JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(5)420–426
doi:10.1093/jjco/hys027
Advance Access Publication 12 March 2012

Extraskeletal Ewing's Sarcoma Family of Tumors in Adults: Prognostic Factors and Clinical Outcome

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Received December 19, 2011; accepted February 12, 2012

Objective: The aim of this study was to evaluate prognostic factors, survival rate and the efficacy of the treatment modalities used in patients with extraskeletal Ewing's sarcoma.
Methods: Data of patients with extraskeletal Ewing's sarcoma followed up at our center between 1997 and 2010 were retrospectively analyzed.
Results: The median age of 27 patients was 24 years (range, 16–54 years). The median follow-up was 31.8 months (range, 6–144 months). Tumor size was between 1.5 and 14 cm (median: 8 cm). Eighty-five percent of patients had localized disease at presentation and 15% had metastatic disease. Local therapy was surgery alone in 16% of patients, surgery combined with radiotherapy in 42% and radiotherapy alone in 27%. All patients were treated with vincristine, doxorubicin, cyclophosphamide and actinomycin-D, alternating with ifosfamide and etoposide every 3 weeks. In patients with localized disease at presentation, the 5-year event-free survival and overall survival were 59.7 and 64.5%, respectively. At univariate analysis, patients with tumor size $\geq$8 cm, high serum lactate dehydrogenase, metastasis at presentation, poor histological response to chemotherapy and positive surgical margin had significantly worse event-free survival. The significant predictors of worse overall survival at univariate analysis were tumor size 8$\geq$ cm, high lactate dehydrogenase, metastasis at presentation, poor histological response to chemotherapy, radiotherapy only as local treatment and positive surgical margin.
Conclusions: Prognostic factors were similar to primary osseous Ewing's sarcomas. Adequate surgical resection, aggressive chemotherapy (vincristine, doxorubicin, cyclophosphamide and actinomycin-D alternating with ifosfamide and etoposide) and radiotherapy if indicated are the recommended therapy for patients with extraskeletal Ewing's sarcoma.

Key words: extraskeletal Ewing's sarcoma family of tumors in adults – prognostic factors – clinical outcome

INTRODUCTION

Ewing's sarcoma of bone and primitive neuro-ectodermal tumor comprise Ewing's sarcoma family of tumors (ESFTs) with similar histological and immunohistochemical characteristics. ESFTs are highly malignant, small, round cell tumors of neuroectodermal origin arising from bone and extraskeletal soft tissue. Most of ESFTs display translocation t(11;22) which creates the EWS/FLI1 gene (1,2). *MIC-2*

gene product CD99 is highly expressed on the cell surface of ESFTs. Although CD99 expression is a sensitive diagnostic marker, it lacks specificity from other tumors (3,4).

ESFTs develop mainly in children and young adults with a peak incidence between 10 and 15 years of age (5,6). Extraskeletal Ewing's sarcoma (EES) is rare comprising 6–47% of all ESFTs (7–10). EES are most commonly found in the trunk, extremities, retroperitoneum and head and neck region (7,11). EES is associated with poor prognosis in published studies (8,12). The principles of management of EES have been extrapolated from treatment of osseous Ewing's sarcoma. The aim of this study was to evaluate prognostic factors, efficacy of treatment modalities and outcome of EES patients referred to our institution in the last 13 years.

PATIENTS AND METHODS

Patients

Medical records of 32 EES patients treated between 1997 and 2010 at the Istanbul University Cerrahpasa Medical School were retrospectively evaluated. All the patients had received their treatment including surgery, chemotherapy and radiotherapy at our institute in a multidisciplinary setting. A total of 27 patients could be analyzed because of missing data. The standard patient evaluation included history and physical examination, complete blood count and serum chemistries, computerized tomography (CT) and/or magnetic resonance imaging (MRI) of primary tumor site, bone scan and optional bone marrow biopsy. Criteria for inclusion in the study were primary soft tissue tumors without any bone involvement on radionuclide bone scan and CT. Patients with any bone involvement were excluded. Diagnosis was confirmed by incisional ($n = 15$) or core needle ($n = 12$) biopsy.

Age at diagnosis, gender, lactate dehydrogenase level (LDH) at diagnosis, primary tumor site, tumor size, metastases at presentation, response to induction chemotherapy, number of chemotherapy cycles, local treatment modality and resection margin were included in the analysis.

Pathology

Pathology material was examined by a pathologist who had special expertise in sarcomas. Immunohistochemistry (IHC) staining was performed using neuron-specific enolase (NSE), periodic acid shiff (PAS), vimentin, CD99 and S-100 protein to confirm neuroectodermal origin. Other small, round cell tumors were ruled out with IHC using epithelial membrane antigen, desmin and muscle actin. All cases showed diffuse membranous staining for CD99. Electron microscopy and cytogenetic studies were also used. Molecular studies were conducted to look for translocation t(11;21) by FISH analysis in one patient who displayed EWS gene rearrangement.

Treatment

All the patients were evaluated in our center in a multidisciplinary manner and their local treatments were planned ($n = 27$). Four patients presented with metastatic disease. Of the 23 patients with non-metastatic EES, 2 patients with resectable tumors underwent surgery as primary local treatment. The remaining 21 patients received preoperative induction chemotherapy. The patients were evaluated at the end of the fourth chemotherapy cycle for response and local treatment. Surgical resectability was determined by the surgeon based on the tumor size and location. Thirteen patients underwent definitive surgery following neoadjuvant chemotherapy. The primary lesions were completely excised with a negative margin in nine patients. Six patients had positive surgical margins. Eleven of 15 patients also received radiotherapy after surgery for positive or close surgical margins or gross residual disease. Following induction chemotherapy, seven patients received local radiotherapy alone without surgery because of localization and unresectability of the tumors. The mean total dose of radiotherapy was 51 Gy (range, 45–61.2). One patient died of sepsis following three cycles of induction chemotherapy before response evaluation.

The principles of management of EES have been extrapolated from the treatment of osseous Ewing's sarcoma. All patients were treated with vincristine 1.4 mg/m^2, doxorubicin 75 mg/m^2, cyclophosphamide 1200 mg/m^2 (VAC) on Day 1 alternating with etoposide 100 mg/m^2, ifosfamide 1800 mg/m^2 and mesna 1800 mg/m^2 (IE) daily for 5 days. Doxorubicin was replaced by actinomycin D (1.25 mg/m^2) after reaching a cumulative dose of 450 mg/m^2. Cycles were administered every 3 weeks to complete a total of 52 weeks. All patients received G-CSF support after chemotherapy. Metastatic patients received chemotherapy until disease progression. For localized disease, the patients received a median of 12 cycles (range, 10–17). Chemotherapy cycles were delayed in most of the patients (91.3%). The median dose delay was 2 weeks (range, 1–5 weeks). Chemotherapy doses were reduced by 25% in six patients because of neutropenia. One patient died of chemotherapy related toxicity (sepsis).

Follow-up

In our department, patients were evaluated every 3 months for 2 years and every 6 months between 2–5 years and annually thereafter. Evaluation included physical examination, serum chemistries and blood counts, with biannual thorax CT and annual radionuclide bone scan. The diagnosis of recurrence was made on the basis of physical examination, imaging and pathology, if required.

Statistical Analysis

Event-free survival (EFS) and overall survival (OS) rates were estimated by using the Kaplan–Meier method. EFS

were defined as the time from therapy initiation until disease recurrence, progression or death from disease or from chemotherapy-related toxicity whichever occurred first. OS was defined as the time from therapy initiation until death. Effects of age, sex, LDH level, primary tumor site, tumor size, metastasis at presentation, response to induction chemotherapy and treatment modality of local tumor on EFS were assessed with univariate analysis. The log rank test was used to compare curves of the univariate analysis. The Cox proportional hazards model was used to assess independent prognostic factors for EFS and OS. EFS and OS were censored at the patient's last contact date.

RESULTS

Patients

A total of 32 patients with EES were evaluated. Five patients were excluded from the analysis because of lack of adequate treatment and follow-up data. Twenty-seven patients (8 females, 19 males) with a median age of 24 years (range, 16–54) were analyzed retrospectively. The median tumor size was 8 cm (range, 1.5–14). Eighty-five percent of patients had localized disease at presentation and 15% had metastatic disease. Fifty-eight percent of primary tumors were localized at the central part of the body and 42% at extremity. The patients' characteristics are shown in Table 1.

Table 1. Clinical characteristics of 27 eligible patients

	Number	%
Age		
Median	23	
Range	17–54	
Gender		
Male	18	67
Female	9	33
Primary tumor site		
Extremity	11	41
Central	16	59
Trunk (chest wall)	10	64
Kidney	1	6
Abdomen/pelvis	2	12
Head and neck	2	12
Paravertebral	1	6
Size of primary tumor (cm)		
Median	8	
Range	1.5–14	
Disease spread		
Localized disease	23	85
Metastatic disease	4	15

Evaluation of Response to Chemotherapy

All tumor specimens were examined specifically to evaluate the surgical margins and the rate of necrosis after induction chemotherapy. Extent of viable tumor cell was evaluated histologically, and the response to chemotherapy was graded according to necrosis rate compared with areas of viable tumor. A total of 13 patients received induction chemotherapy. Eight patients (62%) who received induction chemotherapy had a good response rate with $\geq$90% necrosis rate in resected specimens. But the remaining five patients (38%) had poor response to chemotherapy with $\geq$10% viable tumor.

Local Control

Local control was evaluated in 22 patients. The remaining five patients were excluded because of metastatic disease at presentation ($n = 4$) and early death ($n = 1$). The median time to local recurrence was 18 months (range, 8–37). A total of five patients (23%) developed local recurrence. Fifteen patients (68%) underwent definitive surgery with or without combined radiotherapy as local treatment and 3 (20%) patients developed local recurrences during follow-up. Conversely, of seven patients who received radiotherapy alone, two patients (28%) developed local recurrences. This difference in the local recurrence rate was not statistically significant ($P = 0.1$). In our study, patients who had surgery as local treatment demonstrated a trend favoring local control, but it is difficult to make definite conclusions due to small number of patients in our cohort analysis. Nine patients had resection with wide margins ($\geq$1 cm) and six patients had presence of positive surgical margins. Local recurrence rate was significantly higher for patients with positive surgical margins (50%) compared with patients who had wide surgical margins (0%; $P = 0.018$).

Outcome Analysis

The median follow-up period was 31.8 months (range, 6–144) and for censored patients, the follow-up period was 76 months (range, 24.2–144). At the last censored time, 11 (44%) patients were dead. In patients with localized disease at presentation, three patients developed local recurrence only, two patients developed both distant metastases and local recurrence, five patients developed distant metastases and one patient died of sepsis. The median time to development of metastasis was 16 months (range, 10–31). Most frequent site of first metastasis was lung (65%) followed by bone, bone marrow and pleura.

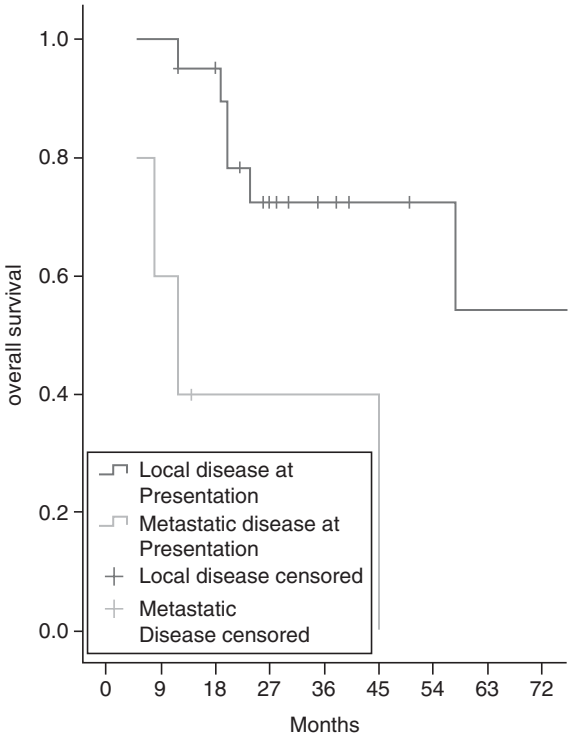

Figure 1. Overall survival analysis in 27 patients with extraskeletal Ewing's sarcoma (EESs).

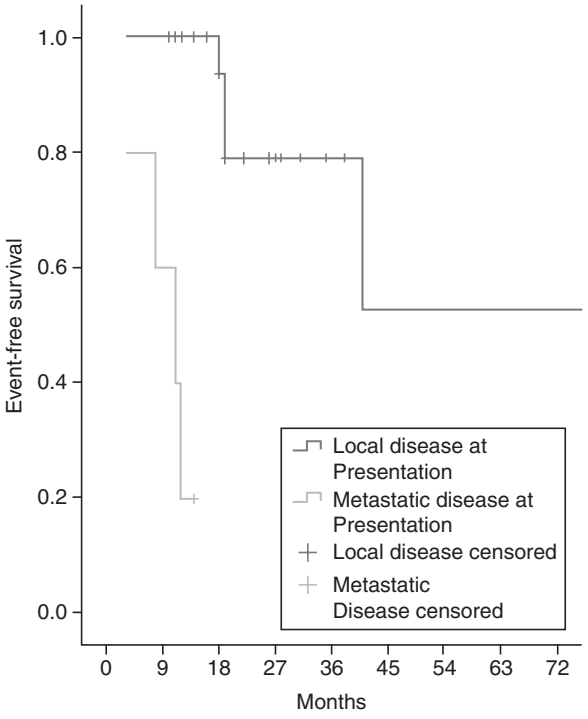

Figure 2. Event-free survival analysis in 27 patients with EESs.

In patients with localized disease at presentation, the 5-year EFS and OS were 59.7 and 64.5%, respectively. For metastatic patients, the median OS was 9.5 months (range, 1–45). In these patients, the 2-year EFS and OS were 25 and 50%, respectively. All the metastatic patients died by the fourth year (Figs 1 and 2). The median EFS and OS rates were significantly less favorable in metastatic patients compared with patients with localized disease ($P = 0.0001$ and $P < 0.003$). Of note, patients who underwent surgery with wide surgical margins following induction chemotherapy ($n = 9$) achieved 100% 5-year EFS and OS.

Univariate Analysis for Survival

At univariate analysis, tumor size $\geq$8 cm ($P = 0.005$), high level of LDH ($P = 0.02$), metastasis at presentation ($P = 0.001$), poor histological response to chemotherapy ($P = 0.001$) and presence of positive surgical margin ($P = 0.001$) had a significantly worse EFS. Significant predictors of worse OS at univariate analysis were tumor size $\geq$8 cm ($P = 0.002$), high level of LDH ($P = 0.01$), metastasis at presentation ($P = 0.003$), poor histological response to chemotherapy ($P = 0.001$), radiotherapy only as local treatment ($P = 0.007$) and presence of positive surgical margin ($P = 0.004$). Detailed clinical variables and their prognostic impact on EFS and OS are shown in Table 2.

Multivariate Analysis for Survival

At multivariate analysis, presence of metastasis at presentation ($P = 0.002$) and positive surgical margins ($P = 0.001$) were associated with a significantly worse EFS. Similarly, patients with metastasis at presentation ($P = 0.02$) and large tumor ($\geq$8 cm; $P = 0.01$) had a significantly worse OS (Table 3).

DISCUSSION

ESFTs are aggressive type of tumors with a high incidence of local recurrence and distant metastasis. EESs were reported to be associated with poorer prognosis compared with osseous ESFTs (8,12). Nowadays, the treatment of ESFTs has utilized more aggressive local control modalities and intensive systemic chemotherapy. The 5-year OS have shown marked improvement from 36 to 56% in periods 1975–1984 and 1985–1994 (13). Grier et al. (14) demonstrated that in patients with non-metastatic EFSTs who received doxorubicin, vincristine, cyclophosphamide and dactinomycin compared with patients who received these four drugs alternating with courses of IE, the 5-year overall survival was better in the alternating treatment group (72 vs. 61%, $P = 0.01$).

Principles of management of EES have been extrapolated from experience from treating ESFTs of bony origin. In the current study, we administered patients with vincristine, doxorubicin, cyclophosphamide and actinomycin-D (VACA) alternating with IE treatment modality. In our series, 5-year OS rate in patients with localized disease (64.5%) was

Table 2. Univariate analysis for event-free survival (EFS) and overall survival (OS)

	Patient (*n*)	5-year EFS (%)	*P* value	5-year OS (%)	*P* value
Disease presentation			***0.001***		***0.003***
Localized	23	59.7		64.5	
Metastatic	4	0		0	
Primary tumor site			*0.5*		*0.7*
Central	16	58		60	
Extremity	11	60.5		69	
Tumor size			0.005		0.002
≥8 cm	14	38		51	
<8 cm	13	80		82	
Age at diagnosis			*0.7*		*0.8*
>23 years	14	56		63	
≤23 years	13	61		67	
Gender			*0.5*		*0.7*
Female	9	58		66	
Male	18	60		64	
Response to chemotherapy ($n = 13$)			**0.001**		***0.001***
Tumor necrosis rate ≥90%	8	87.5		100	
Tumor necrosis rate <90%	5	0		0	
Local treatment modality			***0.09***		***0.007***
Surgery ± radiotherapy	15	71.3		84	
Radiotherapy alone	7	41.3		45	
Surgery/surgery + radiotheraphy			***0.5***		***0.2***
Surgery + radiotherapy	11	61.2		66.7	
Surgery alone	4	58.4		64.3	
Surgical margin			***0.001***		***0.004***
Wide surgical margin	9	100		100	
Positive surgical margin	6	0		25	
LDH			***0.02***		***0.01***
High LDH	8	37.5		30	
Normal LDH[a]	10	66.7		78	

[a]Normal range of LDH level was 0–240 mu/dl.

comparable to 30–64% rates reported in the literature (15–19). Similarly, local recurrence rate in our study was parallel to the results in the literature which ranged between 15 and 46% (16,19,23).

In our cohort, the median age at diagnosis was 23 years, whereas other previous studies' age range was 15–26 years (12,15,16,19). In the current study, univariate analyses did not show age (>23 years) as a predictor factor for EFS and OS. But some studies showed older age to be an independent predictor factor for worse survival (8,9,16,20).

The most commonly observed location of EES in our series was the trunk. Prior studies also showed more frequent trunk localization for EES (18,19,21). On the other hand, some series reported primary locations in extremities more frequently (22–24). In the current study, we did not find any significant difference in EFS and OS with regard to tumor localization. In most of the other prior reported EESs in the adult population, site was not predictive of survival (9,17,18,25). But Kinsella et al. (22) and Ahmad et al. (15) reported a favorable prognosis in extremity lesions.

In the prior reported series, metastatic patients at presentation in EES had worse outcome (16,19,21,23). In the current study, patients who initially presented with metastases had significantly worse prognosis in terms of both EFS and OS.

Tumor size was a significant predictor of EFS and OS in our series. This finding is in complete agreement with most of the prior reports of EES (17,19,21,23,25). In the current

Table 3. Multivariate analysis for EFS and OS

	EFS		OS	
	P	HR (% 95 CI)	*P*	HR (% 95 CI)
Disease presentation	0.002		0.02	
Localized		0.35 (0.13–0.91)		0.18 (0.04–0.75)
Metastatic		1		1
Surgical margin	0.001			
Wide margin		0.4(0.2–088)		
Positive margin		1		
Tumor size			0.01	
≤8 cm				0.3 (0.14–0.65)
>8 cm				1

study, high LDH at the time of diagnosis adversely predicted EFS and OS, probably reflecting initial high tumor burden. This finding is similar to those in the literature for EES and osseous Ewing's sarcoma (18,26,27). The prognostic significance of a histological response to induction chemotherapy has been shown in both skeletal and extraskeletal Ewing's sarcoma (18,28–31). In our study, patients who had ≥90 necrosis (<10% viable tumor) had the best outcome (87.5% 5-year EFS and 100% 5-year OS). Moreover, patients who received induction chemotherapy and achieved negative surgical margins, 5-year EFS and OS were 100%. Prior studies demonstrated the importance of wide surgical margins in terms of survival (19,23,24). Ahmad et al. showed 78% DFS and 100% OS for patients with wide surgical resection margins. However, the question of optimal local control has not been definitively answered, because of lack of head-to-head comparison of radiotherapy with surgery (32).

In conclusion, EESs are aggressive tumors with a high incidence of local recurrence and distant metastasis. Prognostic factors were similar to primary osseous Ewing's sarcomas. Multimodality treatment consisting of adequate surgical resection, aggressive chemotherapy (VACA alternating with IE) and radiotherapy is recommended for patients with EESs.

Conflict of interest statement

None declared.

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