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Scientific Article

Effect of Radiotherapy Dose on Outcome in Nonmetastatic Ewing Sarcoma

Josephine Kersting,[a,b,*] Andreas Ranft, PhD,[a,b,*] Vivek Bhadri, MD, PhD,[c] Bénédicte Brichard, MD,[d] Stéphane Collaud, MD,[e] Sona Cyprová, MD,[f] Hans Eich, MD,[g] Torben Ek, MD, PhD,[h] Hans Gelderblom, MD, PhD,[i] Jendrik Hardes, MD,[b,j] Lianne Haveman, MD,[k] Wolfgang Hartmann, MD,[l] Peter Hauser, MD, PhD,[m] Philip Heesen,[a] Heribert Jürgens, MD,[n] Jukka Kanerva, MD,[o] Thomas Kühne, MD,[p] Anna Raciborska, MD,[q] Jelena Rascon, MD, PhD,[r] Victor Rechl,[a] Arne Streitbürger, MD,[b,j] Beate Timmermann, MD,[b,s] Yasmine Uhlenbruch, MD,[t] and Uta Dirksen, MD[a,b,*]

[a]Pediatrics III, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [b]German Cancer Consortium, Partnersite Essen, Essen, Germany; [c]Chris O' Brien Lifehouse, Camperdown, Australia Faculty of Medicine and Health, University of Sydney, Camperdown, Australia; [d]Cliniques Universitaires Saint Luc, Department of Pediatric Haematology and Oncology, Université Catholique de Louvain, Brussels, Belgium; [e]Department of Thoracic Surgery, Lung Clinic, Cologne-Merheim City Hospital, University of Witten Herdecke, Cologne, Germany; [f]Charles University, Motol Children's Hospital, Prague, Czech Republic; [g]Radiotherapy and Radiooncology, University Hospital Muenster, West German Cancer Center Network, Muenster, Germany; [h]Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [i]Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands; [j]Clinic of Orthopedics, University Hospital Essen, West German Cancer Centre, Essen, Germany; [k]Department of Solid Tumors, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; [l]Gerhard Domagk Institute for Pathology, University Hospital Muenster, West German Cancer Center Network, Muenster, Germany; [m]Second Department of Pediatrics, Semmelweis University, Budapest, Hungary; [n]Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, West German Cancer Center Network, Münster, Germany; [o]HUS Helsinki University Hospital, New Children's Hospital, Div. Hematology and Stem Cell Transplantation, Helsinki, Finland; [p]Department of Oncology/Haematology, University Children's Hospital Basel, Basel, Switzerland; [q]Department of Oncology and Surgical Oncology for Children and Youth, Mother and Child Institute, Warsaw, Poland; [r]Center for Pediatric Oncology and Hematology, Vilnius University Hospital Santaros Klinikos, Vilnius University, Vilnius, Lithuania; [s]Clinic for Particle Therapy, West German Proton Beam Centre, University Hospital Essen, West German Cancer Centre, German Cancer Research Centre (DKTK), Essen, Germany; and [t]St. Josef's Hospital Bochum, University Hospital, Bochum, Germany

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*Corresponding authors: Josephine Kersting, XX; Andreas Ranft, PhD; and Uta Dirksen, MD;; E-mails: Josephine.Kersting@uk-essen.de Andreas.Ranft@uk-essen.de Uta.Dirksen@uk-essen.de

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Purpose: Radiation therapy (RT) is an integral part of Ewing sarcoma (EwS) therapy. The Ewing 2008 protocol recommended RT doses ranging from 45 to 54 Gy. However, some patients received other doses of RT. We analyzed the effect of different RT doses on event-free survival (EFS) and overall survival (OS) in patients with EwS.

Methods and Materials: The Ewing 2008 database included 528 RT-admitted patients with nonmetastatic EwS. Recommended multimodal therapy consisted of multiagent chemotherapy and local treatment consisting of surgery (S&RT group) and/or RT (RT group). EFS and OS were analyzed with uni- and multivariable Cox regression models including known prognostic factors such as age, sex, tumor volume, surgical margins, and histologic response.

Results: S&RT was performed in 332 patients (62.9%), and 145 patients (27.5%) received definitive RT. Standard dose ≤ 53 Gy (d1) was admitted in 57.8%, high dose of 54 to 58 Gy (d2) in 35.5%, and very high dose ≥ 59 Gy (d3) in 6.6% of patients. In the RT group, RT dose was d1 in 11.7%, d2 in 44.1%, and d3 in 44.1% of patients. Three-year EFS in the S&RT group was 76.6% for d1, 73.7% for d2, and 68.2% for d3 ($P = .42$) and in the RT group 52.9%, 62.5%, and 70.3% ($P = .63$), respectively. Multivariable Cox regression revealed age ≥ 15 years (hazard ratio [HR], 2.68; 95% confidence interval [CI], 1.63-4.38) and nonradical margins (HR, 1.76; 95% CI, 1.05-2.93) for the S&RT group (sex, $P = .96$; histologic response, $P = .07$; tumor volume, $P = .50$; dose, $P = .10$) and large tumor volume (HR, 2.20; 95% CI, 1.21-4.0) for the RT group as independent factors (dose, $P = .15$; age, $P = .08$; sex, $P = .40$).

Conclusions: In the combined local therapy modality group, treatment with higher RT dose had an effect on EFS, whereas higher dose of radiation when treated with definitive RT was associated with an increased OS. Indications for selection biases for dosage were found. Upcoming trials will assess the value of different RT doses in a randomized manner to control for potential selection bias.

Introduction

Ewing sarcoma (EwS), a highly aggressive bone and soft tissue tumor is the second-most common bone tumor in children, adolescents, and young adults and accounts for about 2% of cancers in childhood, with a peak incidence at the age between 10 and 20 years.[1,2] Approximately 20% to 25% of the patients present with distant metastases at time of diagnosis.[3] The overall survival (OS) rate for patients without metastases is between 65% and 75%, and for patients with metastases the 5-year survival rate is approximately 30%.[3] Therefore, metastasis at diagnosis is the most important prognostic factor.[3-5] Several other prognostic factors in nonmetastatic EwS have been reported, including older age (>14 years), male sex, fever and anemia at diagnosis, high serum lactate dehydrogenase (LDH) levels, tumor site outside of the extremities, poor histologic response to neoadjuvant chemotherapy,[6-8] and larger tumor volume.[9] Current treatment protocols consist of multiagent systemic therapy and local control with either surgery, radiation therapy (RT), or both.[10] In the Ewing 2008 trial, patients were treated with 6 cycles of VIDE (vincristine, ifosphamide, doxorubicine, etoposide) induction therapy[11] followed by local therapy consisting of either definitive surgery, definitive RT, or a combination of both.[10] Since it was first described by James Ewing, the tumor has been shown to be radiosensitive.[12] Currently, European and North American guidelines recommend a total RT dose of 45 to 54 and at least 55.8 Gy, respectively, to the primary tumor.[1,13] The given radiation dose to an individual patient may vary according to individual risk estimation and may depend on factors such as surgical margins, tumor size, site (critical organ involvement such as the lungs), and the age of the patient. Today, definitive RT is the local treatment option of choice in inoperable tumors,[1] and total doses up to 54 Gy in Europe and at least 55.8 Gy in North America are proposed.[11,13] RT in combination with surgery can be applied either pre- or postoperatively.[1] Postoperative RT is the universal treatment of choice in incomplete resection of the primary tumor with a dosage up to 45 to 54 Gy delivered to the tumor bed.[10,12,14] In Europe, even completely resected tumors presenting a poor histologic response to neoadjuvant chemotherapy[11] receive RT with a total dose of approximately 45 Gy.[14] Current studies have shown that postoperative RT has been significantly effective also in tumors with a volume ≥ 200 mL and 100% tumor necrosis.[3] Preoperative RT is usually applied to ensure operability of the tumor.[15] In the EICESS 92 trial, a high proportion of patients was treated with preoperative RT, and results demonstrated improved local control in these patients; however, there was no difference in event-free survival (EFS) compared with patients treated with postoperative RT.[16] Although systemic treatment has been consequently developed in randomized clinical trials, the optimal local treatment is still discussed controversially.[17] This retrospective analysis aimed to evaluate the effect of different RT dosages on EFS and OS in nonmetastatic EwS by taking into consideration several known prognostic factors.

Methods and Materials

Between 2009 and 2019, a total of 1421 patients with untreated, histologically confirmed EwS were registered in the Ewing 2008 trial database from institutions in Germany, Austria, Belgium, Czech Republic, The

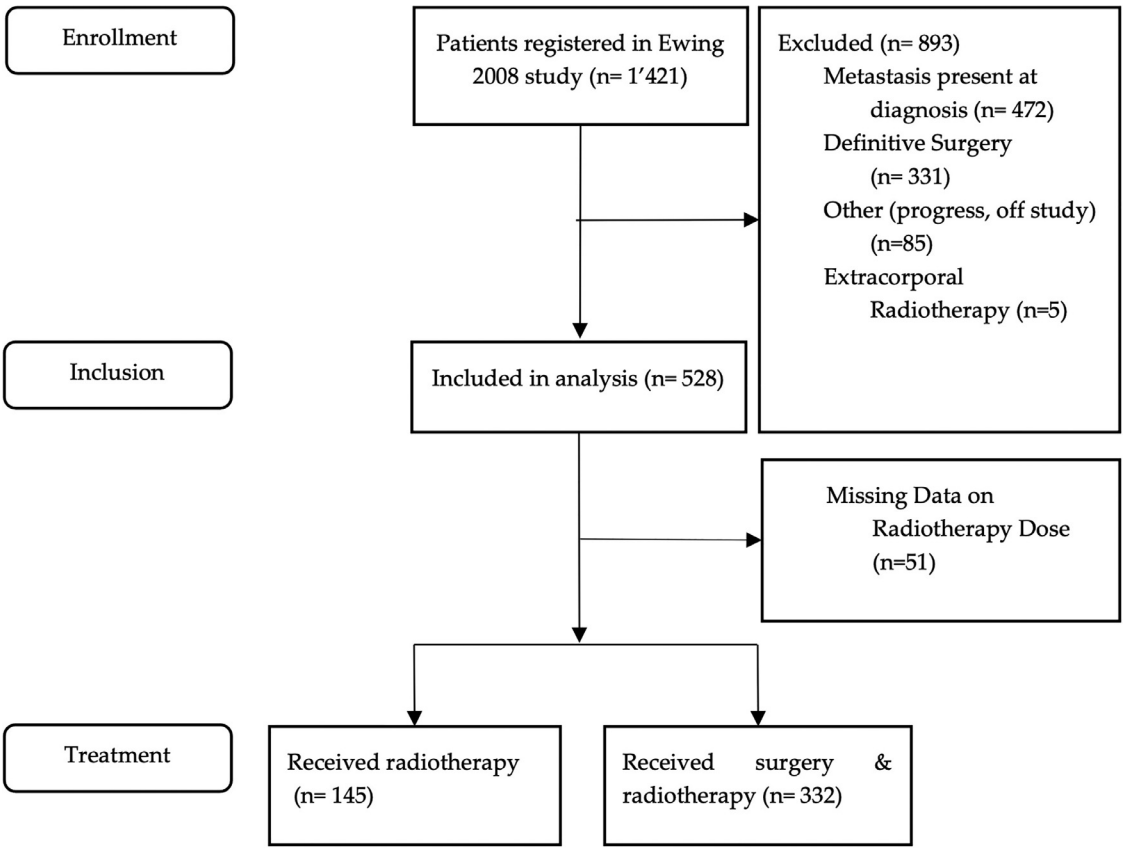

Figure 1 Patient flowchart.

Netherlands, Sweden, Poland, Hungary, Switzerland, Australia, Finland, and Lithuania. In total, 37.2% (528 out of 1421) of the patients met the criteria to be included into this analysis. Specifically, we included patients who did not present with metastatic disease at time of primary diagnosis and received either definitive RT as a local treatment or RT pre- or postoperatively. Excluded were patients who showed a progression during the trial or received extracorporeal RT during surgery (Fig. 1). At time of diagnosis, pulmonary metastases were excluded by chest computed tomography. Bone metastases were excluded by bone scan, positron emission tomography, magnetic resonance imaging (MRI), or biopsy if any doubts were present. Concerning bone marrow metastasis, exclusion was performed by at least aspirates from ≥2 sites and biopsy from ≥1 site, distant from the primary tumor. Soft tissue lesions and regional lymph nodes were excluded by whole-body fluorodeoxyglucose positron emission tomography or MRI and ultrasound. If indicated, abdominal computed tomography or MRI was additionally performed. Finally, metastases were then confirmed by biopsy. In our analysis, 96.8% (511 out of 528) of patients received ≤6 VIDE cycles according to the Ewing 2008 protocol; data of the remaining 3.2% were missing. The decision about the local treatment and consequently pre- or postoperative RT was made according to the surgical margins, location of the tumor, and histologic response to the induction chemotherapy. The Ewing 2008 protocol recommended doses of up to 54.0 Gy in preoperative radiation and postoperative radiation doses up to 54 Gy in intralesional surgery or marginal surgery with poor histologic response (≥10% residual tumor cells). Postoperative radiation with 45 Gy was recommended in marginal surgery with good histologic response (<10% residual tumor cells) and according to national guidelines in wide resection with poor histologic response (≥10% residual tumor cells). Recommendation for RT doses in local treatment with definitive RT was also 54.0 Gy. Patients were then assigned into three risk groups and further treated according to the Ewing 2008 protocol.[5,6,18-20] Table 1 gives an overview of the patient demographics as well as tumor characteristics. As mentioned previously, for this analysis patients were broadly subdivided into 2 main groups according to the local therapy modality they received, specifically a combined local treatment consisting of surgery and RT or definitive RT, including 370 and 158 patients, respectively. Patients within these 2 groups were then further subdivided into 3 groups according to the dose of radiation they received, namely ≤53, 54 to 58, or ≥59 Gy. As mentioned previously, recommended RT doses in the Ewing 2008 protocol were 45 to 54 Gy. The first cutoff was therefore decided

Table 1 Patient demographics and tumor characteristics

	Definitive RT (n = 158)		Surgery and RT (n = 370)		
Variable	**No.**	**%**	**No.**	**%**	***P* value**
Country					.026
Germany	107	67.7	249	67.3	
Austria	3	1.9	34	9.2	
Belgium	7	4.4	10	2.7	
Czech Republic	5	3.2	13	3.5	
The Netherlands	17	10.8	25	6.8	
Sweden	5	3.2	9	2.4	
Poland			6	1.6	
Hungary	3	1.9	5	1.4	
Switzerland	5	3.2	6	1.6	
Australia	6	3.8	7	1.9	
Finland			4	1.1	
Lithuania			2	0.5	
Sex					.924
Male	88	55.7	208	56.2	
Female	70	44.3	162	43.8	
Age					.849
<15 y	83	52.5	191	51.6	
≥15 y	74	46.8	179	48.4	
Primary tumor site					<.001
Pelvis	65	41.1	69	18.6	
Abdomen	4	2.5	13	3.5	
Spine	42	26.6	37	10.0	
Chest	17	10.8	96	25.9	
Head and neck	18	11.4	35	9.5	
Upper extremities	3	1.9	35	9.5	
Lower extremities	9	5.7	85	23.0	
Tumor volume					.488
<200 mL	102	64.6	224	60.5	
≥200 mL	54	34.2	139	37.6	
Histologic response					-
Good (<10% vital tumor cells)			178	48.1	
Poor (≥10% vital tumor cells)			128	34.6	
Surgical margins					-
Radical			242	65.4	
Marginal/intralesional			100	27.0	
Number of completed VIDE courses					.376
2-5	6	3.8	8	2.1	
≥6	149	94.3	348	94.1	

(*continued on next page*)

Table 1 (*Continued*)

	Definitive RT (n = 158)		Surgery and RT (n = 370)		
Variable	**No.**	**%**	**No.**	**%**	***P* value**
RT dose					<.001
≤53 Gy	17	10.8	192	51.9	
54-58 Gy	64	40.5	118	31.9	
≥59 Gy	64	40.5	22	5.9	

Abbreviation: RT = radiation therapy, Gy = gray.

according to the recommendations and by clinical evaluation. The second cutoff was a decision also based on clinical evaluation, the number of patients who received the different dose amounts, and on the upcoming iEuroEwing protocol, in which, within both high-risk groups of patients, a radiation dose of 59.4 Gy is 1 of the 2 possibilities for randomization.

Statistical analysis

EFS and OS rates were estimated using the Kaplan-Meier method.[21] After assessment of the proportional hazards assumption, 2 separate univariable and multivariable analyses were performed by Cox regression models because patients with a combined local treatment modality presented histologic response and surgical margins as prognostic factors and patients treated with definitive RT did not, as these variables are only available after surgery was performed. Overall, prognostic factors such as age, sex, tumor volume, histologic response, and surgical margins for the combined local treatment modality group and age, sex, and tumor volume for the patients treated with definitive RT were included in the analysis. Hazard ratios (HR) and 95% confidence intervals (CI) are presented. Furthermore, χ^2 analyses were performed to evaluate a potential correlation between prognostic factors and RT doses.

Ethical considerations

Approval for the study was obtained from the Ethical Committee of the Westphalia-Lippe Medical Association (Ärztekammer Westfalen-Lippe) of the Westphalien Wilhems University, Münster, Germany. The positive ethics vote was received on December 16, 2008.

Results

A total of 528 patients with a diagnosed nonmetastatic EwS received RT and were therefore included in the analysis. Specifically, 62.9% (332 out of 528) of the patients had surgery and were treated with pre- or postoperative RT. Thirty-two patients received preoperative and the remaining 300 patients received postoperative RT. The last dose of preoperative RT was administered within a range of 21 to 167 days before the date of surgery, with a median of 54 days. Postoperative RT was conducted within a range of 1 to 423 days after surgery, with a median of 79 days. Patients who received extracorporeal RT during surgery were excluded from the analysis. The remaining 27.5% (145 out of 528) of patients were treated with definitive RT. Median follow-up was 3.52 and 2.86 years in the combined local treatment modality and the definitive RT group, respectively. Information on the RT doses received was missing in 51 patients. Figure 1 presents a flow diagram with the number of patients at each stage of the study, as well as the patients excluded and their reason for exclusion. Within the surgery and RT group, 192 patients received a dose of ≤53 Gy, 118 patients received 54 to 58 Gy, and 22 patients ≥59 Gy. The group of patients who received definitive RT as a local treatment included 17, 64, and 64 patients in the ≤53, 54 to 58, and ≥59 Gy groups, respectively. As mentioned previously, Table 1 gives an overview of the patient demographics and tumor characteristics. No differences between the 2 groups, except for the primary tumor site, RT doses received ($P < .001$), and country ($P = .026$), were observed. Specifically, more patients with pelvic and spinal tumors received definitive RT as a local treatment modality. More often, patients with thoracic, lower, and upper extremity tumors received a combined local treatment consisting of surgery and RT. Concerning the differences in countries, all patients treated in Finland, Lithuania, and Poland were treated with surgery and RT. Austrian patients were also more often treated with the combined treatment modality. Regarding RT doses, patients treated with definitive RT received higher doses compared with patients treated with surgery and RT.

Combined local therapy modality (surgery and RT)

Within the surgery and RT group, 192 patients received a dose of ≤53 Gy, 118 patients received 54 to 58

Gy, and 22 patients ≥59 Gy. Kaplan-Meier analysis revealed a 3-year EFS of 76.6%, 73.7%, and 68.2%, respectively, with a total EFS of 75.0% (P = .423), as seen in Fig. 2. Total OS was 85.8%, with no difference between the subgroups (88.5%, 82.2%, and 81.8%, respectively; P = .236).

As shown in Table 2, multivariable Cox-regression analysis revealed that patients ≥15 years of age were at higher risk of any event, with an HR of 2.68 (95% CI, 1.63-4.38; P < .001), compared with younger patients. Similar results were found for OS (HR, 2.31; 95% CI, 1.21-4.42; P = .011). There was no difference in outcome

Table 2 HRs of multivariable analysis (EFS and OS) for patients treated with surgery and radiation therapy

			95% CI	
EFS	***P* value**	**HR**	**Lower**	**Upper**
Age	<.001	2.68	1.63	4.38
Sex	.959	1.01	0.63	1.62
Surgical margins	.032	1.76	1.05	2.93
Histologic response	.068	1.60	0.97	2.64
Tumor volume	.497	1.18	0.73	1.90
≤53 Gy	.098			
54-58 Gy	.782	1.08	0.63	1.84
≥59 Gy	.032	2.61	1.08	6.27
			95% CI	
OS	***P* value**	**HR**	**Lower**	**Upper**
Age	.011	2.31	1.21	4.42
Sex	.774	1.10	0.59	2.05
Surgical margins	.004	2.58	1.35	4.93
Histologic response	.182	1.59	0.81	3.12
Tumor volume	.150	1.60	0.85	3.01
≤53 Gy	.281			
54-58 Gy	.414	1.34	0.66	2.70
≥59 Gy	.121	2.39	0.80	7.15

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

for male or female patients in EFS (HR, 1.01; 95% CI, 0.63-1.62; P = .959) and OS (HR, 1.10; 95% CI, 0.59-2.05; P = .774). Intralesional or marginal surgical margins were associated with an increased risk of any event compared with wide surgical margins (HR, 1.76; 95% CI, 1.05-2.93; P = .032) and with a decreased OS (HR, 2.58; 95% CI, 1.35-4.93; P = .004). Our analysis revealed a risk of any event in poor histologic response, with a HR of 1.60 (95% CI, 0.97-2.64; P = .068) and an OS HR of 1.59 (95% CI, 0.81-3.12; P = .182).

For larger tumor volume (≥200 mL) the EFS HR was 1.18 (95% CI, 0.73-1.90; P = .497) and OS HR was 1.60 (95% CI, 0.85-3.01; P = .150) compared with smaller tumor volume (<200 mL). EFS HR for RT doses of 54 to 58 and ≥59 Gy were 1.08 (95% CI, 0.63-1.84; P = .782) and 2.61 (95% CI, 1.08-6.27; P = .032), respectively. Treatment with RT dose of ≥59 Gy was associated with an increased risk of any event compared with treatment with ≤53 Gy. For OS, the HRs were 1.34 (95% CI, 0.66-2.70; P = .414) and 2.39 (95% CI, 0.80-7.15; P = .17), for the 54 to 58 and ≥59 Gy treatment groups, respectively.

We also analyzed the selection of RT doses based on prognostic factors, namely histologic response to induction chemotherapy and surgical margins. Results show that patients with a wide surgical margin received a lower RT dose compared with patients with marginal or intralesional surgical margins (P < .001). Furthermore, patients with a poor histologial response to induction chemotherapy received higher doses of RT compared with patients with a good histologic respone (P < .001).

Definitive RT

Patients who received definitive RT were treated with total doses ranging from 44 to 73 Gy. Specifically, 17 patients received a dose of ≤53 Gy, 64 patients received 54 to 58 Gy, and 64 patients ≥59 Gy. The 3-year EFS was 52.9%, 62.5%, and 70.3%, respectively, with a total EFS of 64.8% (P = .627; Fig. 3). Three-year OS was 64.7%, 81.3%, and 84.4%, respectively, with a total OS of 80.7% (P = .263).

Table 3 shows the results of the multivariable Cox regression analysis comparing different RT doses in patients treated with definitive RT. Subgroup analyses showed risk of any event in patients' age or sex (≥15 vs <15 years or male vs female patients), with an HR of 1.68 (95% CI, 0.95-2.97; P = .077) and an HR of 1.28 (95% CI, 0.72-2.26; P = .401), respectively. OS results showed an HR of 1.28 (95% CI, 0.60-2.73; P = .520) and an HR of 1.12 (95% CI, 0.52-2.41; P = .766), respectively.

Large initial tumor volume (≥200 mL) was associated with an increased risk of any event (HR, 2.20; 95% CI, 1.21-4.00; P = .009) and a decreased OS (HR, 2.52; 95% CI, 1.14-5.55; P = .022). Concerning RT, for doses of 54 to 58 and ≥59 Gy received, EFS HR were 0.65 (95% CI, 0.28-1.49; P = .307) and 0.42 (95% CI, 0.17-1.04; P = .060), respectively. Furthermore, OS HR were 0.42 (95% CI, 0.15-1.15; P = .091) and 0.32 (95% CI, 0.11-0.92; P = .035), respectively. Thus, patients who received the highest (≥59 Gy) dose of RT, when treated with RT alone, had a better OS than patients treated with the lowest dose of radiation (≤53 Gy).

A χ^2 analysis for the patients treated with definitive RT and doses given according to tumor volume was performed. Results show that patients with a larger tumor volume (≥200 mL) tended to receive higher doses of RT (*P* = .091).

Discussion

In this retrospective analysis, we evaluated the effect of different radiation doses on EFS and OS in patients with nonmetastatic EwS. All patients were prospectively registered in the Ewing 2008 database. We evaluated EFS and OS by using the Kaplan-Meier method and performed 2 different multivariable Cox regression models: one for patients treated with a combined local treatment consisting of surgery and RT and a second for treatment with

definitive RT. In the combined local treatment modality group, patients treated with the highest dose (≥59 Gy) of radiation had an increased risk of any event compared with the patient treated with the lowest dose of radiation (≤53 Gy). No difference in OS was shown. In patients who received definitive RT, high-dose RT (≥59 Gy) was associated with an improved OS, but no difference in EFS was demonstrated in this group. The data were prospectively collected but retrospectively analyzed as the analysis addressed in this paper was not part of the trial objective. It was performed in a large cohort of unselected patients registered into the international Ewing 2008 trial of the

Table 3 HRs of multivariable analysis (EFS and OS) for patients treated with definitive radiation therapy

			95% CI	
EFS	***P* value**	**HR**	**Lower**	**Upper**
Age	.077	1.68	0.95	2.97
Sex	.401	1.28	0.72	2.26
Tumor volume	.009	2.20	1.21	4.00
≤53 Gy	.146			
54-58 Gy	.307	0.65	0.28	1.49
≥59 Gy	.060	0.42	0.17	1.04
			95% CI	
OS	***P* value**	**HR**	**Lower**	**Upper**
Age	.520	1.28	0.60	2.73
Sex	.766	1.12	0.52	2.41
Tumor volume	.022	2.52	1.14	5.55
≤53 Gy	.100			
54-58 Gy	.091	0.42	0.15	1.15
≥59 Gy	.035	0.32	0.11	0.92

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

Cooperative Ewing Sarcoma Study group (CESS). Data on the patients were prospectively collected over a period of approximately 10 years. All patients were treated with the same treatment protocol; therefore, confounding effects of major variations of therapeutic concepts were minimized. Moreover, modern RT techniques, such as intensity modulated RT, tomotherapy, and proton beam RT were available. We are aware that the retrospective study is limited by selection bias, and our data indicate that patients with negative prognostic factors, namely poor histologic response and marginal/intralesional margins for the combined local treatment group and large tumor volume in the definitive RT group, more likely received higher RT dose. The favorable outcome in these high-risk patients may indicate a benefit from high-dose RT that remains to be proven by a systematic randomized clinical trial.

Laskar et al[22] evaluated a dose escalation (70.2 Gy) versus the standard RT dose (55.8 Gy) in a randomized controlled study and found a trend toward an increased OS in the group of patients treated with higher doses of RT (40.4% vs 62.5%; $P = .08$). They also demonstrated in their randomized, controlled study a significantly increased local control in escalated doses compared with standard dose. Local control rate after RT was also retrospectively analyzed after a study conducted by St. Jude Children's Research Hospital, in which patients received higher dose after poor histologic response to chemotherapy or because of a larger tumor size. This study reported a strong correlation between RT doses received, local tumor control, and primary tumor size. Specifically, for patients receiving 35 Gy, local tumor control was 90% for lesions <8 cm versus 52% for tumors ≥8 cm.[23] Furthermore, Paulino et al[24] also retrospectively evaluated the local control of tumors according to dose and tumor size and showed that higher doses of RT (≥49 Gy) for tumors <8 cm and RT doses of ≥54 Gy, thus higher, for tumors >8 cm were associated with a superior 10-year local control. Similar results were shown by Talleur et al,[25] who also found that dose-escalation in unresectable, large tumors (≥8 cm) was associated with an increase in local control. Stahl et al[26] evaluated the risk of recurrence in 714 patients treated within the GPOHCESS 81, CESS 86, or EICESS 92 trials. The analysis demonstrated a long median time of relapse, specifically, 563 days for localized disease compared with 434 days in primary disseminated disease ($P < .001$). Furthermore, early relapse (within 2 years) was associated with a poor prognosis, and patients with a local relapse showed a superior outcome compared with systemic or combined relapse. However, the reason for the difference in relapse and a potential association with treatment modality still remains unclear. One limitation of our analysis is the lack of long-term data to evaluate local recurrence and a potential association with RT doses.

Decisions regarding local treatment modalities for EwS of the pelvis require careful consideration, as these tumors are known to present with a large tumor volume at diagnosis, making a resection with wide surgical margins very challenging. At the same time, surgery and RT in pelvic EwS are both associated with an increased risk of invasion of proximal anatomic structures.[27,28] Andreou et al[27] retrospectively evaluated data from the Euro-E.W.I.N.G.-99 trial of different local treatment modalities in localized pelvic EwS on EFS, OS, and local control. Concerning nonsacral pelvic tumors, treatment with surgery and RT was associated with an increased probability of OS and local control rate. No difference in the EFS, OS, or local control has been shown between definitive RT and RT combined with surgery in sacral EwS.[27] The Scandinavian Sarcoma group showed similar results in their study, suggesting definitive RT as a treatment of choice for these tumors.[29] With new techniques, radiation can be optimized with a high precision, and doses can be adapted, especially using proton therapy,[15] and clinical results are encouraging.[30] Specifically, comparable and even excellent local control and OS results could be achieved with an improved dose distribution.[30]

The timing of RT and with it the question if preoperative RT is beneficial remain unclear. Results of the CESS 86 and EICESS 92 trials, including 153 patients who received postoperative RT, showed that patients with early onset postoperative irradiation demonstrated a trend for improved local control compared with patients with a later onset; however, no effect on EFS and OS was found.[31] Previous analysis of the Euro-E.W.I.N.G.-99 study, CESS 81, and CESS 86 studies on preoperative RT evaluated it as nonbeneficial; however, the EICESS 92

study assessed it as favorable.[16,32] Histologic response is an important prognostic factor in EwS and triggers dose intensification[6,33]; preoperative RT, however, would bias the histologic response assessment.[15,17] Robust predictive biomarker for risk classification may supersede histologic response in the future.[1,3]

The 2 upcoming European EwS trials under the auspice of the EuroEwing Consortium will include randomized questions on RT dose. The Inter-Ewing-1 study is planning a randomization with fixed doses of a high and a low RT dose for patients who qualify for a definitive RT or patients eligible for postoperative RT.[15] The iEuroEwing trial (European Union Drug Regulating Authorities Clinical Trials Database [EUDRACT] No. 2019-004153-93) will perform a risk-adapted stratification in 4 groups and then further randomize the patients within the groups into a higher and a lower RT standard dose with a difference of 9 Gy each[15] and collect RT plans to analyze other possible confounding factors, such as target volume. Our analysis shows that it is time to randomize local therapy modalities to define an optimal treatment for patients with EwS and other solid malignoma that require a multimodal treatment approach.

Conclusion

Patients treated with a combined local therapy modality and higher doses of RT showed an increased risk for any event; however, there was no difference in OS. Patients treated with definitive RT as a local treatment showed an increased OS when treated with higher dose but no difference in EFS. Indications for selection biases for dosage were found, suggesting that higher RT doses might, at least partially, mitigate the unfavorable prognostic factors.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101269.

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