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ONCOLOGY: RESEARCH ARTICLE

Extraskeletal Ewing sarcoma in children, adolescents, and young adults. An analysis of three prospective studies of the Cooperative Weichteilsarkomstudiengruppe (CWS)

Ewa Koscielniak[1,2] | Monika Sparber-Sauer[1] | Monika Scheer[3] | Christian Vokuhl[4] | Bernarda Kazanowska[5] | Ruth Ladenstein[6] | Felix Niggli[7] | Gustaf Ljungman[8] | Michael Paulussen[9] | Stefan S. Bielack[1] | Guido Seitz[10] | Joerg Fuchs[11] | Erika Hallmen[1] | Thomas Klingebiel[12] | on behalf of the CWS Study Group

[1] Klinikum Stuttgart-Olgahospital, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany

[2] University of Tuebingen, Tuebingen, Germany

[3] Department of Pediatric Oncology/Hematology, Charité-Universitätsmedizin, Berlin, Germany

[4] Institute of Children's Pathology, University of Bonn, Bonn, Germany

[5] Department of Pediatric Hematology/Oncology and BMT, University of Wroclaw, Wroclaw, Poland

[6] Pediatric Oncology, St. Anna Kinderspital, Vienna, Austria

[7] Department of Pediatric Oncology, University of Zürich, Zurich, Switzerland

[8] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[9] Witten/Herdecke University, Datteln, Germany

[10] Department of Pediatric Surgery, University Children's Hospital Marburg, Marburg, Germany

[11] Department of Pediatric Hematology and Oncology, Hospital for Children and Adolescents, University of Tuebingen, Tuebingen, Germany

[12] Department for Children and Adolescents, University HospitalGoethe University, Frankfurt, Germany

Correspondence
Ewa Koscielniak, Klinikum Stuttgart, Olgahospital, Zentrum für Kinder-, Jugend- und Frauenmedizin, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany.
Email: e.koscielniak@klinikum-stuttgart.de

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Abstract

Background: We have analyzed the outcome of patients with localized extraskeletal Ewing sarcoma (EES) treated in three consecutive Cooperative Weichteilsarkomstudiengruppe (CWS) soft tissue sarcoma (STS) studies: CWS-91, CWS-96, and CWS-2002P.

Methods: Patients were treated in CWS-91 with four- (vincristine, dactinomycin, doxorubicin, and ifosfamide [VAIA] or cyclophosphamide [VACA II]) or five-drug (+etoposide [EVAIA]) cycles, in CWS-96 they were randomly assigned to receive VAIA or CEVAIE (+carboplatin and etoposide), and in CWS-2002P with VAIA III plus optional maintenance therapy (MT) with cyclophosphamide and vinblastine. Local therapy consisted of resection and/or radiotherapy (RT).

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CT, computed tomography; CWS, Cooperative Weichteilsarkomstudiengruppe; EES, extraskeletal Ewing sarcoma; EFS, event-free survival; ES, Ewing sarcoma; ETS gene family, erythroblast transformation specific; FET gene family, DNA and RNA binding proteins fused in sarcoma (FUS), Ewing sarcoma (EWS) and TATA-box binding protein; IRS, Intergroup Rhabdomyosarcoma Study; MRI, magnetic resonance imaging; MT, maintenance therapy; n.s., not significant; OS, overall survival; RMS, rhabdomyosarcoma; RT, radiotherapy; SM, second malignancy; VAC/VAI, vincristine, dactinomycin, cyclophosphamide/vincristine, dactinomycin, ifosfamide; VDC/IE/VC, vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide/vincristine, cyclophosphamide; VIDE, vincristine, ifosfamide, doxorubicin, etoposide

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Results: Two hundred forty-three patients fulfilled the eligibility criteria. The 5-year event-free survival (EFS) and overall survival (OS) were 63% (95% confidence interval [CI] 57–69) and 73% (95% CI 67–79), respectively. The 5-year EFS by study was 64% (95% CI 54–74) in CWS-91, 57% (95% CI 48–66) in CWS-96, and 79% (95% CI 67–91) in CWS-2002P (n.s.). The 5-year OS was 72% (95% CI 62–82) in CWS-91, 70% (95% CI 61–79) in CWS-96, and 86% (95% CI 76–96) in CWS-2002P (n.s.). In CWS-96, 5-year EFS and OS in the VAIA arm versus the CEVAIE were 65% (95% CI 52–81) versus 55% (95% CI 39–76) log-rank $p = .13$, and 85% (95% CI 75–96) versus 61% (95% CI 45–82), log-rank $p = .09$.

Conclusion: Our analysis provides interesting information on the treatment and specificities of EES, which can be useful for a better understanding of this rare entity and should be considered in the development of future clinical trials for Ewing sarcoma defined as FET–ETS fusion positive tumors.

KEYWORDS
Ewing sarcoma, extraskeletal, pediatric solid tumors, soft tissue sarcoma

1 | INTRODUCTION

Ewing sarcoma (ES), first described as bone tumor, can occur in 10–20% of cases in extraskeletal sites. According to the World Health Organization (WHO) classification, it is a small round cell sarcoma with characteristic chromosomal translocations in which a member of FET (DNA and RNA binding proteins fused in sarcoma [**F**US], Ewing sarcoma [**E**WS], and **T**ATA-box binding protein) gene family is fused with an erythroblast transformation specific (ETS) transcription factor.[1] Askin tumors or peripheral neuroectodermal tumors are included in this definition. Analyses comparing bone ES and extraskeletal Ewing sarcoma (EES) are rare.[2–5] Despite similar genomic features, differences in the gene expression have been reported between bone and EES.[2] Other authors suggest that the relationship between tumor cells and their host microenvironment is critical to tumor pathogenesis.[6,7]

We have analyzed the outcome of patients with localized EES treated prospectively in three consecutive Cooperative Weichteilsarkomstudiengruppe (CWS) studies, in relation to the chemotherapy combination, dose intensity, and cumulative dose.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients with localized EES ≤30 years of age treated on three, prospective CWS trials: CWS-91, CWS-96, and CWS-2002P between 1991 and 2009 were included. All studies were designed as multicenter, international, and in the case of CWS-96 randomized trials. Informed consent was obtained from all parents/guardians or patients according to the legal requirements and the Declaration of Helsinki.

CWS-91 and CWS-96 studies were approved by Ethics Review Boards of the Landesärztekammer Baden-Württemberg (66/91 and 105/95), and in the case of CWS-2002P, of the University of Tübingen (51/2003). All data were collected in the CWS study center in Stuttgart. Results for other soft tissue sarcoma treated on studies included in this analysis have already been partially published.[8–11]

All tumors had a histological reference review. The diagnosis was based on morphological, histochemical, and immunophenotypic criteria (small blue round cell tumor, PAS positive, membranous expression of CD99 [MIC-2], other small round cell tumor entities were excluded using a panel of immunohistochemical markers). Translocation status was not mandatory but recommended.

Staging procedures included magnetic resonance imaging (MRI) of the primary site and if indicated computed tomography (CT) and ultrasound. Metastatic disease was assessed by chest CT, optionally whole-body MRI in the latest study, cerebral MRI or CT, technetium bone scan, bone marrow aspiration, or trephine biopsy.

The tumor node metastasis (TNM) classification was applied to differentiate pretreatment and postsurgical stages.[12] The clinical staging system (IRS I, II, III) adapted from the Intergroup Rhabdomyosarcoma Study (IRS) postsurgical grouping system was used to categorize patients according to primary surgery.[13] Resection was classified as R0 (free resections margins), R1 (microscopically incomplete), or R2 (macroscopically incomplete). Complete remission (CR) was defined as an absence of any tumor on MRI and/or CT imaging.

2.2 | Treatment

In CWS-91, an allocation to risk groups was based on the risk factors: site, TN status, IRS group, and response to preoperative chemotherapy.[8] In CWS-96 and CWS-2002P, all patients with localized EES were treated in the high-risk group. The summary of all therapy arms and cumulative doses is given in Tables 1 and 4. Patients in the low-risk group (Group A) in CWS-91 were treated similarly to

TABLE 1 Chemotherapy regimens and cumulative dose of chemotherapy agent by study

	Study								
	CWS-91					CWS-96		CWS-2002P	
Agent cumulative dose mg/mš↓	1 × VACA II[a]	2 × VACA II[a]	1 × VACA II[a] 2 × EVAIA[b]	1 × EVAIA[b] 1 × VACA II[a]	3 × EVAIA[b]	3 × VAIA[c]	3 × CEVAIE[d]	3 × VAIA III[e]	7 × CYC/VBL[f]
DOX	120	240	360	240	360	240	–	320	–
AMD	3	6	9	6	9	9	4.5	7.5	
CARBO	–	–	–	–	–	–	1500	–	–
CYC	4800	9600	4800	4800	–	–	–	–	7350
EPI	–	–	–		–	–	450	–	–
ETO	–	–	3600	1800	5400	–	1350	–	–
IFO			48,000	24,000	72,000	54,000	51,000	54,000	
VCR	6	12	18	12	18	19.5	19.5	19.5	
VBL									63

Abbreviations: AMD, dactinomycin; CARBO, carboplatin; CYC, cyclophosphamide; DOX, doxorubicin; EPI, epirubicin; ETO, etoposide; IFO, Ifosfamide, VBL, vinblastine; VCR, vincristine.

[a]VACA II: (10 weeks) course consisted of cyclophosphamide 1.2 g/mš/day and vincristine (1.5 mg/mš; maximum 2 mg) on weeks 1, 4, 7, and 10, dactinomycin 0.5 mg/mš/day (maximum, 1.5 mg/day, on 3 consecutive days) on weeks 1 and 7, doxorubcin 20 mg/mš/day (on 3 consecutive days) on weeks 4 and 10.

[b]EVAIA: (10 weeks) course consisted of ifosfamide 2 g/mš/day and VP-16 150 mg/mš/day on three consecutive days given on weeks 1, 4, 7, and 10, vincristine (1.5 mg/mš; maximum, 2 mg) on weeks 1, 4, 7, and 10, dactinomycin (0.5 mg/mš/day maximum, 1.5 mg/day, on 3 consecutive days) on weeks 4 and 10, doxorubicin 20 mg/mš/day (on 3 consecutive days) on weeks 1 and 7.

[c]VAIA: (7 weeks) course consisted of ifosfamide 3 g/mš/day on 2 consecutive days on weeks 1, 4, 7, vincristine (1.5 mg/mš; maximum 2 mg) on weeks 1, 4, 7 (in the two first VAIA courses vincristine was recommended, if feasible, additionally on weeks 2,4,5, and 6), dactinomycin (1.5 mg/mš/day maximum, 1.5 mg/day) on weeks 1 and 7, doxorubicin 40 mg/mš/day (on 2 consecutive days) on week 4.

[d]CEVAIE: (7 weeks) course consisted of ifosfamide 3 g/mš/day on 3 consecutive days on weeks 1, 4, 7, vincristine (1.5 mg/mš; maximum 2 mg) on weeks 1, 4, 7), dactinomycin (1.5 mg/mš/day maximum, 1.5 mg/day) on week 1, epi-doxorubcin 150 mg/mš/day on week 4, carboplatin (CARBO) 500 mg/mš/day on week 4, VP-16 150 mg/mš/d on 3 consecutive days on week 7.

[e]VAIA III: (7 weeks) course consisted of ifosfamide 3 g/mš/day on 2 consecutive days on weeks 1, 4, 7, vincristine (1.5 mg/mš; maximum 2 mg) on weeks 1, 4, 7 (in the two first VAIA courses vincristine was recommended, if feasible, additionally on weeks 2, 4, 5, and 6), dactinomycin (1.5 mg/mš/day maximum, 1.5 mg/day) on week 4, doxorubicin 40 mg/mš/day (on 2 consecutive days) on weeks 1 and 7.

[f]Maintenance therapy cyclophosphamide/vinblastine: seven 3-week cycles of intravenous vinblastine 3 mg/mš on days 1, 8, and 15 and oral cyclophosphamide 2 × 25 mg/mš/day on days 1–21, with 1 week pause between the cycles.

rhabdomyosarcoma (RMS) with only one VACA II cycle, and in the standard-risk group (Group B1) patients received two VACA-II cycles. In the standard-risk group B2 (after the first VACA cycle) and in the high-risk group C (after the first EVAIA cycle), there was a stratification by response and TN characteristics to receive one VACA II cycle or two EVAIA cycles. In CWS-96, all patients with localized EES along with high-risk RMS and undifferentiated sarcoma were randomized between two therapy arms: four drugs (VAIA) and six drugs (CEVAIE). Here we consider only the EES patients. In CWS-2002P, the maintenance chemotherapy with cyclophosphamide and vinblastine (CYC/VBL) was recommended as an option at the end of the multimodal intensive therapy for patients in CR. Local therapy in all trials consisted of primary or secondary resection (after preoperative chemotherapy) if feasible, and radiotherapy (RT) (48 Gy in CWS-91, 44,8 Gy in CWS-96 and CWS-2002P) was recommended for all patients except for those with primary complete resection (R0, IRSI) in CWS-96 and CWS-2002P. Fractionation 2 × 1.6 Gy/day (accelerated, hyperfractionated) was recommended for all RT fields except whole abdomen, neuroaxis, heart, liver, lung, and optic chiasma. In patients whose tumors were not amenable to an R0 after chemotherapy, preoperative RT was recommended.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS statistics 22–25.0.0 (IBM Corporation, Armonk, NY) and R 3.02 (Bell Laboratories, Murray Hill, NJ, USA) software packages. Event-free survival (EFS) and overall survival (OS) were calculated using Kaplan–Meier method. EFS was calculated as the time elapsed between the date of diagnosis and either the occurrence of an event or the date of the last patient contact. Event was defined as relapse of disease (local, metastatic, or combined) in patients who achieved CR, disease progression, or death. Second malignancy (SM) was not defined as event as described in the protocols. OS was defined as time from diagnosis to death or last follow-up for surviving patients. Confidence interval (CI) for the Kaplan–Meier estimator were computed using Greenwoods formula and stated at the 95% level. Patients who had not experienced an event at their last contact were considered censored. For comparison of EFS and OS levels, the long-rank test was used. The differences in distributions were tested with chi-square or Fisher's exact test. Differences in event risk between groups in the univariate setting were evaluated using the Cox-regression analysis, and the significance testing for the hazard ratios was performed with the Wald test. Multivariate analysis was performed using Cox's proportional hazard method.

3 | RESULTS

3.1 | Patients characteristics

Two hundred forty-three patients fulfilled the eligibility criteria for this analysis. The patients' characteristics are shown in Table 2.

3.2 | Outcome

An overview on outcome is given in Table 3. CR by all means was achieved in 224 patients (92%), with no statistical difference in remission rates by study (CWS-91 92%, CWS-96 95%, and CWS-2002P 86%).

The 5-year EFS by study was 64% (95% CI 54–74) in CWS-91, 57% (95% CI 48–66) in CWS-96, and 79% (95% CI 67–91) in CWS-2002P (log-rank not significant [n.s.]). The 5-year OS was 72% (95% CI 62–82) in CWS-91, 70% (95% CI 61–79) in CWS-96, and 86% (95% CI 76–96) in CWS-2002P (log-rank n.s.); Table 3 and Figure 1.

The lowest failure rate was seen in the CWS-2002P (loco-regional 7% and metastatic and combined 5%, $p = .03$).

In CWS-96, 72 patients (Figure S1 consort diagram) were randomized to receive either VAIA or CEVAIE. Patient characteristics according to therapy arm are shown in Table S1. In the intention-to-treat population, 5-year EFS was 65% (95% CI 52–81) for patients who received VAIA versus 55% (95% CI 39–76) for patients who received CEVAIE (log-rank $p = .13$). Five-year OS was 85% (95% CI 75–96) versus 61% (95% CI 45–82) (log-rank $p = .09$); Figure 2. Events according to therapy arm are shown in Table S2. Forty-two patients, who met the eligibility criteria for randomization but were not randomized due to different reasons (Figure S1), were treated with CEVAIE (13) or VAIA (29) based on the decision of treating physician. An analysis of all patients (randomized and nonrandomized) per therapy given (Table 4) showed that the 5-year EFS and OS were 43% (95% CI 30–62) versus 67% (95% CI 57–81) (log-rank $p = .002$), and 54% (95% CI 40–71) versus 85% (95% CI 76–94) (log-rank $p = .0003$) for CEVAIE and VAIA arms, respectively.

When comparing all therapy arms (Table 4), there was a significant difference in 5-year EFS rates. The best 5-year EFS of 84% (95% CI 72%-96%) was obtained for the combination of VAIA III with low-dose maintenance therapy (MT). It is worth mentioning that four patients, who were assigned to the low-risk Group A in the CWS-91 study and treated with only one VACA cycle (one patient was additionally irradiated with 48 Gy), and 12/15 treated in Group B with two VACA cycles, are alive without disease after a median time of 6.6 years (4.5–13.4).

Four patients (1.6%) developed SMs: three acute myeloid leukemia (AML) (one CWS-91 and two CWS-96) and one osteosarcoma (CWS-96), after 1–8 years, three of them had been treated with etoposide. One hundred seventy-two patients were alive after a median follow up of 7 years (2–16).

3.3 | Local therapy

In 26 patients, no exact information concerning the local therapy was available and six patients had no local control measures reported. Of the remaining patients, 39 had surgery only, 46 had radiation only, and 124 had both (Table S3).

TABLE 2 Patient demographics and clinical characteristics

	Study group						
	CWS-91		CWS-96		CWS-2002P		
	No.	%	No.	%	No.	%	*p*-Value
Total	84	35	115	47	44	18	
Gender							.346[a]
Female	38	45	64	56	23	52	
Male	46	55	51	44	21	48	
Age, years							.246[b]
≤1	5	6	2	2	3	7	
>1 to ≤10	29	35	43	37	20	45	
>10 to <21	46	55	62	54	21	48	
≥21 to ≤30	4	5	8	7	0	0	
Tumor extension							.088[b]
T1	20	24	32	28	20	45	
T2	61	73	77	67	22	50	
Tx	3	4	6	5	2	5	
Lymphe node							.138[b]
N0	64	76	100	87	33	75	
N1	7	8	6	5	6	14	
Nx	13	15	9	8	5	11	
Primary tumor size, cm							.133[b]
≤5	21	25	28	24	19	43	
>5	62	74	83	72	24	55	
missing	1	1	4	3	2	5	
IRS group							.640[b]
I	5	6	10	9	4	9	
II	15	18	29	25	10	23	
III	64	76	76	66	30	68	
Primary tumor site							.570[a]
Abdomen[c]	5	6	15	13	4	9	
Extremity	23	27	33	29	9	20	
Head/neck	16	19	16	14	8	18	
Other	5	6	8	7	4	9	
Pelvis[c]	13	15	10	9	3	7	
Spine	5	6	11	10	7	16	
Thorax	17	20	22	19	9	20	

[a]Chi-square test.
[b]Fischer exact test.
[c]Including intestine, rectum, adrenal gland, vulva, cervix, perineum.

3.4 | Univariate and multivariate analyses

The following clinical variables were considered potential prognostic factors for EFS and OS: sex, age (≤10, >10 years), tumor status (T1 vs. T2), tumor size (≤5 vs. >5 cm), IRS group, primary tumor site (as in Table 2), and were evaluated with univariate Cox regression analysis. Univariate hazard ratios for EFS and OS were significantly influenced by tumor size, T status, and three categories of primary site (extremities, other, head/neck) plus primary site pelvis for OS additionally (Table S4). The variables with a $p < .15$ in the univariate log-rank test (IRS, T status, T size, primary site) were included in a multivariate Cox regression model. In the multivariate analysis, the hazard ratios of the follow-

TABLE 3 Events and outcome according to study

	CWS-91*n* (%)	CWS-96*n* (%)	CWS-2002P*n* (%)	Total*n* (%)	*p*-Value
	84 (100)	115 (100)	44(100)	243 (100)	
CR achieved	77 (92)	109 (95)	38 (86)	224 (92)	
Relapse					
Local	9 (11)	19 (17)	3 (7)	31 (13)	n.s.
Metastatic/combined	15 (18)	24 (21)	2 (5)	41 (17)	.03
Progression	6 (7)	6 (5)	3 (7)	15 (6)	
DOT as first event	1 (1)	0	0	0	
Total failures	31 (37)	49 (43)	8 (18)	88 (36)	
EFS% 5-year [95% CI]	64 [54–74]	57 [48–66]	79 [67–91]	63 [57–69]	n.s.
Alive	56 (67)	77 (67)	38 (86)	171	
Dead	28 (33)	38 (33)	6 (14)	72 (30)	
DOD	25	37	6	68	
DOT[a]	3	0	0	3	
DOC	0	1	0	1	
OS% 5-year [95% CI]	72 [62–82]	70 [61–79]	86 [76–96]	73 [67–79]	n.s.
FU year	8 [2.3–16]	10 [2–16][b]	5 [2–6.4][c]	7 [2–16]	
Second malignancy	1	3			

Abbreviations: CR, complete remission; DOC, dead of other causes; DOD, dead of disease; DOT, dead of therapy; FU, median follow-up [min–max] for patients alive.

[a]DOT: (1) gastrointestinal infection; (2) intravascular coagulation, heart failure after relapse therapy; (3) pulmonary hypertension, cardiomyopathy, heart failure,.

[b]CWS-96: 3 patients lost, follow-up ≤2 years.

[c]CWS-2002P: 2 patients lost, follow-up ≤2 years.

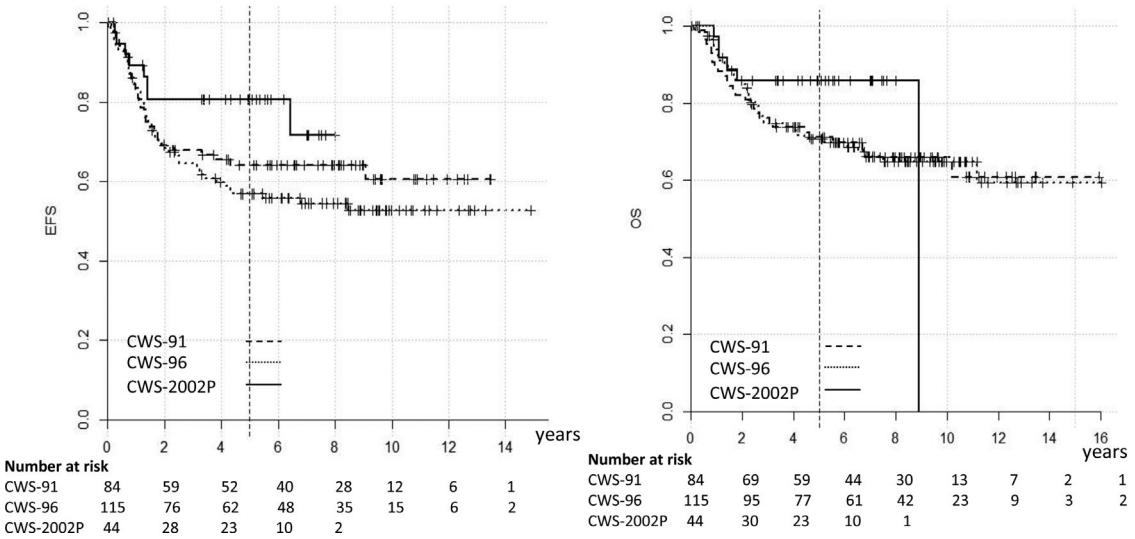

FIGURE 1 Probability of event-free survival (EFS) and overall survival (OS) by study

ing categories of primary site were significantly different (lower) from the HR of the reference category (abdomen) HR (EFS) extremities (0.35 $p = .01$), "other" (0.28 $p = .05$), HR (OS) extremities (0.27, $p = .004$), "other" (0.11 $p = .03$), pelvis (0.38 $p = .05$), and spine (0.37 $p = .05$) (Table S5).

4 | DISCUSSION

It is open to debate whether soft tissue and bone tumors belonging to the same histological group should be treated in the same way. Apart from EES and bone ES, there are many other examples like osteosar-

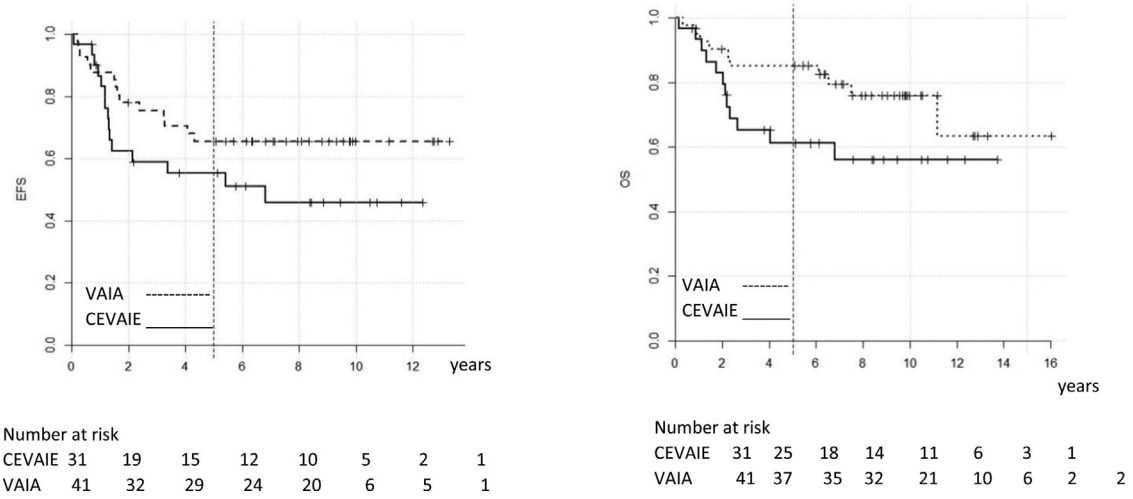

FIGURE 2 CWS-96. Probability of event-free survival (EFS) and overall survival (OS) by randomly assigned regimen. Five-year EFS CEVAIE 55% (95% CI 39–76), VAIA 65% (95% CI 52–81), log-rank $p = .13$; 5-year OS CEVAIE 61% (95% CI 45–82), VAIA 85% (95% CI 75–96), log-rank $p = .09$

TABLE 4 Outcome according to study and chemotherapy arm

Study		First cycle	Further cycles	Duration(weeks)	n[a]	5-year EFS%[95% CI]	5-year OS%[95% CI]
CWS-91	A	VACA II	No further therapy	10	6	83 [54–112]	83 [54–112]
	B1	VACA II	VACA II	23	13	76 [52–100]	92 [68–116]
	B2	VACA II s	2 × EVAIA	37		57	57
	C	EVAIA[c]	VACA II	23	7	[22–82]	[22–82]
			2 × EVAIA	37	52	57 [43–71]	65 [52–78]
CWS-96[b]		VAIA	2 × VAIA	25	70	67 [57–81]	85 [76–94]
		Per therapy given[c]					
		CEVAIE	2 × CEVAIE	25	44	43 [31–62]	54 [40–71]
CWS-2002P		VAIA III	2 × VAIA III	25	11	50 [20–80]	60 [31–89]
Log-rank test			2 × VAIA III +CYC/VBL	25+26	33	84 [72–96]	88 [77–99]
						$p = .008$	$p = .003$

Note: Patients in the IRS III group allocated to B2 or C risk groups were stratified (S) after one cycle (VACA II or EVAIA) depending on response and T status to receive one VACA II or two EVAIA cycles.

[a]Six patients in CWS-91 who received modified chemotherapy are not included.

[b]One patient in CWS-96 who received modified chemotherapy is not included.

[c]Analysis per therapy given: randomized and nonrandomized patients included.

coma or undifferentiated high-grade pleomorphic sarcoma, which can occur as bone and rarely as soft tissue tumor, for which no uniform consensus concerning the therapy has been achieved.[14–16] The main experience in the treatment of ES comes from trials including predominantly patients with bone tumors. After the discovery of the common genetic alterations, there has been an increasing trend to treat EES in studies designed for bone ES, without special risk stratification and therapy recommendations considering specificities of this clinically different group. The survival rates in patients with localized ES range from 60% to 73%, with different doses and schedules of administration of cyclophosphamide, ifosfamide, etoposide, dactinomycin, and vincristine, which have not changed much in the last 25 years.[17–19]

The benefit of replacing cyclophosphamide by ifosfamide is still debatable.[20–23] Cumulative doses of ifosfamide of 54–102 g/mš have been used without any clear evidence for a relationship between the dose and survival.[17–19,24] No benefit for ifosfamide in consolidation was shown.[18,24] The role of etoposide for outcome was investigated in many trials, which showed conflicting results.[18,21] Since a single treatment standard for ES was not internationally defined, the EURO-Ewing 2012 trial aimed to address this issue and randomized the six VIDE (vincristine, ifosfamide, doxorubicin, etoposide) cycles, which is regarded as a standard induction therapy in Europe followed by eight VAC/VAI (vincristine, dactinomycin, cyclophosphamide/vincristine, dactinomycin, ifosfamide) cycles versus

VDC/IE/VC (vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide/vincristine, cyclophosphamide), mainly used in the United States. The results showed a significantly better progression-free and OS in the VDC/IE/VC arm.[25] VDC/IE/VC therapy should therefore form the backbone of future interventional studies for ES.

Few studies have reported on EES treated as soft tissue sarcoma with opposing results. Castex et al. compared the outcome of 30 patients treated on MMT-89 without anthracyclines, with 33 treated on Ewing protocol 93 with doxorubicin (5 year EFS 44% vs. 75%, respectively) and concluded that anthracyclines improved outcome[4] in contrast to data reported by Raney and Asmar[26] where 10-year survival rates for patients with EES treated on three IRS clinical trials (IRS-I, -II, and -III) from 1972 to 1991 with vincristine, cyclophosphamide, and dactinomycin (VAC) were 62%, 61%, and 77% with no benefit achieved by the addition of doxorubicin for gross residual tumors, although in the IESS study doxorubicin improved outcome in patients with bone ES.[27]

Applebaum et al. compared 683 EES with 1519 ES patients registered in Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2007 and concluded that patients' characteristics and outcome differ between EES and ES (10-year EFS was 62.6% for EES and 55.3% for ES) and that EES is an important subtype of ES and may require different treatment strategies.[28]

Patients with EES treated on contemporary treatment ES protocols INT-0154 and AEWS0031 had different clinical characteristics and superior EFS in comparison to ES.[2] Despite similar genomic features, 119 genes, especially in tumor microenvironment and angiogenesis, were differentially expressed. The 5-year unadjusted EFS for patients with EES was 76% compared to 69% for patients with skeletal ES, $p = .05$.[2]

All these cited trials conducted over a 40-year period beginning with IRSIII (1971–1991)[26] showed similar EFS of about 70% (65–77%) for patients with localized EES despite basic differences in chemotherapy.[2]

The clinical differences between ES and EES determined also a different approach in the therapy stratification. The most predictive risk factor defined for bone ES is the extent of chemotherapy-induced necrosis assessed histologically in resected tumors.[20] Since EES show different degrees of volume regression, the comparable quantification of the extent of necrosis in resected residual tumors is difficult to report. The stratification of therapy in EES cannot therefore be based on similar risk factors as used for bone ES.

EES have been included in the CWS studies. The Soft Tissue Sarcoma Committee of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) also decided to treat EES due to their clinical similarity according to modified recommendations for high-risk soft tissue sarcoma.

Our data presented here on the therapy strategies for EES in three prospective CWS studies provide what we consider interesting information regarding changes in the strategy over time, specifically the stratification, drugs used, their cumulative doses, and influence on prognosis.

The outcome in CWS-91 and CWS-96 was slightly inferior and in CWS-2002P comparable to the results published for contemporaneous studies that included mainly bone ES[18,20,24] or EES,[2,4,26,28] and this despite the fact that the cumulative doses of ifosfamide and doxorubicin were lower (Table S6).

As the therapy stratification in CWS-91 was identical for RMS and EES, a very small group of patients with primary resected tumors with favorable characteristics was treated successfully with only one or two VACA cycles, this means an extremely low therapy burden. While no one would probably currently treat ES patients with such minimal therapy, it should be considered in the discussion about the optimization of therapy stratification for EES.

Adding etoposide (cumulative doses 5400 mg/mš) to the VAIA cycle in CWS-91 has not improved survival. Similarly, in the randomized EICESS-92 study there was no difference in EFS between VAIA and EVAIE (52% vs. 47%).[18]

The randomized comparison of six drugs cycles CEVAIE (experimental arm) versus four drugs VAIA III (standard arm) in the CWS-96 study showed better EFS and OS in the VAIA arm, without statistical significance. In the "per therapy arm" analysis, the outcome in the VAIA arm was significantly better for EFS and OS. The randomization between CEVAIE and three drugs (IVA) in the MMT95 Study showed no difference in outcome in patients with RMS, EES, and undifferentiated sarcoma.[29]

The poor results in the experimental arm CEVAIE of the CWS-96 randomized trial can possibly be explained by a lower dose of dactinomycin (4.5 mg/m^2 vs. 9 mg/mš in the standard arm), as cumulative doses of ifosfamide, vincristine, and anthracyclines (epirubicine 450 mg/mš, equivalent doxorubicine dose ca. 330 mg/mš) were comparable with the standard arm. The VP-16 and carboplatin given additionally in the CEVAIE regimen were in this combination not effective enough to improve outcome.

In the CWS-2002P study, following completion of intensive, multimodal therapy, there was the option to treat with 6-month MT consisting of cyclophosphamide and vinblastine. There was a trend toward better outcome for patients who received MT. The inferior outcome of 11 patients who did not receive MT must however be interpreted with caution due to the small number of patients and large CI.

The recently published RMS 2005 study demonstrated that MT with cyclophosphamide and vinorelbine improved OS in high-risk RMS patients.[30] Our results could suggest that low-dose metronomic therapy may also have a role in the therapy of ES and hence might deserve further investigation.

Local therapy options for ES consist of surgery, RT, or both. The choice is determined by multiple factors like tumor localization and size, age, and response to chemotherapy. Surgery is recommended whenever possible with or without adjuvant RT. In nonresectable lesions, definitive RT is advised.[20] In the CWS studies, the preoperative RT was recommended when additional tumor reduction to facilitate function-preserving surgery was expected. Examining the role of local control therapy and the ultimate outcome for ES has been very problematic.[31] In the large comparative evaluation of local therapy in localized bone ES treated on three consecutive Children's Oncology Group (COG) protocols (INT-0091, INT-0154, AEWS0031), the local therapy modality was not significantly related to EFS or OS or

distant failure rate but the local failure rate was higher for definitive radiation.[32] EES had been however excluded from this analysis, as they required different local treatment strategies. Randomized studies of local therapy approaches have been limited to two trials evaluating RT and as stated by Gaspar et al. "a future randomized local control study does not seem feasible,"[20] which opinion we share. Because many factors influenced choice of local treatment in our series, patient numbers in different local therapy strategies are low, making it impossible to assess the role of local therapy modality on outcome. Our analysis has some other limitations. Due to many different chemotherapy strategies, the patient numbers in each arm are low and CIs large, limiting the interpretation of EFS and OS. Another is the retrospective nature of the analysis, which includes three studies carried out over 20 years.

In four patients (1.6%), SMs were diagnosed, three AML and one osteosarcoma, 2, 5, 7, and 8 years after diagnosis, three of them were treated with etoposide. In the analysis of Paulussen et al., the cumulative SM 5 years risk after diagnosis of ES was 0.0093, zero for patients without etoposide and 0.0118 for patients with etoposide.[33] It is worthwhile stressing that two SM in our patients occurred at 7 and 8 years after diagnosis, a longer observation time is therefore obviously needed to assess the entire risk for SM.

In summary, the results of our analysis provide interesting information on the treatment and specificities of EES, which can be useful for a better understanding of this rare entity and should be considered in the development of future clinical trials for ES defined as FET–ETS fusion positive tumors.

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CONFLICT OF INTEREST

The authors made no disclosure.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Bernarda Kazanowska https://orcid.org/0000-0002-1519-7569
Ruth Ladenstein https://orcid.org/0000-0001-9551-2399
Gustaf Ljungman https://orcid.org/0000-0002-4138-4536
on behalf of the CWS Study Group https://orcid.org/0000-0001-9280-1451

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SUPPORTING INFORMATION

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

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