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Original Research

Association between local treatment modalities and event-free survival, overall survival, and local recurrence in patients with localised Ewing Sarcoma. Report from the Ewing 2008 trial

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Abstract ***Background:*** Local treatment is a crucial element in the standard of care for Ewing sarcoma (EWS). While systemic treatment is improved in randomised clinical trials, local treatment modalities are discussed controversially. We analysed the association between local therapy and event-free survival (EFS), overall survival (OS), and local recurrence (LR) in prospectively collected data of patients with localised EWS.

Patients and methods: We analysed data from the international Ewing 2008 study registered between 2009 and 2019 in 117 centres. After induction chemotherapy, patients received surgery, radiotherapy, or a combination thereof. We performed Cox regression, conducted propensity score-weighted sensitivity analysis, and performed subgroup analyses. Hazard ratios (HRs) and 95% confidence intervals are reported.

Results: We included 863 patients with localised EWS (surgery alone: 331, combination therapy: 358, definitive radiotherapy: 174). In patients treated with combination therapy compared to surgery alone, EFS HR was 0.84 (0.57–1.24; $p = 0.38$), OS HR was 0.84 (0.57–1.23; $p = 0.41$), and LR HR was 0.58 (0.26–1.31; $p = 0.19$). Hazards of any event were increased in patients treated with definitive radiotherapy compared to surgery only, HR 1.53 (1.02–2.31; $p = 0.04$). Patients with poor responses to chemotherapy benefitted from combination therapy over definitive surgery with an EFS HR 0.49 (0.27–0.89; $p = 0.02$). Patients with pelvic tumours benefitted from combination therapy over surgery only regarding LR, HR 0.12 (0.02–0.72; $p = 0.02$).

Conclusion: Patients with poor responses to chemotherapy benefitted from radiotherapy added to surgery. In the whole group, radiotherapy alone as opposed to surgery alone increased the hazards of any event.

1. Introduction

Ewing sarcoma (EWS) is a rare malignant small-blue-round-cell cancer that can arise in soft tissue or bone [1,2]. It is the second most common malignant bone sarcoma in children and young adults [3]. In addition to systemic therapy, local therapy (radiotherapy, surgery, or a combination thereof) is an integral part of the treatment [4]. However, it is unclear which local therapy modality is best. The choice of local treatment modality is based on tumour-specific factors and patient's preference [5]. When the tumour is deemed operable, surgery is the preferred local therapy option [6]. EWS is a radiosensitive tumour; hence, patients with inadequate surgical margins or poor response to chemotherapy are treated with a combination of surgery and radiotherapy [6,7]. Because of the potential adverse effects of radiation, several retrospective studies were conducted to quantify the benefit of adding radiotherapy to surgery. However, these studies either had a small sample size [8], did not specifically compare adjuvant radiotherapy to surgery alone [9], or only assessed local recurrence (LR) [10]. A small sample size means that these studies were unable to capture smaller treatment effects, while studies that were performed several years ago do not reflect current treatment standards. Furthermore, it is important to not only focus the analysis on LR but also on event-free

survival (EFS) and overall survival (OS) because it has been described that local control only has a relatively low contribution to EFS and OS in EWS [11].

We performed a secondary analysis of patients with localised EWS treated according to the Ewing 2008 trial protocol and compared EFS, OS, and LR after different local treatment modalities. We conducted subgroup analyses to identify which local therapy modality improved the outcome in defined subgroups of patients.

2. Methods

The EWING 2008 trial and associated registry included patients with a histologically confirmed EWS of the bone or soft tissue considered eligible for neoadjuvant chemotherapy. Patients were enroled between 1st October 2009 and 31st March 2019. The EWING 2008 study was an international, phase III randomised controlled trial for patients with localised or metastatic EWS, conducted in 117 centres from 13 countries [12].

Details on chemotherapy treatment were described previously [12]. Patients received an induction chemotherapy (6 cycles vincristine, ifosfamide, doxorubicin, and etoposide [VIDE]), followed by local treatment and consolidation chemotherapy with eight courses of vincristine, actinomycin D, ifosfamide (VAI)/vincristine, actinomycin D, cyclophosphamide or one course VAI and busulfan–melphalan high-dose chemotherapy followed by retransfusion of autologous hematopoietic stem cells. According to the Ewing 2008 trial protocol, surgery aimed for a complete resection of the tumour. The decision regarding adjuvant radiotherapy considered surgical margins and histological response to chemotherapy.

We included patients with localised disease at diagnosis (n = 949, 66.8%). Patients who received no local therapy or had an event before the initiation of local therapy were excluded from the analysis. Because the amount of missing data was low (n = 47, 3.3%), we performed a complete case analysis [13]. Supplementary Table 1 (S1) presents the number of participants with missing data for each relevant variable.

The primary outcome of this study was EFS, and the secondary outcomes were OS and LR rates. EFS, OS, and LR were defined as the time from registration of the patient for the study to any event (tumour progression, local and/or systemic relapse, secondary malignancy, death), all-cause death, or LR, respectively.

2.1. Data management and statistical analysis

The data were processed with SAS 9.4 and analysed with R [14]. The time-to-event was calculated from the date of study registration. We defined surgery as a surgical intervention with curative intent. This is in line with the Ewing 2008 protocol, which states that surgery should aim towards complete resection of the tumour. Therefore, surgeries that only aimed towards symptom reduction (such as spine decompression) were not counted as a surgery. Time to local therapy was defined as the time between the first cycle of induction chemotherapy and the date of surgery or date of first radiotherapy treatment, whichever occurred first.

A sensitivity analysis was conducted by introducing inverted propensity scores as weights in the Cox model [15,16]. Propensity scores were calculated by a multinomial logistic regression model using tumour volume (< 200 mL, ≥200 mL), tumour site (extremity, trunk, and head/neck), sex, and age as independent variables. We performed multivariable Cox regressions adjusting for the variables mentioned above. For comparisons between surgery and combination therapy, histological response to chemotherapy (good: < 10% vital tumour cells, poor: ≥10% vital tumour cells) and surgical margins (wide, marginal/intralesional) were available and included in the model. Unweighted hazard ratios (HRs) along with 95% confidence intervals (CIs) are reported. Weighted HRs along with 95% CIs are reported in the Supplementary Table 2 (S2).

3. Results

We included 863 patients in our analysis. Of these, 358 were treated with a combination of surgery and radiotherapy (320 adjuvant radiotherapy, 38 neoadjuvant radiotherapy), 331 were treated with surgery alone, and 174 were treated with definitive radiotherapy. A flow diagram of patient inclusion is presented in Fig. 1.

Table 1 summarised the patients' characteristics. We performed a sensitivity analysis by introducing propensity score weights into the multivariable Cox regression model. Our sensitivity analysis did not lead to different results. Detailed results from the sensitivity analysis are shown in the Supplementary Table 2 (S2).

Patients were followed up until an event occurred or last time of follow-up. For EFS, the median time of follow-up was 3.0 years (first quartile, third quartile; 1.4, 4.9 years). For OS, patients were followed up for a median of 3.4 years (1.8, 5.2 years), and patients with LR were followed up for a median of 1.4 years (0.9, 2.0 years). The following first events were reported: new metastases (115; 13.3%), loco-regional recurrence (51; 5.9%), combined relapse (28; 3.2%), secondary malignancy (12; 1.4%), and death (7; 0.8%). Of all deaths (119), 111 (93.3%) were deaths of disease, one (0.8%) was the death of therapy, two (1.7%) were due to a secondary malignancy, four (3.4%) were due to other reasons, and for one patient (0.8%), no reason for death was reported.

The median 5-year EFS was 70% (95% CI; 67%, 74%), OS was 82% (79%, 86%), and LR-free survival was 92% (90%, 94%). Further survival probabilities are presented in the Supplementary Table 3 (S3).

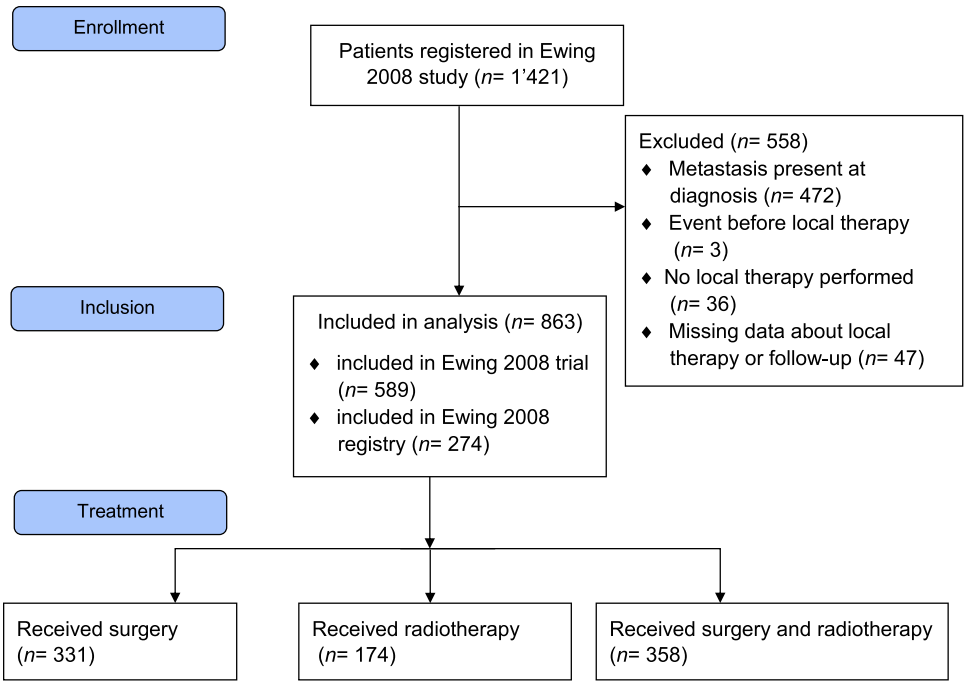

Fig. 1. Flowchart of patient inclusion.

Table 1
Patent characteristics.

	Overall		Surgery and radiotherapy		Surgery		Radiotherapy		*p*-value
	863		358		331		174		
	N	%	N	%	N	%	N	%	
Country									0.05
Australia	22	2.5	7	2.0	9	2.7	6	3.4	
Austria	54	6.3	34	9.5	17	5.1	3	1.7	
Belgium	33	3.8	10	2.8	16	4.8	7	4.0	
Czech Republic	36	4.2	11	3.1	18	5.4	7	4.0	
Germany	577	66.9	236	65.9	220	66.5	121	69.5	
Sweden	24	2.8	9	2.5	10	3.0	5	2.9	
Switzerland	15	1.7	6	1.7	4	1.2	5	2.9	
The Netherlands	68	7.9	25	7.0	26	7.9	17	9.8	
Others	34	3.9	20	5.6	11	3.3	3	1.7	
Male	497	57.6	201	56.1	199	60.1	97	55.7	0.49
Age [years]	14.4 (10.2, 19.4)		14.8 (11.3, 20.9)		13.7 (9.2, 18.5)		14.6(10.4, 19.5)		0.05
Tumour volume ≥200 mL	277	32.8	138	39.3	83	25.8	56	32.6	0.001
Poor histological response	172	24.9	129	36.0	43	13.0	NA		< 0.001
Positive surgical margin	125	18.1	93	26.0	32	9.6	NA		< 0.001
Tumour site									< 0.001
Abdomen	26	3.0	13	3.6	9	2.7	4	2.3	
Chest	167	19.4	96	26.5	54	16.3	18	10.3	
Head/Neck	72	8.3	34	9.5	19	5.7	19	10.9	
Pelvis	153	17.7	66	18.4	20	6.0	67	38.5	
Spine	85	9.8	35	7.0	6	1.8	54	31.0	
Extremity	360	41.4	125	34.9	223	67.4	12	6.9	

Variables are presented as numbers (%), while age is presented as the median (first quartile, third quartile). Two-sided *p*-values were calculated. SD, standardised difference; NA, not available.

3.1. Analysis of the whole cohort

The adjusted hazards for any event were increased by 53% in patients treated with definitive radiotherapy versus surgery alone, HR 1.53 (1.02, 2.31; $p = 0.04$). Adjusted hazards of any event were decreased by 33% in patients that underwent a combination of surgery and radiotherapy versus definitive radiotherapy, HR 0.67

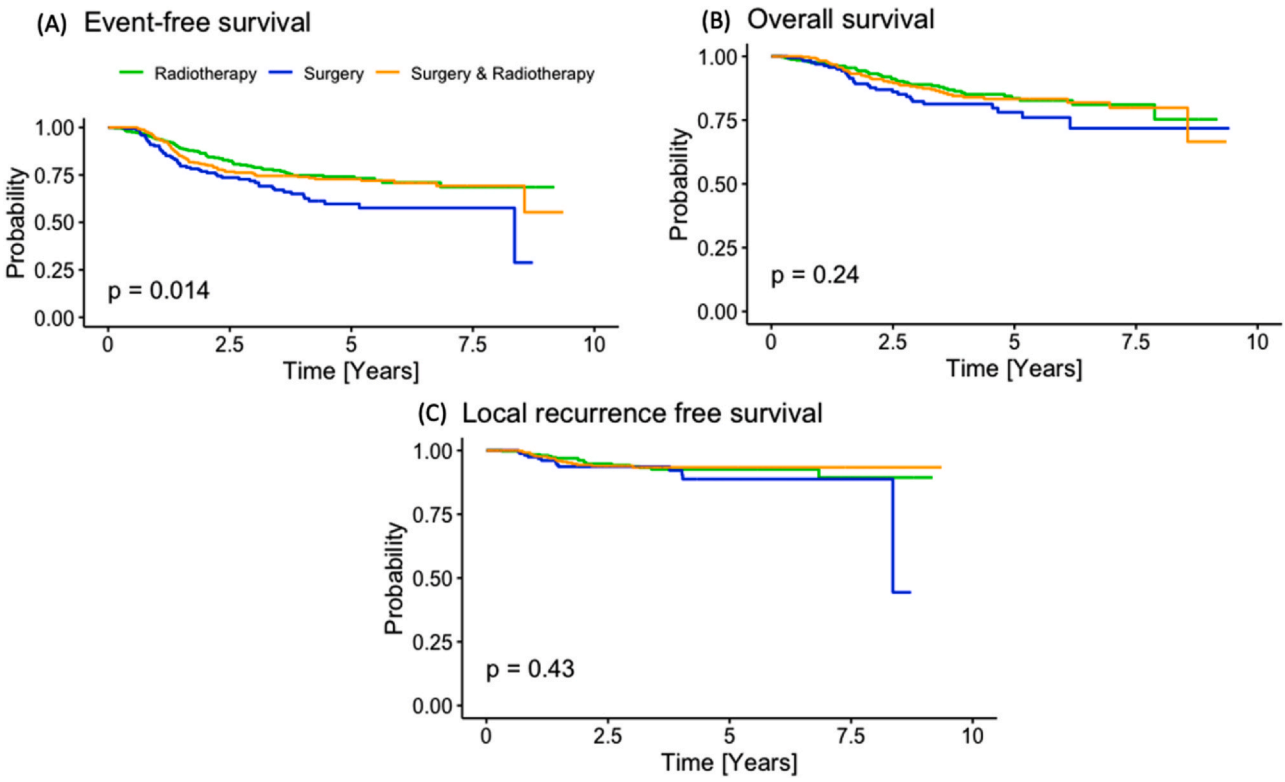

Fig. 2. Kaplan–Meier curves of event-free survival (A), overall survival (B), and local recurrence-free survival (C) by treatment modality. Survival distributions between treatment modalities were compared using the log-rank test.

(0.47, 0.95; $p = 0.02$). The HR for EFS for patients treated with a combination of surgery and radiotherapy versus surgery was 0.84 (0.57, 1.24; $p = 0.38$).

Adjusted HRs for OS were 1.26 (0.73, 2.16; $p = 0.41$) for radiotherapy versus surgery, 0.73 (0.46, 1.17; $p = 0.19$) for combination of surgery and radiotherapy versus radiotherapy, and 0.84 (0.57, 1.23; $p = 0.41$) for a combination of surgery and radiotherapy versus surgery.

Adjusted HRs for LR were 0.90 (0.42, 1.95; $p = 0.79$) for radiotherapy versus surgery, 0.69 (0.34, 1.42; $p = 0.31$) for combination therapy versus radiotherapy, and 0.58 (0.26, 1.31; $p = 0.19$) for combination therapy versus surgery.

Kaplan–Meier curves for OS, EFS, and LR are presented in Fig. 2. Probabilities for EFS, OS, and LR are presented in the Supplementary Table 3 (S3).

There was no substantial difference between 5-year EFS in patients with a time to local therapy above 15 weeks (0.70 [0.67,0.74]) compared to 15 weeks or below (0.74 [0.65, 0.84]), $p = 0.70$. Likewise, no substantial difference was found for 5-year OS ($p = 0.71$) or 5-year LR ($p = 0.31$). In multivariable regression analysis, time to local therapy above 15 weeks was not found to be predictive of EFS (HR 1.04 [0.65, 1.65], $p = 0.88$), OS (HR 1.01 [0.54, 1.89], $p = 0.98$), or LR (HR 0.65 [0.29, 1.47], $p = 0.30$). The median radiotherapy dose was 54 gray for patients treated with combination therapy and intralesional or marginal surgical margins, whereas it was 45 gray for patients with wide surgical margins. When including the radiotherapy dose in the multivariable regression model, we did not find an association between radiotherapy dose and EFS (HR 1.01 [0.98, 1.04], $p = 0.46$), OS (HR 1.02 [0.98, 1.06], $p = 0.43$), or LR (HR 1.00 [0.93, 1.06], $p = 0.87$).

3.2. Analysis of prognostic subgroups

Kaplan–Meier curves for certain subgroups are presented in Fig. 3, and survival probabilities are presented in Table 2. Notable findings are described below.

In patients with large tumour volume, a combination of surgery and radiotherapy compared to radiotherapy seemed beneficial for EFS, HR 0.52 (0.30, 0.90; $p = 0.02$). For OS, the HR was 0.61 (0.31, 1.22; $p = 0.16$), and for LR, it was HR 0.78 (0.26, 2.33; $p = 0.66$). Definitive radiotherapy compared to surgery only led to EFS HR of 1.94 (0.99, 3.81; $p = 0.05$), OS HR of 1.48 (0.63, 3.49; $p = 0.37$), and LR HR of 0.61 (0.23, 1.61; $p = 0.33$).

Patients with poor tumour response to chemotherapy who received a combined local therapy were at decreased risk of any event, HR 0.49 (0.27, 0.89; $p = 0.02$) and at decreased risk of death from any cause compared to patients that only underwent surgery, HR 0.34 (0.17, 0.68; $p = 0.002$), but not of LR, HR 0.50 (0.12, 2.13; $p = 0.41$).

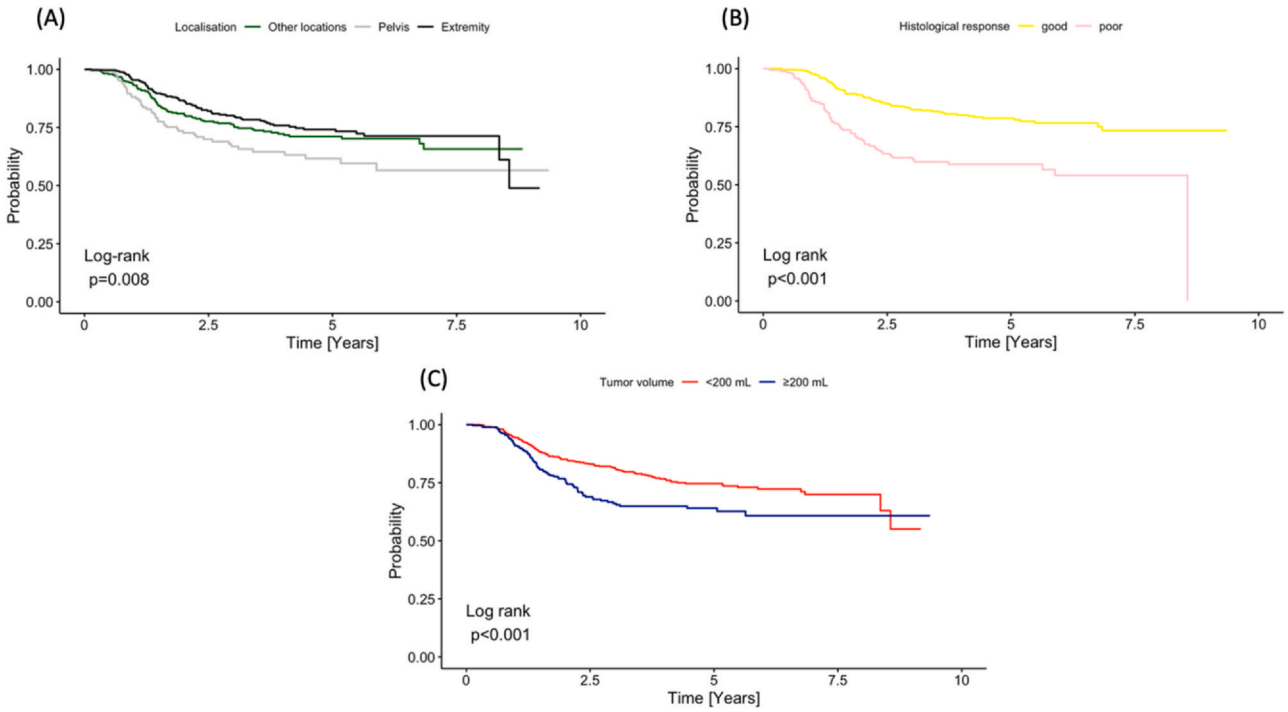

Fig. 3. Kaplan–Meier curves of event-free survival by tumour localisation (A), histological response to chemotherapy (B), and tumour volume (C). Good histological response to chemotherapy was defined as < 10% vital tumour cells. Survival distributions between treatment modalities were compared using the log-rank test.

Table 2
Probability and 95% confidence interval of event-free survival, overall survival, and survival without local recurrence at 3 and 5 years after registration for the study for different subgroups of patients.

Subgroups	EFS			OS			LR		
3 years	%	LL	UL	%	LL	UL	%	LL	UL
Tumour volume									
≥200 mL	62	54	70	76	69	83	90	86	94
< 200 mL	82	79	86	93	90	96	96	94	98
Gender									
Male	75	71	79	85	82	89	93	91	96
Female	78	74	83	90	86	93	94	92	97
Surgical complications									
Yes	82	72	94	83	72	95	94	87	100
No	77	74	81	89	86	92	94	92	96
Histological response to chemotherapy									
Poor (≥10% vital tumour cells)	62	54	70	76	69	83	91	86	96
Good (< 10% vital tumour cells)	82	79	86	93	90	96	95	93	97
5 years									
Tumour volume									
≥200 mL	59	51	68	70	63	79	90	86	94
< 200 mL	79	74	83	87	84	91	94	91	96
Gender									
Male	70	65	75	81	77	85	92	89	95
Female	72	67	78	85	80	89	93	90	96
Surgical complications									
Yes	74	62	90	80	68	93	94	87	100
No	73	70	77	84	81	87	93	90	95
Histological response to chemotherapy									
Poor (≥10% vital tumour cells)	59	51	68	70	63	79	91	86	96
Good (< 10% vital tumour cells)	79	74	83	87	84	91	95	92	97

EFS, event-free survival; OS, overall survival; LR, local recurrence; LL, lower limit of the 95% confidence interval; UL, upper limit of the 95% confidence interval.

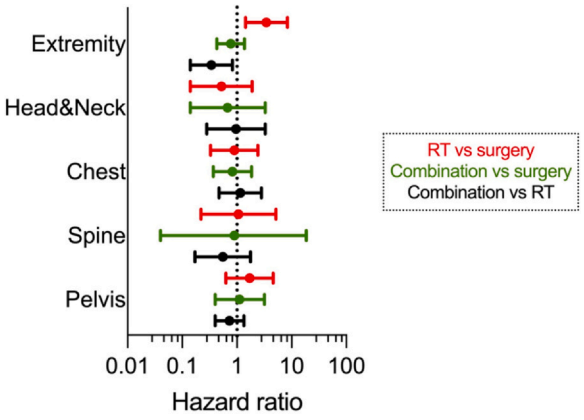

Fig. 4. Forest plot of adjusted hazard ratios and 95% confidence intervals for any event (event-free survival) for different tumour localisations. Tumours at the abdomen are not presented due to the low number of patients and events in this group.

3.3. Analysis of tumour localisation subgroups

Hazards of experiencing any event were increased in patients with tumours at the extremities that were treated with definitive radiotherapy compared to surgery alone and decreased in patients treated with a combination therapy compared to radiotherapy alone, HR 3.46 (1.44, 8.33; $p = 0.006$) and HR 0.34 (0.14, 0.83; $p = 0.02$), respectively. We did not find a difference in hazards between patients treated with combination therapy compared to surgery only, HR 0.77 (0.43, 1.38; $p = 0.42$).

In patients with a pelvic tumour, the hazards of any event were 0.73 (0.40, 1.32; $p = 0.30$) for combination therapy compared to definitive radiotherapy. For OS, the HR was 0.67 (0.31, 1.44; $p = 0.30$), and for LR, the HR was 0.26 (0.05, 1.31; $p = 0.10$). We found evidence of decreased hazards of LR in patients with pelvic tumours treated with combination therapy versus surgery alone, HR 0.12 (0.02, 0.72; $p = 0.02$).

Detailed results for all primary tumour localisations are presented in Fig. 4. Kaplan–Meier estimates are described in Supplementary Table 4 (S4).

4. Discussion

With this analysis of patients treated according to the Ewing 2008 protocol, we were able to gain further knowledge on the impact of local treatment modalities in a large cohort of prospectively collected data within the international Ewing 2008 trial. In the subgroup of patients with a poor response to chemotherapy, combination therapy was associated with better EFS and OS compared to surgery alone. When looking at EFS, OS, and LR in the whole cohort, patients did not benefit from combination therapy compared to surgery only. Moreover, our analysis of the whole cohort showed that, in patients treated with definitive radiotherapy compared to definitive surgery, adjusted hazards of any event were increased, but not the adjusted hazards of all-cause death or LR.

We found that patients treated with combination therapy (LR 5.3%) compared to surgery alone (LR 5.7%) did not have meaningfully decreased hazards of LR. This contrasts a prior study in which the local failure rate was lower after surgery alone (3.9%) compared to combination therapy (6.6%) [17]. This study included patients from three trials that were treated between 1988 and 2005 [17]. The chemotherapy regimen differed between those three trials and was also different from the regimen used in the Ewing 2008 study. In contrast to our study, no proton radiotherapy was applied.

In a subgroup of patients with pelvic tumours and in regard to LR, combination therapy was more beneficial than surgery alone, and we thereby corroborate the results by Andreou et al. who included 180 patients with pelvic EWS treated in line with the Ewing 99 protocol between 1998 and 2009 [18]. As in the Ewing 2008 protocol, the Euro-EWING 99 protocol also prescribed induction chemotherapy using VIDE. The authors found that 5-year LR rates were lower in patients treated with combination therapy (14%) compared to definitive surgery (33%). Similarly, Yock et al. presented Kaplan–Meier plots including 75 patients suggesting lower local failure rates in 518 patients with pelvic tumours treated with combination therapy compared to definitive surgery or radiotherapy [19]. However, Ahmed et al. found no significantly reduced hazards after combination therapy compared to surgery alone (HR 1.31 [95%CI; 0.19, 9.28], $p = 0.78$) [17]. A possible reason for the contradiction in our results is that, in the study by Ahmed et al., patients were treated between 1988 and 2005 when proton therapy was not yet commonly applied and when a different chemotherapy regimen was given [17,20].

In the overall cohort, we did not find a difference in the hazards of any event after combination therapy compared to surgery only which contradicts the results of Whelan et al. [21] In their analysis of the EICESS-92 randomised controlled trial, two countries that applied different local treatment modalities were compared [21]. In the country that used less combination therapy (18% of patients), the risk of an EFS event was 44% higher than in the country that used more combination therapy (59% of patients) [21]. The EICESS-92 trial enroled 647 patients between 1992 and 1998 and randomised patients to high- or standard-risk group. Patients were treated with vincristine, dactinomycin, ifosfamide, doxorubicin (VAIA); or vincristine, dactinomycin, cyclophosphamide, doxorubicin; or VAIA + etoposide [21].

Our finding that definitive radiotherapy compared to surgery only increased the hazards of any event corroborates the earlier study by Schuck et al. who found that EFS was lower after definitive radiotherapy compared to surgery with or without radiotherapy [9]. In contrast

to our analysis, Schuck et al. found that the rate of local failure was significantly lower in patients after surgery with or without postoperative radiotherapy compared to patients with definitive radiotherapy [9]. The study included 1058 patients who were treated as part of the CESS 81 (145 patients), CESS 86 (382 patients), and EICESS 92 (531 patients) trials and were diagnosed between 1981 and 1991 [9]. Patients treated with definitive radiotherapy as part of the CESS 81 trial received 46–60 gray using conventional fractionation (1.8–2 gray per day), whereas patients in the CESS 86 trial received 60 gray and were randomised to either conventional fractionation or hyperfractionation (1.6 gray twice per day) and patients in the EICESS 92 trial received 54 gray using conventional fractionation. In our cohort of patients, the median radiotherapy dose including boost was 54.0 gray (54.0, 59.4).

We found that patients with a large tumour (≥200 mL) benefitted from combination therapy compared to radiotherapy only in regard to EFS but not in regard to OS or LR. We did not find that any specific local therapy modality was superior in patients with a tumour in the chest. A possible reason for these findings is that the EWING2008 protocol included some local therapy recommendations, and the Cooperative Ewing Sarcoma Study group offered a multidisciplinary tumour conference for patients. Recommendations were provided on the base of previous published analysis on the value of local treatment by the group [18,22], and others and risk-adjusted local treatment recommendations were provided. As local treatment is an essential part of EWS, this might have had an impact on outcome and overcoming of old prognostic factors such as tumour size [18,22].

We performed a propensity score-weighted sensitivity analysis to assess whether the results found in our study are attributable to selection bias or due to baseline imbalance. This additional analysis did not change our results, thereby further confirming the confidence in our results.

4.1. Strengths

Strengths of this article are the large sample size and the fact that all patients were treated with the same protocol. The Ewing 2008 trial is a recently conducted trial which ensures that current techniques and medications were used for surgery, RT, and chemotherapy. We included advanced statistical methods to control for baseline differences in the patient groups treated with different local modalities, performing a propensity score-weighted sensitivity analysis.

4.2. Limitations

This study was a secondary analysis of the Ewing 2008 trial that randomised patients for systemic therapy. However, we focused on local therapy. As patients in the Ewing 2008 trial were not randomised by local therapy, we were not able to control for unknown and unmeasured confounders. Moreover, due to the observational nature of our study, selection bias cannot be ruled out. However, we tried to reduce potential selection bias by conducting a propensity score-weighted analysis. To date, all current evidence is based on retrospective studies only, which all carry the risk of selection bias. A trial that randomises patients between local therapy groups is not feasible [23]. Another limitation is the lack of details about radiotherapy in the Ewing 2008 trial. This drawback is addressed by the upcoming iEuroEwing trial that will randomise patients by radiotherapy doses and will therefore shed more light on the value of radiotherapy in EWS.

4.3. Conclusion

In the analysed cohort of patients with a localised EWS, we found that combination therapy was especially valuable for patients with unfavourable prognostic factors such as poor histological response to neoadjuvant chemotherapy. Patients with a tumour at the extremity had decreased hazards of any event when treated with combination therapy compared to radiotherapy alone. In the overall cohort, patients treated with definitive radiotherapy had increased hazards of experiencing any event.

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None declared.

CRediT authorship contribution statement

Philip Heesen: Conceptualization, Methodology, Formal analysis, Writing – Original draft preparation. **Andreas Ranft:** Conceptualization, Methodology, Formal analysis, Writing – Reviewing and editing. **Vivek Bhadri:** Writing – Reviewing and editing. **Benedicte Brichard:** Writing – Reviewing and editing. **Stephane Collaud:** Writing – Reviewing and editing. **Sona Cyprova:** Writing – Reviewing and editing. **Hans Eich:** Writing – Reviewing and editing. **Torben Ek:** Writing – Reviewing and editing. **Hans Gelderblom:** Writing – Reviewing and editing. **Jendrik Hardes:** Writing – Reviewing and editing. **Lianne Haveman:** Writing – Reviewing and editing. **Susanne Jabar:** Data curation, Writing – Reviewing and editing. **Wolfgang Hartmann:** Writing – Reviewing and editing. **Dimosthenis Andreou:** Writing – Reviewing and editing, Conceptualization. **Peter Hauser:** Writing – Reviewing and editing. **Josephine Kersting:** Writing – Reviewing and editing. **Heribert Juergens:** Writing – Reviewing and editing. **Jukka Kanerva:** Writing – Reviewing and editing. **Thomas Kühne:** Writing – Reviewing and

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Declaration of Competing Interest

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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113260.

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