Children and Adolescents with Metastatic Rhabdomyosarcoma

Short running title: Impact of radiotherapy on survival in mRMS

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DATA SHARING

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Abstract

Purpose: There is limited evidence to define the role of radiotherapy in children with metastatic rhabdomyosarcoma (mRMS). In the international BERNIE study, children with mRMS or non-RMS soft tissue sarcoma were randomized to receive standard chemotherapy with/without bevacizumab, with radiotherapy recommended to all disease sites after chemotherapy cycle 6. We retrospectively evaluated the impact of radiotherapy on survival in the mRMS cohort.

Methods and Materials: Patients were grouped according to the radiotherapy they received: radical, partial or none. Radical irradiation was defined as radiotherapy delivered to all disease sites, unless a site was completely surgically resected. Partial irradiation was defined as radiotherapy to ≥1, but not all, disease sites. Landmark analysis excluded patients with an event prior to Day 221. Overall survival (OS) and event-free survival (EFS) were modelled using Cox proportional hazards models.

Results: Of 102 patients with mRMS, 97 were included in the analysis for OS and 85 for EFS. Overall, 27 patients received radical irradiation, 46 partial irradiation and 24 no irradiation. EFS was not significantly different between patient groups after adjustment for prognostic factors (hazard ratio [HR] = 0.520; P = 0.054 for any vs no irradiation). Radiotherapy was associated with improved OS compared with no radiotherapy (adjusted HR = 0.249; P = 0.00025), with OS greater for radical versus partial irradiation (HR = 0.245; P = 0.039). The 3-year OS rate was 84%, 54% and 23% for patients receiving radical, partial and no irradiation, respectively. Radical treatment (surgery, irradiation or both) of the primary site improved EFS and OS compared with no treatment.

Conclusions: These findings demonstrate variability in the application of radiotherapy for mRMS and support the routine use of radical treatment to the primary site. Radical irradiation to metastatic sites may further improve OS. The burden of such treatment should be balanced against prognosis; further studies are needed.

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children.[1] When the disease is metastatic at presentation, approximately 15% of cases, outcomes are poor with a 3-year event-free survival (EFS) of just 27%.[2] Optimization of treatment combinations and development of new therapies is needed. In metastatic RMS (mRMS), radiotherapy can be used to treat the primary site, distant disease sites, or both, with the aim of controlling symptoms and improving disease control. The use of radiotherapy in mRMS is variable with limited evidence supporting its use.[3–10]

In patients with RMS and lung-only metastases, conflicting results have been published regarding the benefit of whole-lung radiotherapy. A retrospective non-randomized analysis of the North American Intergroup Rhabdomyosarcoma Studies IV Pilot and IV trials of 46 patients suggested that those who received lung radiotherapy had improved 4-year overall survival (OS) (47% vs 31% without radiotherapy) and failure-free survival (48% vs 12% without radiotherapy).[5] However, the German Cooperative Soft Tissue Sarcoma Study Group's retrospective analysis of four consecutive trials noted no improvement in OS, EFS or local control in 29 patients with embryonal RMS, only 10 of whom had received local treatment for lung metastases.[6]

Small single-center series report local control of non-lung metastatic sites with radiotherapy (fractionated 18–50.4 Gy) of 73–100%[3,4,7,8] and of whole-lung irradiation (15 Gy in 10 fractions) of 56%.[9] In addition, a series of 35 patients with mRMS suggested a survival advantage for patients receiving radiotherapy to all sites compared with less than all metastatic sites (5-year progression-free survival 31% vs 0%, respectively, $P = 0.002$; 5-year OS 37% vs 0%, respectively, $P < 0.001$), although the groups were imbalanced, with considerably more patients with lung-only metastases in the radiotherapy group.[9] The largest series of patients with mRMS, treated between 1998 and 2011, considered the local treatment of 88 children and young adults and noted that those who received both radiotherapy and surgery had improved OS. On both univariate and multivariate analyses, 5-year OS was 44% for patients treated with surgery and radiotherapy, 19% following

surgery alone and 16% for radiotherapy alone.[10] The authors concluded that aggressive local therapy was important in the treatment of mRMS. No comment was made on the role of radiotherapy to distant metastatic sites, except that only 34% of patients received such irradiation.

The multicenter, randomized, phase II BERNIE study investigated whether the addition of bevacizumab to standard chemotherapy extended EFS in patients with untreated mRMS and non-RMS soft tissue sarcoma (NRSTS).[11] Radiotherapy was recommended to all sites of disease if feasible in BERNIE, but not all patients received radiotherapy; patients received radiotherapy to none, some or all known disease sites. The reason for this variation was not recorded. Within BERNIE, 102 patients had mRMS, thus enabling the largest analysis to date of radiotherapy use in this patient group.

The aim of this non-randomized, retrospective analysis was to describe the use of radiotherapy in the BERNIE study and to explore the impact of radiotherapy on EFS and OS in mRMS to inform future radiotherapy treatment guidelines and trial protocols.

Methods and materials

Study design

Full methodology of the BERNIE study (BO20924/ITCC-006; ClinicalTrials.gov: NCT00643565) has been published.[11] In brief, 154 patients aged 0.5 to <18 years with untreated mRMS or NRSTS were randomized to receive bevacizumab or not in addition to 9 cycles of 3-weekly induction and 12 cycles of 4-weekly maintenance chemotherapy (Fig. E1). The protocol recommended local therapy with surgery (if indicated) after cycle 7, and radiotherapy between cycles 7 to 9 of induction chemotherapy. Radiotherapy was recommended to all sites of disease, where feasible, except extremity post-amputation and paratesticular primary after complete surgical resection. The trial suggested a dose of 41.4–55.8 Gy to the primary site dependent on response to chemotherapy and surgical

resection, 41.4–50.4 Gy to regional lymph nodes and varying doses to metastatic sites (30 Gy to bone and brain metastases; 15 Gy to whole lung; rarely 40–50 Gy to limited sites).

The study protocol was approved by applicable ethics committees and institutional review boards, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from the parents, patients or legally acceptable representatives prior to any study-related procedures.

Landmark analysis

The current analysis included only patients with mRMS who were alive without progression at Day 221 (planned end of cycle 9 plus 1 month grace period), to reduce the risk of immortality bias in those receiving radiotherapy – a landmark approach.[12] This approach resulted in only surgery and radiotherapy prior to Day 221 and only OS and EFS post-Day 221 being considered.

Patients were classified according to the radiotherapy they received: radical, partial or none. Radical irradiation was defined as radiotherapy to all disease sites (primary [unless completely resected paratesticular or limb site], nodal and metastatic [except bone marrow]) identified at trial entry and delivered at a dose consistent with radical irradiation (as per doses stated above, although where whole abdomen was irradiated, minimum 24 Gy was considered acceptable[4]). Partial irradiation was defined as radiotherapy to ≥1 site of disease, but not fulfilling the definition of radical irradiation. Additionally, patients were classified as receiving any radiotherapy (partial or radical) or no radiotherapy.

Oberlin score[2] was determined for all patients, with 0–1 considered good prognosis and 2–4 considered poor prognosis.

Regarding treatment of the primary site: “radical surgery alone” was defined as complete surgical resection without any additional radiotherapy to that site prior to Day 221; “radical irradiation alone” was defined as no surgery but radiation at a radical dose to the primary site prior to Day 221; “radical radiotherapy and surgery” was defined as per “radical

irradiation alone" with the addition of a partial or complete surgical resection; and "no radical local therapy" was used for all patients outside these definitions.

Statistical analyses

EFS and OS were modelled using Cox proportional hazards models for the different radiotherapy classifications, treatment of primary site and sites of metastases, and corrected for risk factors that may influence outcome in mRMS. Risk factors were defined as: bevacizumab treatment; disease risk (high-risk disease: age ≥10 years, unfavorable primary site, bone or bone marrow metastasis, >2 metastatic sites); age (<1 vs 1–9 vs ≥10 years); histological type (alveolar vs embryonal vs other); and metastatic lesion count (1 vs 2–3 vs >3). No correction was applied for EFS and OS analysis of the Oberlin factors. Pearson's Chi-squared test was used for comparison between groups. Descriptive analysis was used to explore differences in patients who received radiotherapy and those who did not.

Results

Patients

In total, 102/154 patients enrolled in BERNIE had mRMS. Of these, 97 were alive (85 were event-free) at the landmark point of Day 221 and were included in this analysis. Overall, 24/97 (25%) patients received no radiotherapy. Of the 73/97 (75%) patients who did receive radiotherapy, 46 (47%) received partial and 27 (28%) received radical irradiation. Six patients who received radiotherapy after Day 221 were considered not to have received radiotherapy for the purpose of this analysis.

Baseline patient demographic and clinical characteristics are shown in Table 1. Not all potential risk factors were balanced across the groups at baseline. A greater proportion of patients receiving radical irradiation had a good prognosis Oberlin score (score 0–1: 70% [19/27], 26% [12/46] and 50% [12/24] for radical, partial and none, respectively) and oligometastatic disease (1–3 metastatic lesions: 59% [16/27], 22% [10/46] and 21% [5/24], respectively).

Treatment delivered to each disease site is shown in Table 2. In the partial radiotherapy group, 93% of patients (43/46) had radical treatment of the primary site, but none had radical treatment of all regional lymph node/metastatic sites. In the no radiotherapy group, 9% of patients (2/22) had surgery to the primary site, which required no adjuvant radiotherapy (paratesticular), whilst 91% (20/22) did not receive radical treatment of the primary site.

The radiotherapy dose to the primary site ranged from 30–61.4 Gy (median 50.4 Gy), to regional lymph nodes from 30–55.4 Gy (median 41.4 Gy) and to distant metastases 10.5–59.4 Gy (median 41.4 Gy). Regarding doses to metastatic sites, one patient received 10.5 Gy (to peritoneum, not considered 'radical'), 10 patients 15 Gy to lungs (five exclusively), 15 patients 30–33 Gy, 17 patients 40–45 Gy and 17 patients 50–59.4 Gy. None of the patients received stereotactic body radiotherapy and all were delivered in 1.5–1.8 Gy/fraction where documented.

Effect of irradiation

Radiotherapy was associated with improved EFS compared with no radiotherapy (unadjusted hazard ratio [HR] = 0.505; 95% confidence interval [CI], 0.289–0.881; *P* = 0.016) (Fig. 1A and Table 3). However, once risk factors were adjusted for, this became a non-significant trend (HR = 0.520; 95% CI, 0.267–1.011; *P* = 0.054). Three-year EFS was 61% (95% CI, 44–85), 41% (95% CI, 27–62) and 9% (95% CI, 2–56) for radical, partial and no irradiation, respectively (Fig. 1B).

Radiotherapy was associated with improved OS compared with no radiotherapy (unadjusted HR = 0.292; 95% CI, 0.153–0.555; *P* = 0.00018) (Fig. 2A and Table 3) and this remained significant when risk factors were adjusted for (adjusted HR = 0.249; 95% CI, 0.119–0.524; *P* = 0.00025). OS was improved at 3 years with radical (adjusted HR = 0.115; 95% CI, 0.027–0.482; *P* = 0.0031) or partial (adjusted HR = 0.296; 95% CI, 0.141–0.623; *P* = 0.00132) irradiation compared with no irradiation, and when comparing radical versus

partial irradiation (HR = 0.245; 95% CI, 0.064–0.938; *P* = 0.039) (Fig. 2B and Table 3). Three-year OS was 84% (95% CI, 70–100), 54% (95% CI, 40–72) and 23% (95% CI, 10–56) for radical, partial and no irradiation, respectively (Fig. 2B).

Effect of metastatic sites

Patients with lung-only metastases (*n* = 9 for EFS; *n* = 11 for OS) did not experience improved EFS (adjusted *P* = 0.39) or OS (adjusted *P* = 0.49). However, only two of these patients received radiotherapy to their lung metastases.

Of nine patients with bone-only metastases, four had a single metastasis, one had two metastases and four had multiple bone metastases. Three patients had their single bone metastasis irradiated, three had some of their bone lesions irradiated and three had none irradiated. In patients with bone-only metastases, 3-year EFS and OS were 78% (95% CI, 55–100) and 89% (95% CI, 71–100), respectively, compared with 29% (95% CI, 16–52; adjusted *P* = 0.10) and 30% (95% CI, 17–52; adjusted *P* = 0.001), respectively, for those with bone and other metastatic sites.

In the adjusted analysis, EFS and OS were significantly longer in patients with a single metastatic site versus 2–3 (*P* = 0.026 EFS; *P* = 0.0002 OS) or ≥4 involved sites (*P* = 0.034 EFS; *P* = 0.023 OS) (Fig. E2). Three-year EFS was 52% (95% CI, 36–73), 38% (95% CI, 23–64) and 17% (95% CI, 5–54) for patients with 1, 2–3 or ≥4 metastatic sites, respectively. Corresponding 3-year OS was 74% (95% CI, 59–93), 54% (95% CI, 40–73) and 16% (95% CI, 5–55), respectively. There was no significant difference in EFS or OS in 19 patients with a single metastatic lesion compared with those with >1 lesion.

Effect of Oberlin prognostic score

Oberlin score was prognostic for OS but not EFS. Three-year OS was 71% (95% CI, 57–89) for the good prognostic group versus 41% (95% CI, 29–58) for the poor prognostic group (*P* = 0.004). When dividing radiotherapy delivered by Oberlin prognostic group, EFS and OS were significantly better in patients who received irradiation compared with those who did

not. In patients in the Oberlin good prognostic group, 3-year OS was 89% (95% CI, 77–100) with radiotherapy and 29% (95% CI, 10–87) without. In the Oberlin poor prognostic group, OS was 48% (95% CI, 34–68) with radiotherapy and 14% (95% CI, 3–76) without (Fig. 3).

The proportion of patients receiving radiotherapy was similar between good or poor prognostic Oberlin groups (72% vs 78%, respectively (*P* = 0.519). However, the extent of radiation differed. Of 43 patients (44%) in the good Oberlin prognostic group, 19 (44%), 12 (28%) and 12 (28%) received radical, partial or no irradiation, respectively, compared with eight (15%), 34 (63%) and 12 (22%) patients, respectively, in the poor Oberlin prognostic group (*P* = 0.0009). Table E1 shows the composition of the different Oberlin groups.

Effect of local therapy

In total, 36% (34/95) of patients received radical radiation alone, 12% (11/95) underwent radical surgery alone, 33% (31/95) had surgery and radiotherapy, and 20% (19/95) received no radical local therapy. Compared with no radical local therapy, EFS (adjusted *P* = 0.01366, 0.00009 and 0.03865) and OS (adjusted *P* = 0.00095, 0.00873 and 0.00003) were improved with radical irradiation, radical surgery and both, respectively (Fig. E3). Three-year OS was 48% (95% CI, 33–70), 68% (95% CI, 43–100), 84% (95% CI, 71–100) and 13% (95% CI, 3–66) for irradiation, surgery, both and none, respectively.

Decisions regarding local therapy to individual sites of disease are complex, but may be influenced by the status of the site. Overall, 16/85 patients (19%) had a complete response to induction chemotherapy prior to cycle 7. Similar proportions of these patients received radiotherapy (88%) compared with those without a complete response prior to cycle 7 (84%).

A greater proportion of target lesions (primary site and/or site(s) of bulky, measurable metastases) were irradiated if they were still present prior to cycle 7 than if these had resolved (*P* = 0.001). In total, 56/85 patients (66%) had a target lesion present prior to cycle 7, of whom 53 (95%) received radiotherapy, compared with 19/29 patients (66%) whose target lesions had completely resolved.

Radical local therapy to the primary site was given to 88% (56/64) of patients in whom the primary tumor was still present, and to 61% (17/28) of those who had experienced a complete response at the primary site ($P = 0.035$). Radical local therapy to regional lymph nodes was similar whether there was a nodal complete response or not (63% [12/19] vs 61% [11/18], respectively). For patients with ≥1 site of distant metastatic disease present prior to cycle 7, 24% (14/58) received radical local therapy to all sites of distant metastases. If a complete response at all sites was seen, 38% (15/39) of patients received radical local therapy to all sites ($P = 0.13$).

Overall, 56 patients had ≥2 sites irradiated: 45 patients received this radiation as a single course (21 of those received radical irradiation); and 11 patients received this split into two consecutive courses (seven of those received radical irradiation).

Discussion

There are few published data to guide the use of radiotherapy in mRMS. The main objective of this study was to expand the currently available evidence. The study represents the largest series to date, and, although post-hoc, and not randomized, still benefits from the rigor of being multicenter and subject to trial data collection standards.

Our findings demonstrate that pediatric patients with mRMS within the BERNIE study showed significantly improved EFS and OS when they received radiotherapy as part of their treatment. As this was not a randomized analysis, it is unclear whether this improvement related to a positive effect from irradiation or a difference in the patient population who received radiotherapy. After adjusting for potential prognostic factors, there was no statistically significant difference in EFS between the radiotherapy groups. However, this adjustment did not change the statistical analysis of an OS benefit from radiotherapy. Analysis of the treatment of the primary site demonstrated that, compared with no treatment, radical treatment (86% of whom had radiation as a component of this) significantly improved EFS and OS, confirming the importance of radical treatment of the primary site. Irradiation of

all disease sites versus only some sites increased OS, suggesting that irradiation of metastatic sites may also be important.

BERNIE recommended radical irradiation of all disease sites where feasible. The reason for not incorporating irradiation into the treatment strategy was not recorded for individual patients. The reason for this is undoubtedly multifactorial, including perceived feasibility, concern regarding acute and late side effects including impact on delivery of chemotherapy, uncertainty regarding the benefit this provides and the lack of radiotherapy quality assurance within the trial. Thus, individual radiation oncologists did not have the reassurance provided by the support that this creates. In addition, risk factors were not balanced between the groups receiving radical, partial or no radiotherapy. A patient with a good versus a poor Oberlin score was significantly more likely to receive radical treatment to all their disease sites. This may reflect that a greater proportion of these patients had disease considered feasible to treat with radiotherapy. Similarly, differences were seen in patients who received radiotherapy based on responses to initial induction chemotherapy. The trial collected data on target and non-target lesions; non-target lesions were usually smaller or more difficult to measure accurately. If a target lesion was still present before cycle 7, then it was much more likely that the patient received radiotherapy than if there was a complete response of all target lesions. Likewise, if the primary site was still present before cycle 7, it was more likely that this site received irradiation. However, status of the metastatic lesions did not impact treatment decisions.

These two differing treatment scenarios suggest that some clinicians were adjusting their decision to proceed with radiotherapy dependent on the Oberlin score and the response to chemotherapy. In a potentially conflicting rationale for administering radiotherapy, they chose patients with better prognostic outcomes and those whose bulky or primary site of disease (but not metastatic sites) had responded less well to chemotherapy. This underlines that treatment decisions made regarding the use of radiotherapy lack evidence and its use has been arbitrarily applied. However, one could propose that for patients where the primary site was still present, clinicians were taking into account both the

impact on quality of life from an uncontrolled bulky lesion and that, in the non-metastatic setting, the omission of radical treatment (radiotherapy) to the primary site resulted in a significant worsening of survival.[13,14] Similarly, in those with a better prognosis, clinicians may have deemed that the impact of administering radiotherapy was worthwhile where there was a realistic chance of long-term survival.

Patients in BERNIE who received radiotherapy and had a good Oberlin prognostic score had a 3-year OS of 89%. In light of these data, the ongoing European Paediatric Soft Tissue Sarcoma Study Group Frontline and Relapsed RMS (FaR-RMS) study in adults and children with newly diagnosed and relapsed RMS (EudraCT number: 2018-000515-24), has recommended that such patients receive radiotherapy to all sites of disease. Patients enrolled in FaR-RMS will have the added benefit of prospective radiotherapy quality assurance, as part of the International Society of Paediatric Oncology – Europe (SIOP-E) project.[15] Patients with a poor Oberlin prognostic score in BERNIE had an overall significantly worse outcome. In the FaR-RMS trial, such patients will be randomized to receive radiotherapy to all sites of disease or only the primary locoregional site. The addition of radiotherapy to all sites of disease in these patients will result in a potential increase in the burden of treatment, including acute and late toxicity. The acute toxicity includes impact on the bone marrow and therefore, potentially, the ability of patients to be treated with chemotherapy. In addition, treating all disease sites may result in patients requiring two consecutive courses of radiotherapy, thereby doubling the delivery time. Such factors may have a negative impact on quality of life, which is especially important in patients with a limited life expectancy. Finally, those who are cured, will need to live with the long-term toxicity from their treatment as a child. The results of the FaR-RMS study will help guide the use of radiotherapy in this population.

Our study allowed analysis of other potential prognostic factors. As per the Oberlin cooperative analysis, the number of metastatic organ sites was prognostic.[2] Oberlin found that those with lung-only metastases had an improved prognosis,[2] but we did not confirm these findings, probably due to the small patient numbers. Bone metastases are a poor

prognostic factor according to Oberlin.[2] In our series, there was a small number of patients with bone-only metastases; this group had a 3-year OS of 89%, reminding us that those with disease limited to a single organ site have a better prognosis, even if that organ is the bone. Within the radiotherapy community there is a trend to consider that those with oligometastatic disease have a better prognosis and should be offered radical radiotherapy.[16] However, within our series, patients with mRMS with a single metastasis did not have a better prognosis than those with ≥1 metastases.

Our analysis is limited by the biases that result from a non-randomized, post-hoc analysis. We compensated for this by adjusting for prognostic factors, and by the adoption of the landmark analysis, removing patients whose prognosis was limited. Six patients who received radiotherapy later than specified in the protocol were considered not to have received radiotherapy for the purpose of this analysis. This could have diluted the positive effect of irradiation observed, but we wanted to exclude patients who were only given radiotherapy due to concerns of progression

Conclusion

The use of irradiation in pediatric patients with mRMS is associated with improved OS. All children treated with radical intent, who have an identifiable primary site, should receive radical treatment to their primary site. Radical irradiation of metastatic sites may further improve OS, particularly for patients with an overall better prognosis. Results of the FaR-RMS study will help guide the use of radiotherapy in children with newly diagnosed and relapsed mRMS.

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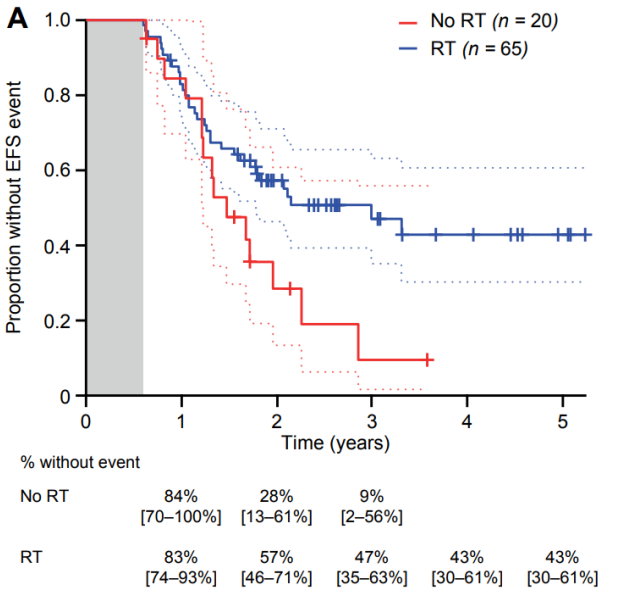
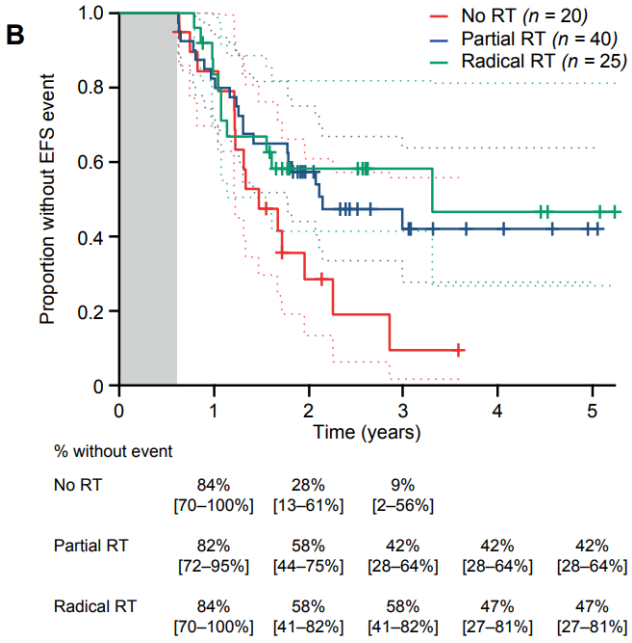
FIGURES

Fig. 1. Kaplan-Meier plot of EFS: (A) in patients receiving versus not receiving radiotherapy and (B) in patients receiving radical, partial or no radiotherapy.

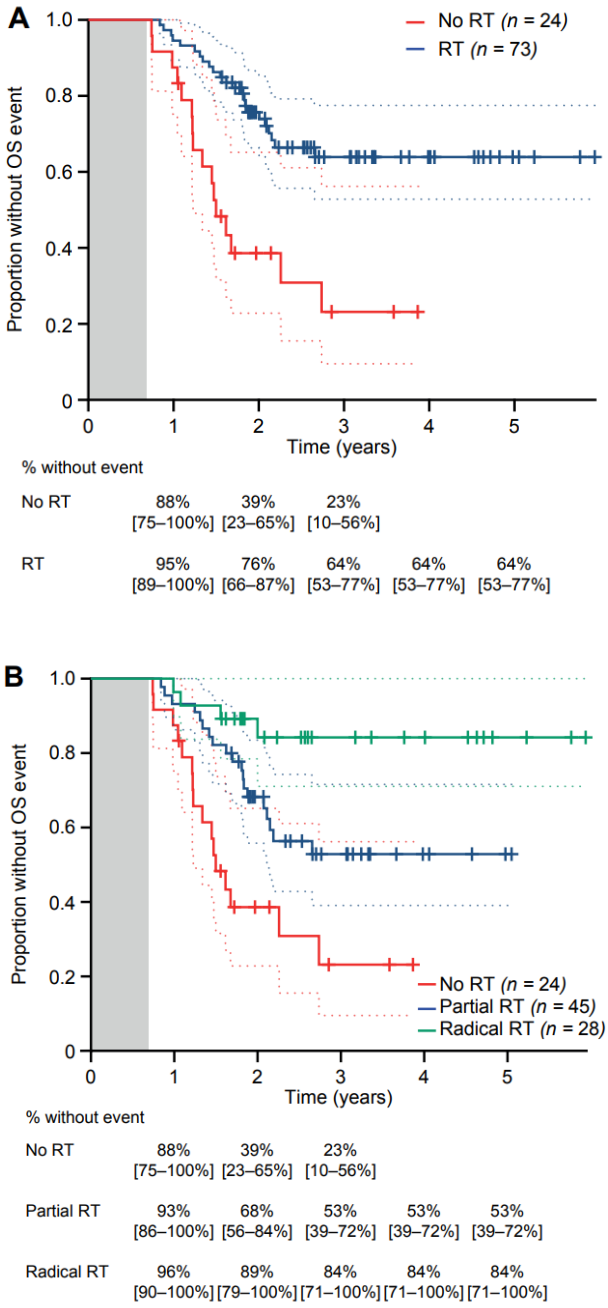




Dotted lines represent upper and lower 95% confidence intervals.

Abbreviations: EFS = event-free survival; RT = radiotherapy.

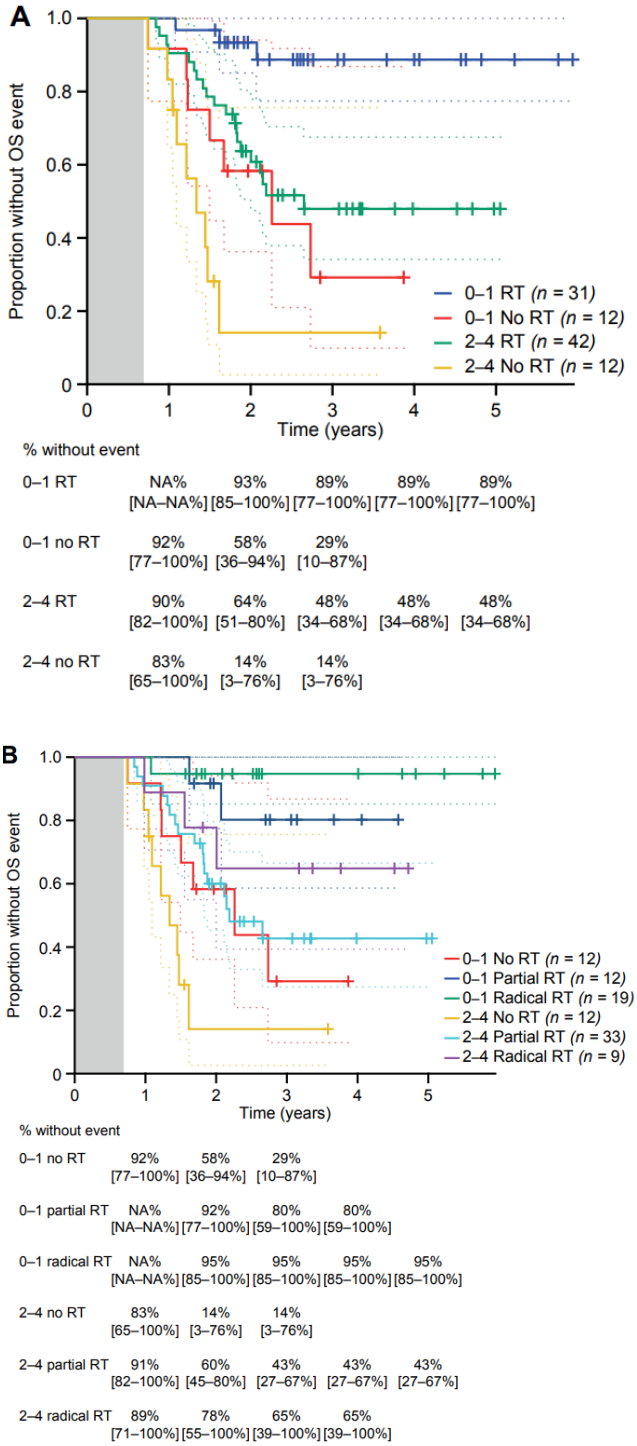
Fig. 2. Kaplan-Meier plot of OS: (A) in patients receiving versus not receiving radiotherapy and (B) in patients receiving radical, partial or no radiotherapy.



Dotted lines represent upper and lower 95% confidence intervals.

Abbreviations: OS = overall survival; RT = radiotherapy.

Fig. 3. Kaplan-Meier plots of OS by Oberlin prognostic score (0–1 or 2–4) in patients receiving versus not receiving radiotherapy and in patients receiving radical, partial or no radiotherapy.



Dotted lines represent upper and lower 95% confidence intervals.

Abbreviations: NA = not available; OS = overall survival; RT = radiotherapy.

Table 1. Baseline characteristics of patients in the landmark analysis

Characteristic	**Irradiation received, *n* (%)**			***P* value**
	Radical (*n* = 28)	Partial (*n* = 45)	None (*n* = 24)	
Median age, years (range)	5.6 (1–18)	10.1 (1–16)	11.1 (2–17)	0.095
Age group, *n* (%)				0.179
<1 year (*n* = 5)	3 (11)	1 (2)	1 (4)	
1–9 years (*n* = 48)	17 (61)	21 (47)	10 (42)	
≥10 years (*n* = 44)	8 (29)	23 (51)	13 (54)	
Disease risk, *n* (%)				0.503
High-risk mRMS[a]	19 (68)	36 (80)	19 (79)	
Non-high-risk mRMS	9 (32)	9 (20)	5 (21)	
Histology, *n* (%)				0.129
Embryonal	11 (39)	18 (40)	6 (25)	
Alveolar	14 (50)	27 (60)	17 (71)	
Other	3 (11)	0	1 (4)	
Primary site, *n* (%)				0.260
Favorable[†]	3 (11)	3 (7)	2 (8)	
Unfavorable[‡]	25 (89)	42 (93)	20 (83)	
No primary site identified	0	0	2 (8)	
Metastatic lesions, *n* (%)				0.001
1	10 (36)	4 (9)	5 (21)	
2–3	7 (25)	5 (11)	0	
≥4/ bone marrow involved/ multiple non-target	11 (39)	36 (80)	19 (79)	
Metastatic sites, *n* (%)				0.007
1	18 (64)	15 (33)	10 (42)	

2	7 (25)	19 (42)	7 (29)	
3	3 (11)	5 (11)	6 (24)	
4	0	6 (13)	1 (4)	
Metastatic site location, *n* (%)				
Lung	8 (29)	17 (38)	14 (58)	0.083
Bone	7 (25)	31 (59)	9 (38)	0.001
Bone marrow	2 (7)	8 (18)	3 (13)	0.473
Distant lymph node	8 (29)	13 (29)	8 (33)	0.919
Other	16 (57)	23 (51)	12 (50)	0.868
Randomized treatment, *n* (%)				0.240
Chemotherapy	18 (64)	20 (44)	11 (46)	
Bevacizumab + chemotherapy	10 (36)	25 (56)	13 (54)	
Oberlin score, *n* (%)[§]				0.026
0	7 (25)	5 (11)	4 (17)	
1	12 (43)	7 (16)	8 (33)	
2	4 (14)	12 (27)	1 (4)	
3	3 (11)	13 (29)	5 (21)	
4	2 (7)	8 (18)	6 (25)	

Abbreviations: mRMS = metastatic rhabdomyosarcoma.

P values compare radical versus partial versus no radiotherapy.

[*]The definition of high-risk mRMS (age ≥10 years, unfavorable primary site, bone or bone marrow metastasis and >2 metastatic sites) was based on the BERNIE study and did not exactly match the Oberlin criteria.

[†]Favorable sites: orbit, non-parameningeal, parameningeal, bladder/prostate, paratesticular/vagina.

[‡]Unfavorable sites: limbs, other.

[§]Oberlin score: based on the number of unfavorable prognostics factors present (age, site, bone or bone marrow involvement and number of metastatic sites).[2]

Table 2. Treatment delivered to primary, regional nodal and metastatic sites of disease divided by radical, partial or no irradiation group

	Treatment delivered		
Radiotherapy group	**Primary site**	**Local lymph nodes**	**Metastatic sites**
Radical (*n* = 28)	• 11 radiotherapy only • 14 radiotherapy and surgery – 10 complete resection – 2 partial resection – 2 uncertain • 3 surgery only – 3 complete resection testes/limb	• 7 radiotherapy only • 2 radiotherapy and surgery • 1 surgery only – 1 complete resection • 18 not applicable	• 24 radiotherapy only – 24 100% lesions irradiated • 4 radiotherapy and surgery – 4 100% lesions irradiated and partial resection
Partial (*n* = 45)	• 23 radiotherapy only • 17 surgery and radiotherapy • 2 surgery only – complete resection limb • 3 no treatment	• 14 radiotherapy only • 1 radiotherapy and surgery • 7 no treatment • 23 not applicable	• 22 radiotherapy only – 20 <100% lesions irradiated – 2 100% lesions irradiated at low (non-radical) dose • 23 no treatment
None (*n* = 24)	• 8 surgery only – 2 resection paratesticular primary – 4 complete resection – 2 partial resection • 14 no treatment • 2 no primary site identified	• 8 no treatment • 16 not applicable	• 3 surgery – 2 partial resection – 1 uncertain • 21 no treatment

Table 3. Effect of radiotherapy on EFS and OS for landmark analysis Day 221

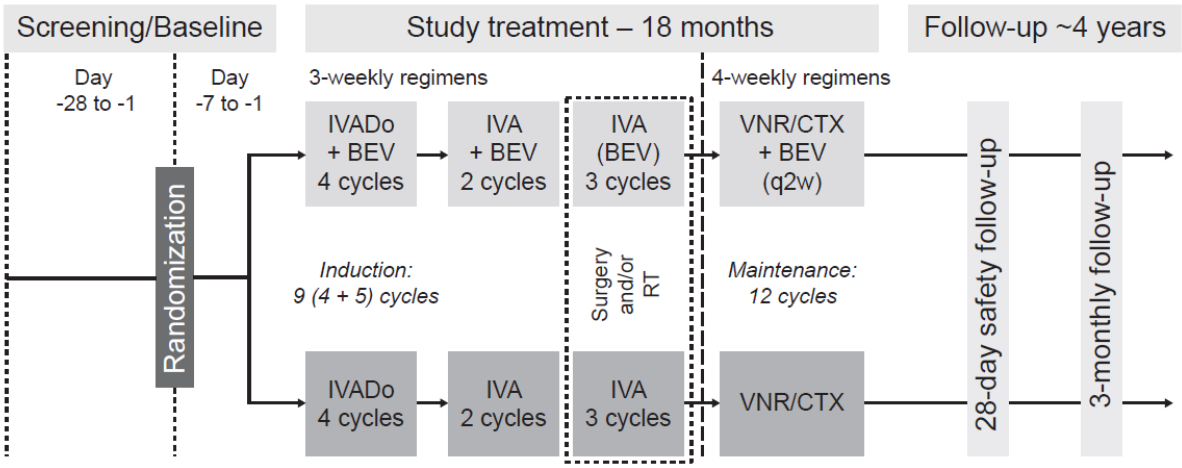
Comparison vs no radiotherapy		**EFS**				**OS**			
		HR	SE	95% CI	*P* value	HR	SE	95% CI	*P* value
Any irradiation	Unadjusted	0.505	0.284	0.289–0.881	0.01620	0.292	0.329	0.153–0.555	0.00018
	Adjusted	0.520	0.340	0.267–1.011	0.05405	0.249	0.379	0.119–0.524	0.00025
Partial irradiation	Unadjusted	0.522	0.310	0.285–0.959	0.03620	0.402	0.338	0.207–0.778	0.00688
	Adjusted	0.512	0.359	0.253–1.035	0.06211	0.305	0.385	0.143–0.648	0.00202
Radical irradiation	Unadjusted	0.475	0.385	0.223–1.009	0.05290	0.126	0.575	0.041–0.390	0.00032
	Adjusted	0.536	0.469	0.214–1.345	0.18413	0.110	0.715	0.027–0.446	0.00200

Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; OS = overall survival; SE = standard error.

Variables: treatment (as randomized), disease risk, age, histological classification, and metastatic lesion count.

SUPPLEMENTARY MATERIAL

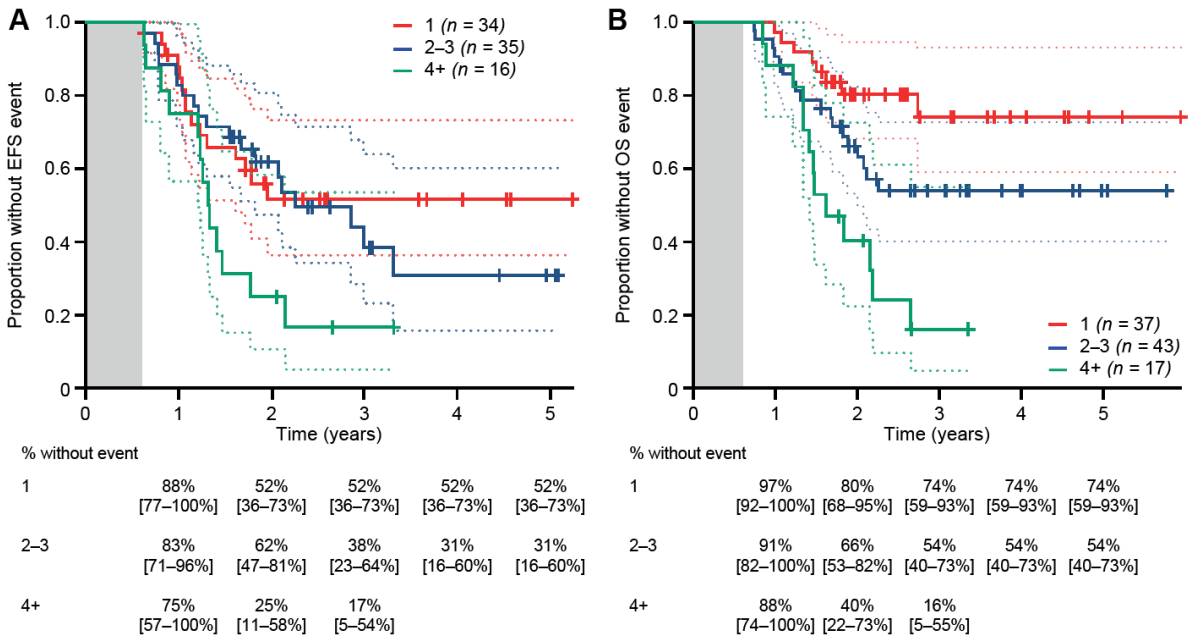
Supplementary Figure S1. BERNIE study design.



A = actinomycin-D; BEV = bevacizumab; CTX = cyclophosphamide; Do = doxorubicin;

I = ifosfamide; q2w = every 2 weeks; RT = radiotherapy; V = vincristine; VNR = vinorelbine.

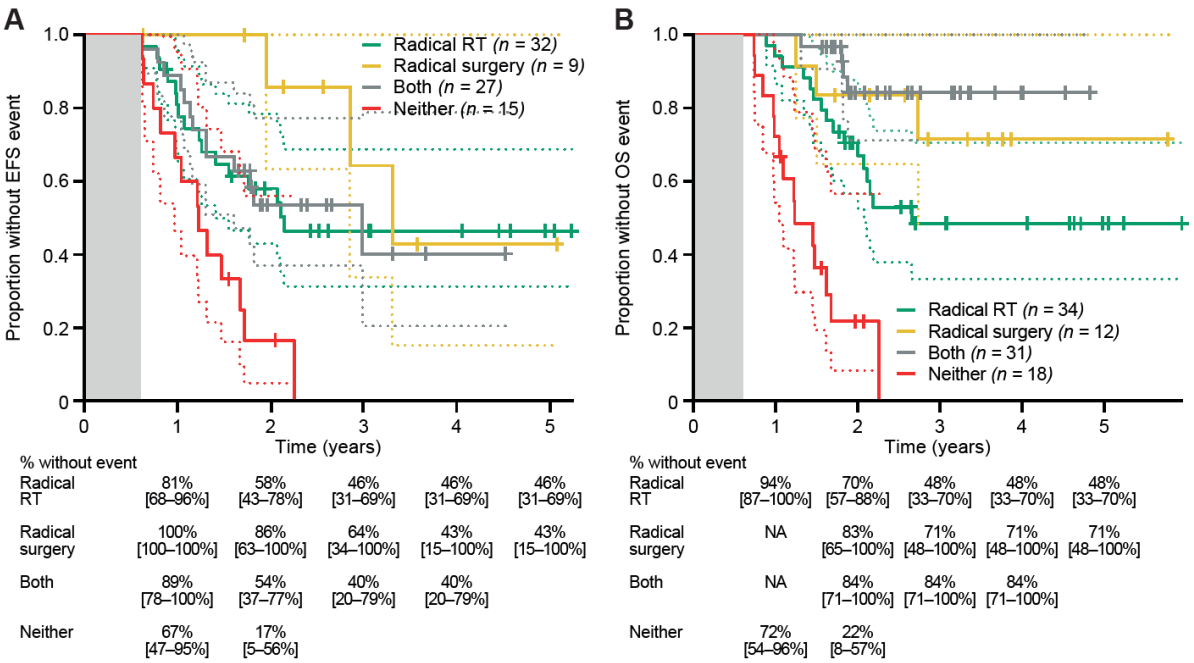
Supplementary Figure S2. Kaplan-Meier plot of (A) EFS and (B) OS by number of metastatic sites.



Dotted lines represent upper and lower 95% confidence intervals.

EFS = event-free survival; OS = overall survival.

Supplementary Figure S3. Kaplan-Meier plot of (A) EFS and (B) OS by local therapy to primary site.



% without event					
Radical RT	81% [68–96%]	58% [43–78%]	46% [31–69%]	46% [31–69%]	46% [31–69%]
Radical surgery	100% [100–100%]	86% [63–100%]	64% [34–100%]	43% [15–100%]	43% [15–100%]
Both	89% [78–100%]	54% [37–77%]	40% [20–79%]	40% [20–79%]	
Neither	67% [47–95%]	17% [5–56%]			

% without event					
Radical RT	94% [87–100%]	70% [57–88%]	48% [33–70%]	48% [33–70%]	48% [33–70%]
Radical surgery	NA	83% [65–100%]	71% [48–100%]	71% [48–100%]	71% [48–100%]
Both	NA	84% [71–100%]	84% [71–100%]	84% [71–100%]	
Neither	72% [54–96%]	22% [8–57%]			

Dotted lines represent upper and lower 95% confidence intervals.

EFS = event-free survival; OS = overall survival; RT = radiotherapy

Supplementary Table S1. Factors contributing to the Oberlin prognostic score.

	Oberlin score					
Patients, *n*	0 (*n* = 16)	1 (*n* = 27)	2 (*n* = 17)	3 (*n* = 21)	4 (*n* = 16)	Total (*N* = 97)
Unfavorable site (limbs or other)	0	18	11	17	16	62
≥3 metastatic sites	0	0	4	12	16	32
Bone or bone marrow involvement	0	4	12	18	16	50
Age (<1 or ≥10 years at diagnosis)	0	5	7	16	16	44