Prognostic and therapeutic factors influencing the clinical outcome of metastatic Ewing's sarcoma family of tumors: a retrospective report from the Japan Ewing Sarcoma Study Group

Journal:	*Pediatric Blood & Cancer*
Manuscript ID	PBC-20-1595.R2
Wiley - Manuscript type:	Oncology: Research Article
Date Submitted by the Author:	n/a
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Keywords:	Ewing's sarcoma family of tumors, metastatic, Chemotherapy, Stem Cell Transplantation

RESEARCH ARTICLE

Prognostic and therapeutic factors influencing the clinical outcome of metastatic Ewing's sarcoma family of tumors: a retrospective report from the Japan Ewing Sarcoma Study Group

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Running head: Clinical outcome of metastatic ESFT

Text word count: 2,214

Abstract word count: 195

Tables: 3, Figures: 2

Supplementary Tables: 3, Supplementary Figures: 1

References: 29

ABBREVIATIONS

ACT	Actinomycin D
BU	Busulfan
CI	Confidence interval
CPA	Cyclophosphamide
CR	Complete response
DXR	Doxorubicin
ESFT	Ewing's sarcoma family of tumors
ETP	Etoposide
EWSR	Ewing's sarcoma breakpoint region
FISH	Fluorescent in situ hybridization
IE	Ifosfamide+etoposide
IFM	Ifosfamide
OS	Overall survival
MEL	Melphalan
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
SCT	Stem cell transplantation

TPT	Topotecan
VACA	Vincristine+actinomycin D+cyclophosphamide+doxorubicin
VAIA	Vincristine+actinomycin D+ifosfamide+doxorubicin
VCR	Vincristine
VDC	Vincristine+doxorubicin+cyclophosphamide
VIDE	Vincristine+ifosfamide+doxorubicin+etoposide

ABSTRACT

Background. The prognosis of patients with metastatic Ewing's sarcoma family of tumors (ESFT) remains poor. ***Procedure.*** We retrospectively analyzed 57 patients diagnosed with metastatic ESFT between 2000 and 2018 to identify prognostic and therapeutic factors affecting the clinical outcome. ***Results.*** The 3-year overall survival (OS) rate of the entire cohort was 46.8% [95% confidence interval (CI), 33.0–59.4%]. Treatment-related death was not observed. Multivariate analysis identified stem cell transplantation (SCT), response to first-line chemotherapy, and bone metastasis as independent risk factors for OS. Objective response rate to first-line chemotherapy was 65.1% in the 43 evaluable patients. There was no significant difference in the response to different types of first-line chemotherapy. Among patients with lung metastasis alone, the 3-year OS rate was higher in 13 patients who received local treatment than in four who did not, although the difference was not significant. ***Conclusions.*** One possible reason for the high OS rates was the absence of treatment-related mortality even in patients receiving SCT, which could be attributed to advances in the management of post-SCT complications. Novel first-line chemotherapy strategies need

62 to be established to improve the disease status prior to SCT in a higher proportion of
63 patients.
64
65 Keywords: Ewing's sarcoma family of tumors; metastatic; chemotherapy; stem cell
66 transplantation.
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1 | INTRODUCTION

Ewing's sarcoma family of tumors (ESFT), the second most frequent bone tumor in children and young adults, is driven by an Ewing's sarcoma breakpoint region (EWSR)1 fusion oncogene.[1] Metastasis, which most commonly affects the bone, lung, and bone marrow, is detected in approximately 20–30% of patients with ESFT at initial diagnosis.[1,2] The long-term survival rate of patients with metastatic ESFT is <30%,[1–6] which is lower than that of localized ESFT.[1,2,7–9] The main prognostic factors in patients with ESFT are age at diagnosis, tumor volume, modality of metastasis (i.e., bone marrow involvement, number of bone metastasis, and additional lung metastasis), and histological or radiological response of the primary tumor to first-line chemotherapy.[6,10–12]

One of the main causes of a poor outcome in patients with metastatic ESFT is a poor response to chemotherapy. Multidrug chemotherapy regimens established as first-line chemotherapy for localized ESFT, such as vincristine (VCR)+doxorubicin (DXR)+cyclophosphamide (CPA; VDC) alternating with ifosfamide (IFM)+etoposide (ETP; IE), VCR+actinomycin D (ACT)+CPA+DXR (VACA), VCR+ACT+IFM+DXR (VAIA), and VCR+IFM+DXR+VP16 (VIDE), are often ineffective for metastatic ESFT.[3,6,13] In Western countries, the efficacy of intensified chemotherapy has been investigated by adding another anticancer drug to these combination chemotherapies, or by increasing the dose of each anticancer drug. However, these therapeutic approaches have increased the incidence of acute and late adverse effects without improving the curative rate.[7,13–15] Furthermore, evidence supporting the clinical benefit of stem cell

transplantation (SCT)[5,10,11,16–22] or local treatment (surgery and radiotherapy) for primary site or metastatic disease in ESFT remains limited.[23–25]

Here, we retrospectively analyzed the clinical outcomes of patients with metastatic ESFT to evaluate the prognostic and therapeutic factors affecting patient outcome in the recent era.

2 | MATERIALS AND METHODS

Study design and data collection

This study was approved by the Clinical Research Review Committee of the Japan Children's Cancer Group, and the institutional ethics committee of Kyoto University Hospital. A questionnaire was distributed to 51 institutions (see Appendix for detail) to gather information about patient characteristics, treatment, and clinical outcome of patients who were diagnosed with metastatic ESFT between 2000 and 2018 from medical records. Data from 67 patients were obtained from the 29 institutions. Of the 67 patients, eight were excluded due to a lack of data on survival status (n = 2) or EWS-ETS fusion gene (n = 6). One patient with central nervous system ESFT and another with Ewing-like sarcoma harboring the BCOR-CCNB fusion gene were also excluded. EWS-ETS fusion genes, including *EWS-FLI1* (n = 39) and *EWS-ERG* (n = 2), were detected in 41 patients by reverse transcription polymerase chain reaction. In the remaining 16 patients, the EWSR1 translocation was detected by fluorescent in situ hybridization (FISH). In total, 57 patients with metastatic ESFT were analyzed.

The radiological response to chemotherapy was evaluated according to RECIST guidelines (version 1.1).[26]

Statistical analysis

The characteristics of patients in the two groups were compared using Fisher's exact test for categorical variables. The probability of overall survival (OS), defined as the duration of survival between the diagnosis and either death or the last follow-up, and progression-free survival (PFS), defined as the duration of survival between the diagnosis and either disease progression, death, or the last follow-up, were estimated using the Kaplan-Meier method; the log-rank test and Cox proportional hazard model were used for univariate and multivariate analyses, respectively. The factors included in the analyses were patient age group (0–12 years *vs.* ≥13), gender (male *vs.* female), fusion gene (*EWS-FLI1 vs*. *EWS-ERG vs*. *EWS-FEV vs*. EWSR1-FISH), primary tumor origin (bone *vs.* soft tissue), primary tumor site (extremity *vs.* axial *vs.* other), primary tumor size (<200 ml *vs.* ≥200 ml), lung metastasis (isolated *vs*. combined *vs*. no), bone marrow metastasis (no *vs.* yes), bone metastasis (no *vs*. 1–4 *vs*. ≥5), response to first-line salvage chemotherapy [complete response (CR)/partial response (PR) *vs*. stable disease (SD)/progressive disease (PD)], SCT (no *vs.* yes), and type of SCT (single autologous SCT *vs.* other types of SCT, including tandem autologous SCT, single allogeneic SCT, and tandem autologous-allogeneic SCT). Factors with P <0.1 in the univariate analysis were included in the multivariate analysis. The response to first-line chemotherapy was evaluated by univariate analysis using Pearson's chi-square test. All

statistical analyses were performed using EZR (version 1.32, Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (the R Foundation for Statistical Computing).[27]

3 | RESULTS

Patient characteristics

Of 51 surveyed institutions, 29 (56.9%) responded. The characteristics of the 57 patients included in the study are shown in Table 1. Of the 57 patients, 35 received SCT [SCT (+) group], whereas 22 patients did not [SCT (-) group]. Patients in the SCT (+) group were more likely to be younger at diagnosis and to have a primary tumor in the bone. Fifty patients were initially treated with chemotherapy before local treatment, including VDC/IE at 2-week (n = 11) or 3-week (n = 24) intervals, VIDE (n = 7), and VAIA (n = 3). Five of the remaining seven patients received chemotherapy, including VCR+ACT+IFM (n = 2), VDC/IE at 3-week intervals (n = 1), VIDE (n = 1), and VAIA (n = 1), after local treatment for primary site tumors or metastasis. Nine patients underwent surgery, 29 received radiotherapy, and 14 received both as local treatment for primary site tumors. One patient underwent surgery, 32 received radiotherapy, and four received both as local treatment for metastasis.

Factors affecting overall and progression-free survival

The 3-year OS rate of the entire cohort was 46.8 % [95% confidence interval (CI), 33.0–59.4%]. Treatment-related death was not observed. One female patient developed

a secondary follicular thyroid carcinoma outside the irradiated field 5 years and 10 months after the treatment. In the multivariate analysis, in addition to bone metastasis and response to first-line chemotherapy, SCT was identified as the independent risk factor for OS (adjusted hazard ratio, 0.14; 95% CI, 0.05–0.46, $P = 0.001$; Table 2). The 3-year PFS rate of the entire cohort was 41.4% (95% CI, 28.0–54.2%). Multivariate analysis of factors affecting PFS showed that in addition to lung metastasis and response to first-line chemotherapy, SCT was identified as the independent risk factor (adjusted hazard ratio, 0.23; 95% CI, 0.08–0.65, $P = 0.005$; Supplementary Table 1). The 3-year OS and PFS rates grouped by SCT and adjusted for other potential confounding factors were 74.8% (95% CI, 59.0–94.7%) and 60.4% (95% CI, 43.4–84.0%), respectively, in patients who underwent SCT, and 22.5% (95% CI, 7.8–64.5%) and 15.2% (95% CI, 9.9–74.7%), respectively, in those who did not (Fig. 1a and b).

Among the 43 patients evaluable for radiological response to first-line chemotherapy before local treatment, there were 4 CR, 24 PR, 10 SD, and 5 PD, with an objective response rate (CR+PR) of 65.1%. There was no significant difference in the response to different types of first-line chemotherapy ($P = 0.960$, Fig. 2).

Clinical significance of SCT

The clinical information of 35 patients undergoing SCT is shown in Supplementary Table 2. The 35 patients received median 6 (range, 2–16) cycles of firs-line chemotherapy. The attending physicians at each hospital chose the conditioning regimen or modality of SCT. Twenty-three patients received single autologous SCT,

eight received tandem autologous SCT, one received single allogeneic SCT, and three received tandem autologous-allogeneic SCT. The most common conditioning regimens were busulfan (BU)+melphalan (MEL) (n = 18), ETP+MEL (n = 7), CBDCA+ETP+MEL (n = 6), and topotecan (TPT)+CPM+MEL (n = 4).

The effect of other confounding factors on the benefits of SCT was analyzed. Univariate analysis of factors affecting OS in patients receiving SCT identified primary tumor site, response to first-line chemotherapy, type of SCT, and disease status before SCT as significant factors (Table 3). Univariate analysis of factors affecting PFS demonstrated similar tendencies (Supplementary Table 3). Multivariate analysis of factors affecting OS and PFS was not performed because of the low number of patients included in the study. The 3-year OS and PFS rates in patients receiving single autologous SCT were significantly lower than those in patients receiving other types of SCT ($P = 0.018$ and 0.035, Supplementary Fig. 1a and b). Among patients who underwent single autologous SCT, the 3-year OS rate was significantly higher in patients receiving BU+MEL than in those receiving other conditioning regimens (53.8%; 95% CI, 24.8–76.0% *vs*. 0%; $P = 0.035$), as previously reported.[20]

Impact of local treatment of lung metastasis on clinical outcome

The 3-year OS rate in 17 patients with lung metastasis alone was 68.8% (95% CI, 40.0–85.9%). After grouping patients by local treatment for lung metastases, the 3-year OS rate was higher in 13 patients who received local treatment than in four patients who did

not, although the difference was not statistically significant [100% *vs.* 59.3% (95% CI 27.5–81.0%), $P = 0.176$].

4 | DISCUSSION

In the present study, OS and PFS rates in patients with metastatic ESFT were higher than those reported previously.[1,3–6] One possible reason for the encouraging outcome is the absence of treatment-related mortality even in patients receiving SCT, which could be attributed to advances in the management of post-SCT complications. Another possible explanation is that the present study included a higher proportion of younger patients with a better outcome, although OS and PFS rates did not differ significantly between younger and older age groups.

The present study identified response to first-line chemotherapy and SCT as independent risk factors for both OS and PFS. Previous reports demonstrating the clinical benefit of SCT excluded patients who did not achieve CR or PR, which introduces selection bias favoring patients with a better clinical course.[10,17,20] By contrast, the present study, which included such chemotherapy-resistant patients, demonstrated the contribution of SCT to increasing OS after adjusting for other potential confounding factors, including lung metastasis, bone metastasis, and response to first-line chemotherapy.

Allogeneic SCT for metastatic ESFT is not regarded favorably because it is associated with a higher rate of complications, and because there is a lack of evidence supporting the immune-mediated graft-versus-Ewing tumor effect.[11,16,18] The clinical

benefit of tandem SCT also remains controversial.[18,19,21,22] The present study demonstrated that OS and PFS are somewhat better in patients treated with other types of SCT (tandem and/or allogeneic SCT) than in those receiving single autologous SCT, although the clinical significance of tandem or allogeneic SCT was not evaluated individually because of the low number of patients included in the study. There was no treatment-related mortality among patients receiving other types of SCT, which can be attributed to advances in the management of post-SCT complications. However, the data should be interpreted with caution because treatment bias (i.e., contraindication of other types of SCT in patients with worse disease status or general conditions) may affect the clinical outcome.

Histological or radiological response to first-line chemotherapy is a strong prognostic factor in patients with metastatic ESFT.[12] The radiological objective response rate in the present study (65.1%) was almost equivalent to that reported previously,[12] although there is still room for improvement. Intensification of chemotherapy with established activity against localized ESFT has reached maximal efficacy and toxicity; therefore, novel first-line therapies need to be established to improve disease status prior to SCT in a higher proportion of patients with metastatic ESFT. Among novel therapies, interval-compressed chemotherapy, which has increased efficacy without increasing toxicity,[8] should lead to favorable results. Alternatively, recently established salvage chemotherapy regimens for recurrent or refractory ESFT, such as TPT+CPA and irinotecan+temozolomide,[27,28] are good candidates for first-line therapy.

Consistent with previous analyses,[3,6,14] the present study demonstrated that the prognosis of patients with lung metastasis alone is better than that of patients with bone and/or bone marrow metastasis. Furthermore, surgery or whole lung irradiation have a potentially significant therapeutic effect in patients with lung metastasis alone.[23–25] However, these results may be associated with treatment selection bias because local treatment was performed according to the response to first-line chemotherapy or disease status. The clinical significance of local treatments for metastatic disease needs to be evaluated in prospective analyses of larger populations. The ongoing Euro-Ewing-Intergroup EE99 trial, which compares whole lung irradiation with high-dose chemotherapy plus SCT following standard chemotherapy in patients with lung metastasis alone will clarify this point.

The present study had several limitations. First, it is a retrospective analysis of data from a heterogeneous group of patients. Second, the association between surgical margin or histological response to first-line chemotherapy and clinical outcome was not examined because these data were lacking in most patients, which hampered more extensive evaluation of their clinical significance. Lastly, the follow-up period was too short to evaluate late adverse effects, particularly secondary malignancies. Nonetheless, the present study demonstrated that SCT contributes to a significantly better clinical outcome in patients with metastatic ESFT, especially in those with a better disease status prior to SCT.

ACKNOWLEDGEMENTS

We thank all doctors who responded to the questionnaire.

AUTHOR CONTRIBUTIONS

KU, TM, KY, MC, and TO designed the research and organized the project. KU, TM, and HS performed statistical analyses and analyzed the data. KU wrote the manuscript. TK, NM, HF, RJ, AW, YS, DH, ST, and SN collected data. HS, AH, MS, HO, MC, and TO assisted with the interpretation of data and provided insightful comments. All authors interpreted the data and reviewed and approved the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

374 **Fig. 1** OS (a) and PFS rates (b) grouped by SCT. The survival curves were adjusted for
375 other potential confounding factors. OS, overall survival; PFS, progression-free
376 survival.
377
378 **Fig. 2** Radiological response to first-line chemotherapy before local treatment grouped
379 by type of chemotherapy. CR, complete response; PR, partial response; SD, stable
380 disease; PD, progressive disease; VDC, vincristine+doxorubicin+cyclophosphamide;
381 IE, ifosfamide+etoposide; VIDE, vincristine+ifosfamide+doxorubicin+etoposide;
382 VAIA, vincristine+actinomycin D+ifosfamide+doxorubicin.
383
384 **Supplementary Fig. 1** OS (a) and PFS rates (b) grouped by type of SCT. OS, overall
385 survival; PFS, progression-free survival; auto-SCT, autologous stem cell
386 transplantation.

Figure 1

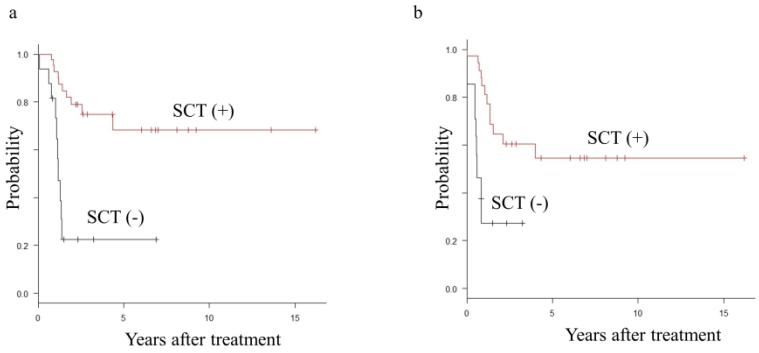


Fig. 1

338x190mm (300 x 300 DPI)

Figure 2

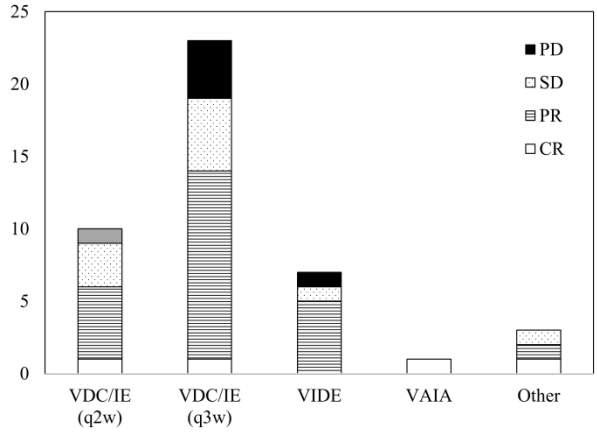


Fig. 2

338x190mm (300 x 300 DPI)

Table 1. Patient characteristics at initial diagnosis and treatment

Characteristics	All patients (n = 57)		SCT (-) (n = 22)		SCT (+) (n = 35)		P-value
	No.	%	No.	%	No.	%	
Gender							
Male	29	50.9	11	50.0	18	51.4	1.000
Female	28	49.1	11	50.0	17	48.6	
Age at diagnosis, years							
Median (range)	14 (3–33)		15 (3–33)		12 (4–26)		
0–12	22	38.6	4	18.2	18	51.4	0.014
≥13	35	61.4	18	81.8	17	48.6	
Primary tumor site							0.291
Axial	29	50.9	9	40.9	20	57.1	
Extremity	16	28.0	6	27.3	10	28.6	
Other	9	15.8	6	27.3	3	8.6	
Missing	3	5.3	1	4.6	2	5.7	
Primary tumor origin							0.023
Bone	37	64.9	10	45.5	27	77.1	
Soft tissue	20	35.1	12	54.5	8	22.9	
Primary tumor volume, ml							
Median (range)	314 (19–1,953)		408 (19–1,953)		314 (19–1,383)		
<200 ml	13	22.8	5	22.7	8	22.9	0.940
≥200 ml	27	47.4	11	50.0	16	45.7	

Missing	17	29.8	6	27.3	11	31.4	
Fusion gene							0.786
EWS-FLI1	39	68.5	16	72.7	23	65.7	
EWS-ERG	2	3.5	1	4.6	1	2.9	
EWS-FISH	16	28	5	22.7	11	31.4	
Sites of metastasis							0.105
Lung alone	18	31.6	6	27.3	12	34.3	
Bone (plus lung)	29 (15)	50.9	9 (3)	40.9	20 (12)	57.1	
BM and bone (plus lung)	4 (2)	7.0	2 (2)	9.1	2 (0)	5.7	
Other	6	10.5	5	22.7	1	2.9	
Initial chemotherapy beofe local treatment							0.237
VDC/IE q2w	11	19.4	7	31.8	4	11.4	
VDC/IE q3w	25	43.9	10	45.5	14	40.0	
VIDE	7	12.3	1	4.6	6	17.1	
VAIA	3	5.3	0	0	3	8.6	
Other	5	8.8	1	4.6	4	11.4	
No	7	12.3	3	13.6	4	11.4	
Local treatment for primary site							0.386
Surgery	9	15.8	2	9.1	7	20.0	
Radiotherapy	29	50.9	10	45.5	19	54.3	
Surgery and radiotherapy	14	24.5	8	36.4	6	17.1	
No	5	8.8	2	9.1	3	8.6	

Local treatment for metastasis							0.316
Surgery	1	5.8	1	4.6	0	0	
Radiotherapy	32	56.1	10	45.5	22	62.9	
Surgery and radiotherapy	4	7.0	1	4.6	3	8.6	
No	20	35.1	10	45.5	10	28.6	
Follow-up period, months							
Median (range)	27 (0–177)		15 (0–162)		31 (0–177)		

SCT, stem cell transplantation; EWSR, Ewing's Sarcoma Region; FISH, fluorescent in situ hybridization; VDC, vincristine-doxorubicin-cyclophosphamide, IE, ifosfamide-etoposide; q2w, every 2 weeks; q3w, every 3 weeks; VAIA, vincristine-actinomycin-ifosfamide-doxorubicin; VIDE, vincristine--ifosfamide-doxorubicin-etoposide.

Table 2. Univariate and multivariate analyses of factors affecting OS

Variables	Factors (n)	3yr OS, % (95% CI)	Univariate analysis *P*-value	Multivariate analysis HR (95% CI)	Multivariate analysis *P*-value
Age group	0–12 (22)	56.8 (33.0–75.0)	0.178	N.E.	N.E.
	≥13 (35)	39.9 (23.3–55.9)			
Gender	Male (29)	48.2 (28.2–65.6)	0.995	N.E.	N.E.
	Female (28)	45.4 (26.4–62.6)			
Fusion gene	EWS-FLI1 (39)	48.5 (31.5–63.6)	0.989	N.E.	N.E.
	EWS-ERG (2)	50.0 (0.6–91.0)			
	EWS-FISH (16)	41.7 (17.4–64.5)			
Primary tumor origin	Bone (37)	52.4 (34.9–67.2)	0.307	N.E.	N.E.
	Soft tissue (20)	37.0 (15.9–58.5)			
Primary tumor site	Axial (29)	57.8 (37.8–73.5)	0.274	N.E.	N.E.
	Extremity (16)	40.4 (16.7–63.1)			
	Other (9)	27.8 (4.4–59.1)			
Primary tumor size	<200 ml (13)	40.3 (13.7–66.0)	0.965	N.E.	N.E.
	≥200 ml (27)	40.3 (20.9–59.0)			
Lung metastasis	Isolated (18)	70.0 (41.5–86.5)	0.009	Reference	
	Combined (17)	46.3 (22.1–67.6)		0.77 (0.12–5.18)	0.790
	No (22)	29.0 (11.9–48.7)		2.89 (0.58–14.4)	0.194
Bone marrow metastasis	No (53)	46.4 (32.0–59.5)	0.942	N.E.	N.E.
	Yes (4)	50.0 (5.8–84.5)			
Bone metastasis	No (24)	60.9 (37.9–77.6)	0.065	Reference	

	1–4 (19)	49.7 (25.4–70.0)		2.77 (0.55–13.9)	0.216
	≥5 (12)	25.0 (6.0–50.5)		7.23 (1.09–47.8)	0.040
Response to initial chemotherapy	CR/PR (28)	61.7 (40.3–77.4)	0.017	Reference	
	SD/PD (15)	26.7 (8.3–49.6)		9.17 (2.64–31.9)	<0.001
SCT	No (22)	31.5 (12.9–52.1)	0.039	Reference	
	Yes (35)	51.5 (33.0–67.3)		0.14 (0.05–0.46)	0.001

OS, overall survival; CI, confidence interval; HR, hazard ratio; N.E., not evaluated; EWSR, Ewing's Sarcoma Region; FISH, fluorescent in situ hybridization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SCT, stem cell transplantation.

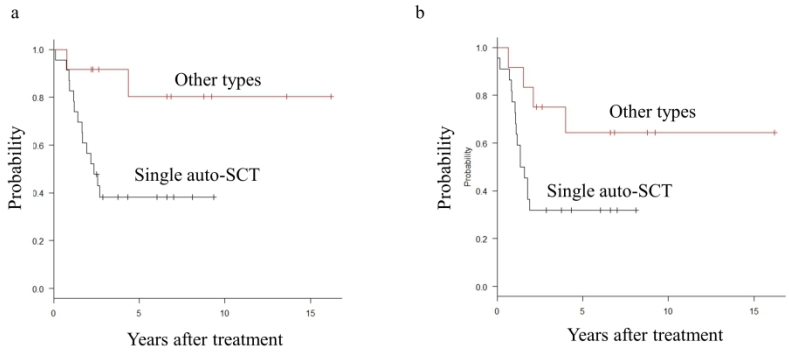
Table 3. Univariate analysis of factors affecting OS in patients receiving SCT

Variables	Factors (n)	3-yr OS, % (95% CI)	Univariate analysis *P*-value
Age group	0–12 (18)	57.8 (30.6–77.6)	0.657
	≥13 (17)	52.9 (27.6–73.0)	
Gender	Male (18)	52.5 (26.5–73.2)	0.512
	Female (17)	58.8 (32.5–77.8)	
Fusion gene	EWS-FLI1 (23)	55.5 (33.0–73.2)	0.700
	EWS-ERG (1)	0	
	EWSR1-FISH (11)	50.9 (18.2–76.6)	
Primary tumor origin	Bone (27)	55.3 (34.9–71.7)	0.633
	Soft tissue (8)	56.2 (14.7–84.2)	
Primary tumor site	Extremity (10)	40.0 (12.3–67.0)	0.021
	Axial (20)	74.0 (48.2–88.3)	
	Other (3)	0	
Primary tumor size	<200 ml (8)	46.9 (12.0–76.3)	0.851
	≥200 ml (16)	46.9 (20.8–69.4)	
Lung metastasis	No (11)	36.4 (11.2–62.7)	0.071
	1–4 (11)	71.6 (35.0–89.9)	
	≥ 5 (11)	53.0 (20.9–77.3)	
Bone marrow metastasis	No (33)	56.1 (37.1–71.3)	0.720
	Yes (2)	50.0 (0.6–91.0)	

Bone metastasis	No (13)	75.2 (40.7–91.4)	0.081
	1–4 (12)	58.3 (27.0–80.1)	
	≥5 (9)	33.3 (7.8–62.3)	
Response to initial chemotherapy	CR/PR (17)	75.6 (47.3–90.1)	0.042
	SD/PD (10)	40.0 (12.3–67.0)	
Local treatment for primary site	No (3)	0	0.477
	Radiotherapy (19)	50.7 (26.3–70.8)	
	Surgery (7)	57.1 (17.2–83.7)	
	Surgery and radiotherapy (6)	83.3 (27.3–97.5)	
Local treatment for metastasis	No (10)	60.0 (25.3–82.7)	0.985
	Radiotherapy (22)	53.4 (30.6–71.7)	
	Surgery and radiotherapy (3)	66.7 (5.4–94.5)	
Type of SCT	Single auto SCT (23)	38.3 (18.9–57.4)	0.018
	Other types (12)	91.7 (53.9–98.8)	
Disease status before SCT	CR/PR (23)	68.7 (45.3–83.8)	0.042
	SD/PD (9)	33.3 (7.8–62.3)	

OS, overall survival; CI, confidence interval; HR, hazard ratio; N.E., not evaluated; EWSR, Ewing's Sarcoma Region; FISH, fluorescent in situ hybridization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SCT, stem cell transplantation; auto, autologous.

Supplementary Figure 1



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Supplementary Table 1. Univariate and multivariate analyses of factors affecting PFS

Variables	Factors (n)	3yr PFS, % (95% CI)	Univariate analysis *P*-value	Multivariate analysis HR (95% CI)	Multivariate analysis *P*-value
Age group	0–12 (22)	45.5 (24.4–64.3)	0.674	N.E.	N.E.
	≥13 (32)	38.5 (21.6–55.2)			
Gender	Male (27)	35.2 (17.9–53.1)	0.227	N.E.	N.E.
	Female (27)	47.6 (28.1–64.9)			
Fusion gene	EWS-FLI1 (37)	44.5 (28.0–59.8)	0.976	N.E.	N.E.
	EWS-ERG (2)	50.0 (0.6–91.0)			
	EWSR1-FISH (15)	33.3 (12.2–56.4)			
Primary tumor origin	Bone (35)	50.2 (32.7–65.5)	0.051	Reference	
	Soft tissue (19)	23.7 (7.6–44.7)		2.27 (0.85–6.06)	0.102
Primary tumor site	Axial (28)	50.0 (30.6–66.6)	0.189	N.E.	N.E.
	Extremity (15)	36.7 (13.6–60.4)			
	Other (8)	16.7 (0.9–50.8)			
Primary tumor size	<200 ml (13)	35.2 (11.2–60.7)	0.962	N.E.	N.E.
	≥200 ml (25)	34.7 (16.9–53.2)			
Lung metastasis	Isolated (18)	53.8 (28.4–73.7)	0.055	Reference	
	Combined (16)	50.0 (24.5–71.0)		1.74 (0.56–5.40)	0.336
	No (20)	21.7 (6.8–41.9)		3.41 (1.09–10.6)	0.035
Bone marrow metastasis	No (50)	40.6 (26.8–54.0)	0.771	N.E.	N.E.
	Yes (4)	50.0 (5.8–84.5)			
Bone metastasis	No (24)	44.6 (24.3–63.2)	0.456	N.E.	N.E.

	1–4 (19)	45.1 (22.1–65.7)			
	≥5 (10)	30.0 (7.1–57.8)			
Response to initial chemotherapy	CR/PR (27)	58.2 (37.3–74.4)	0.045	Reference	
	SD/PD (13)	23.1 (5.6–47.5)		4.30 (1.62–11.4)	0.003
SCT	No (20)	33.3 (14.1–54.0)	0.036	Reference	
	Yes (34)	47.1 (29.8–62.5)		0.23 (0.08–0.65)	0.005

PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; N.E., not evaluated; EWSR, Ewing's Sarcoma Region; FISH, fluorescent in situ hybridization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SCT, stem cell transplantation.

Supplementary Table 2. Clinical information of patients undergoing SCT

No.	Age at diagnosis (yr)	Sex	Lung metastasis	Bone metastasis	BM metastasis	Local treatment for primary site (timing)	Local treatment for metastatic site (timing)	Cycle number of first-line chemotherapy	Disease status before SCT	First SCT source (regimen)	Second SCT source (regimen)	Outcome (mo)
1	15	M	1 to 4	Yes (NA)	No	R (post-SCT)	R (post-SCT)	6	PR	Auto-PB (CBDCA, ETP, MEL)	–	28 (DOD)
2	11	F	No	No	No	R (pre-SCT)	R (pre-SCT)	7	PR	Auto-PB (BU, MEL)	–	80 (AWD)
3	11	F	5	No	No	R (pre-SCT)	No	5	NA	Auto-PB (ETP, MEL)	–	32 (DOD)
4	15	M	No	1 to 4	No	R (post-SCT)	R (post-SCT)	8	PD	Auto-PB (BU, MEL)	–	20 (DOD)
5	8	M	Yes (NA)	No	No	S (pre-SCT)/R (post-SCT)	R (post-SCT)	4	CR	Auto-PB (MEL, TEPA)	–	30 (NED)
6	10	F	No	1 to 4	No	S (pre-SCT)	R (pre-SCT)	5	NA	Auto-PB (BU, MEL)	–	45 (NED)
7	14	F	1 to 4	1 to 4	No	R (pre-SCT)	R (pre-SCT)	16	PR	Auto-PB (BU, MEL)	–	34 (NED)

8	16	M	1 to 4	1 to 4	No	S (pre-SCT)	S (pre-SCT)/R (pre-SCT)	8	CR	Auto-PB (BU, MEL)	–	73 (NED)
9	7	F	No	1 to 4	No	S (pre-SCT)	R (post-SCT)	2	PD	Auto-PB (MEL, TEPA)	–	10 (DOD)
10	20	M	5	No	No	S (pre-SCT)/R (pre-SCT)	No	4	CR	Auto-PB (CBDCA, ETP, MEL)	–	113 (NED)
11	10	F	5	No	No	R (pre-SCT)	No	5	PR	Auto-PB (BU, MEL)	–	98 (NED)
12	12	F	No	5	Yes	S (pre-SCT)	R (pre-SCT)	6	NA	Auto-PB (TPT, CPM, MEL)	–	8 (DOD)
13	13	M	1 to 4	1 to 4	No	S (pre-SCT)	R (post-SCT)	6	PR	Auto-PB (TPT, CPM, MEL)	–	20 (DOD)
14	12	M	No	5	No	R (post-SCT)	R (post-SCT)	8	PR	Auto-PB (BU, MEL)	–	31 (DOD)
15	14	M	No	5	No	No	R (pre-SCT)	11	PR	Auto-PB (BU, MEL)	–	14 (DOD)
16	8	M	5	1 to 4	No	S (pre-SCT)/R (post-SCT)	R (post-SCT)	4	PR	Auto-PB (BU, MEL)	–	52 (NED)
17	17	F	5	1 to 4	No	R (pre-SCT)	R (post-SCT)	6	SD	Auto-PB (BU, MEL)	–	26 (DOD)

18	11	F	5	5	No	R (pre-SCT)	R (pre-SCT)	6	PR	Auto-PB (ETP, MEL)	–	14 (DOD)
19	12	F	1 to 4	No	No	R (pre-SCT)	No	3	PR	Auto-PB (ETP, TEPA)	–	17 (DOD)
20	12	M	5	No	No	R (post-SCT)	No	5	SD	Auto-PB (BU, MEL)	–	10 (DOD)
21	12	F	1 to 4	No	No	S (pre-SCT)	No	5	CR	Auto-PB (BU, MEL)	–	85 (NED)
22	26	M	No	5	No	S (pre-SCT)/R (pre-SCT)	S (pre-SCT)/R (pre-SCT)	7	CR	Auto-PB (BU, MEL)	–	1 (DOD)
23	16	F	5	5	No	No	No	4	SD	Auto-PB (MEL, TEPA)	–	23 (DOD)
24	15	M	No	1 to 4	No	R (post-SCT)	R (post-SCT)	3	SD	Auto-PB (CBDCA, ETP, MEL)	Auto-PB (BU, MEL)	9 (DOD)
25	4	M	5	No	No	S (pre-SCT)	No	4	CR	Auto-PB (ETP, TEPA)	Auto-PB (CBDCA, ETP, MEL)	165 (NED)
26	13	M	1 to 4	No	No	R (post-SCT)	R (post-SCT)	5	CR	Auto-PB (ETP, MEL)	Auto-PB (ETP, MEL)	80 (NED)
27	13	F	No	5	Yes	R (post-SCT)	R (post-SCT)	2	PR	Auto-PB (TPT, CBDCA, TEPA)	Auto-PB (BU, MEL)	197 (NED)

28	4	M	5	No	No	R (post-SCT)	S (post-SCT)/R (post-SCT)	6	PD	Auto-PB (TPT, CPM, MEL)	Auto-PB (BU, MEL)	26 (AWD)
29	14	M	1 to 4	5	No	R (post-SCT)	R (post-SCT)	6	SD	Auto-PB (TPT, CPM, MEL)	Auto-PB (BU, MEL)	31 (NED)
30	15	M	No	1 to 4	No	R (pre-SCT)	No	6	CR	Auto-PB (ETP, TEPA)	Auto-PB (ETP, MEL)	53 (DOD)
31	10	F	1 to 4	No	No	R (post-SCT)	No	6	SD	Auto-PB (ETP, MEL)	Auto-PB (ETP, MEL)	83 (NED)
32	10	M	1 to 4	1 to 4	No	No	R (post-SCT)	6	CR	MMR-PB (FLU, MEL, ATG)	–	27 (NED)
33	14	F	5	No	No	S (post-SCT)/R (pre-SCT)	R (post-SCT)	6	PR	Auto-PB (CBDCA, ETP, CPM)	MR-BM (CPM, MEL)	112 (NED)
34	11	F	1 to 4	5	No	S (post-SCT)/R (pre-SCT)	R (post-SCT)	6	PR	Auto-PB (CBDCA, ETP, CPM)	MMR-BM (CPM, MEL)	112 (NED)
35	13	F	Yes (NA)	1 to 4	No	R (post-SCT)	R (post-SCT)	2	PR	Auto-PB (BU, MEL)	MMR-PB (FLU, MEL)	106 (NED)

SCT, stem cell transplantation; yr, years; mo, months; F, female; M, male; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Auto-PB, autologous peripheral blood stem cells; MMR-PB, HLA-mismatched related peripheral blood stem cells; MR-PB, HLA-matched related peripheral blood stem cells; UR-CB, unrelated cord blood; ETP, etoposide; BU, busulfan; MEL,

melphalan; FLU, fludarabine; ATG, anti-thymocyte globulin; IFO, ifosfamide; CBDCA, carboplatin; TEPA, thiotepa; TBI, total body irradiation; DOD, died of disease; DOC, died of complications; AWD, alive with disease; NED, no evidence of disease.

Supplementary Table 3. Univariate analysis of factors affecting PFS in patients receiving SCT

Variables	Factors (n)	3-yr PFS, % (95% CI)	Univariate analysis *P*-value
Age group	0–12 (18)	50.0 (25.9–70.1)	0.930
	≥13 (16)	43.8 (19.8–65.6)	
Gender	Male (18)	33.3 (13.7–54.5)	0.072
	Female (16)	62.5 (34.9–81.1)	
Fusion gene	EWS-FLI1 (22)	50.0 (28.2–68.4)	0.630
	EWS-ERG (1)	0	
	EWSR1-FISH (11)	36.4 (11.2–62.7)	
Primary tumor origin	Bone (26)	50.0 (29.9–67.2)	0.980
	Soft tissue (8)	37.5 (8.7–67.4)	
Primary tumor site	Extremity (10)	30.0 (7.1–57.8)	0.014
	Axial (19)	63.2 (37.9–80.4)	
	Other (3)	0	
Primary tumor size	<200 ml (8)	37.5 (8.7–67.4)	0.714
	≥200 ml (15)	33.3 (12.2–56.4)	
Lung metastasis	No (11)	27.3 (6.5–53.9)	0.051
	1–4 (11)	72.7 (37.1–90.3)	
	≥5 (10)	40.0 (12.3–67.0)	
Bone marrow metastasis	No (32)	46.9 (29.1–62.8)	0.896
	Yes (2)	50.0 (0.6–91.0)	

Bone metastasis	No (13)	53.8 (24.8–76.0)	0.525
	1–4 (12)	50.0 (20.8–73.6)	
	≥5 (8)	37.5 (8.7–67.4)	
Response to initial chemotherapy	CR/PR (17)	70.6 (43.1–86.6)	0.082
	SD/PD (9)	33.3 (7.8–62.3)	
Local treatment for primary site	No (2)	0	0.961
	Radiotherapy (19)	42.1 (20.4–62.5)	
	Surgery (7)	57.1 (17.2–83.7)	
	Surgery and radiotherapy (6)	50.0 (11.1–80.4)	
Local treatment for metastasis	No (9)	44.4 (13.6–71.9)	0.922
	Radiotherapy (22)	50.0 (28.2–68.4)	
	Surgery and radiotherapy (3)	33.3 (0.9–77.4)	
Type of SCT	Single auto-SCT (22)	31.8 (14.2–51.1)	0.035
	Other types (12)	75.0 (40.8–91.2)	
Disease status before SCT	CR/PR (23)	56.5 (34.3–73.8)	0.136
	SD/PD (8)	25.0 (3.7–55.8)	

PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; N.E., not evaluated; EWSR, Ewing's Sarcoma Region; FISH, fluorescent in situ hybridization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SCT, stem cell transplantation; auto, autologous.

SUPPLEMENTARY APPENDIX

List of participating hospitals

The following institutions participated in the study: Department of Pediatrics, Hirosaki University Hospital, Hirosaki, Japan; Department of Pediatrics, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan; Department of Orthopedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; Division of Pediatric Oncology, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Saitama, Japan; Department of Pediatrics, St. Luke's International Hospital, Tokyo, Japan; Department of Hematology and Oncology, Children's Cancer Center, Kobe Children's Hospital, Kobe, Japan; Department of Orthopedic Surgery, Osaka University Graduate School of Medicine, Suita, Japan; Department of Pediatrics, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan; Department of Pediatrics, Mie University Graduate School of Medicine, Tsu, Japan; Department of Pediatrics, Faculty of Medicine, University of Toyama, Toyama,

Japan; Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan; Department of Pediatrics, National Hospital Organization, Kyusyu Cancer Center, Fukuoka, Japan; Department of Pediatrics, University of Tsukuba, Tsukuba, Japan; Department of Pediatrics, Niigata University Graduate School of Medicine and Dental Sciences, Niigata, Japan; Department of Orthopedic Surgery, Aichi Cancer Canter Hospital, Nagoya, Japan; Department of Pediatrics, Yokohama City University School of Medicine, Yokohama, Japan; Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan; Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Japan; Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan; Center of Bone Marrow Transplantation, Ryukyu University Hospital, Okinawa, Japan; Department of Pediatrics, Wakayama Red Cross Hospital, Wakayama, Japan; Department of Pediatrics, Osaka Medical College, Takatsuki, Japan; Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan; Division of Hematology and Oncology, Children's Medical Center, Japanese Red Cross

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