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Original Article

Clinical outcomes and prognostic factors of Ewing sarcoma: A clinical analysis of 12 patients in Taiwan

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Abstract

Background: Ewing sarcoma is extremely rare in people from East and Southeast Asia.
Methods: The records of 12 patients diagnosed with primary Ewing sarcoma and treated at our institution from 1997 to 2009 were retrospectively reviewed.
Results: There were seven male and five female patients and their mean age at diagnosis was 22 years (range, 12–48 years). Two patients (16.7%) had distant metastasis at diagnosis. The primary tumor sites were the trunk in seven patients (58.3%) and the extremities in five patients (41.7%). Eleven patients received neoadjuvant chemotherapy followed by wide excision surgery, and then adjuvant chemotherapy. One patient received only chemotherapy without surgical intervention due to poor cardiac and pulmonary function. At a mean follow-up of 33 months, the 2-year overall survival rate (OS) was 45.5%. Distant metastasis was the only statistically significant prognostic factor of OS in our study. The 2-year OS rates of patients with lung metastasis and without lung metastasis were 0% and 42.9%, respectively ($p = 0.021$). The t(11;22)(q24:q12) translocation was present in all patients in our series.
Conclusion: We confirmed that distant metastases is highly predictive of a poor outcome, and that the t(11;22)(q24:q12) translocation was present in all patients in our series.
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Keywords: Ewing sarcoma; genetic translocation; overall survival rate; prognostic factor

1. Introduction

Ewing sarcoma is a highly malignant, small round-cell tumor arising from bone or in soft tissue, and is a common malignancy of bone in patients younger than 30 years of age. The incidence varies among different racial groups, and is much lower in black populations and in Eastern and Southeastern Asians.[1] The current treatment of Ewing sarcoma is neoadjuvant chemotherapy, followed by wide excision surgery, and then adjuvant chemotherapy. The long-term survival rate is reported to range from 60–75%. We conducted a retrospective study to assess the clinical outcomes and to identify the prognostic factors of Ewing sarcoma at our institution for greater understanding of the condition and therapeutic decisions making.

2. Methods

The records of 12 patients diagnosed with primary Ewing sarcoma and treated at our institution from 1997 to 2009 were

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Table 1
Demographic data for patients with Ewing sarcoma.

Case no.	Age (y)	Sex	Lesion site	Greatest tumor dimension (cm)	Type of surgery	Current status (2009/05)
1	42	Female	Femur	11	Hip disarticulation	DOD
2	29	Female	Femur	5	Wide excision with APC reconstruction	CDF
3	30	Female	Scapula	15	Total scapulectomy	DOD
4	16	Male	Pelvis	5	Wide excision	DOD
5	17	Male	Scapula	4	Wide excision	CDF
6	12	Male	Pelvis	13	Wide resection with hip arthrodesis	DOD
7	19	Male	Clavicle	8	Wide excision	DOD
8	48	Male	Extra-skeletal, inguinal mass	Nil	Nil	DOD
9	15	Male	Humerus	7	Wide excision with APC reconstruction	CDF
10	22	Female	Tibia	9	Wide excision with autograft reconstruction	CDF
11	22	Female	Pelvis	12	Wide excision with hip arthrodesis	CDF
12	20	Male	Scapula	9	Wide excision	CDF

APC = allograft/recycled autograft prosthesis reconstruction; CDF = continuously disease-free; DOD = died of disease; Nil = No pathology measurement due to no surgical intervention.

retrospectively reviewed. Institutional review board approval was obtained for the study. There were seven male and five female patients and the mean age at diagnosis was 22 years (range, 12–48 years). Two patients (16.7%) had distant metastasis at diagnosis. The primary tumor sites were the trunk in seven patients (58.3%) and the extremities in five patients (41.7%) (Table 1). All of the patients were diagnosed by pathological examination. *EWS* gene translocation was determined by fluorescence *in situ* hybridization using LSI EWSR1 Dual Color Breakapart Probe (Cat# 32-190059, Abbott Park, Illinois, USA).

Eleven patients received neoadjuvant chemotherapy followed by wide excision surgery, and then adjuvant chemotherapy. One patient received only chemotherapy without surgical intervention due to poor cardiac and pulmonary function. The main chemotherapy regimen consisted of vincristine, actinomycin, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Of five patients who required reconstruction after wide excision surgery, two received hip arthrodesis, one reconstruction was performed with an extracorporeal irradiated autograft prosthesis composite, one with an allograft prosthesis composite (Fig. 1), and one with a liquid nitrogen-processed autograft (Fig. 2).

The response to chemotherapy was evaluated by tumor necrosis, graded according to the modified criteria of Rosen et al. [2] In brief, 100% tumor necrosis is classed as grade 3; <10% viable tumor is grade 2; from 10% to 50% viable tumor is grade 1; and from 50% to 100% viable tumor is grade 0.

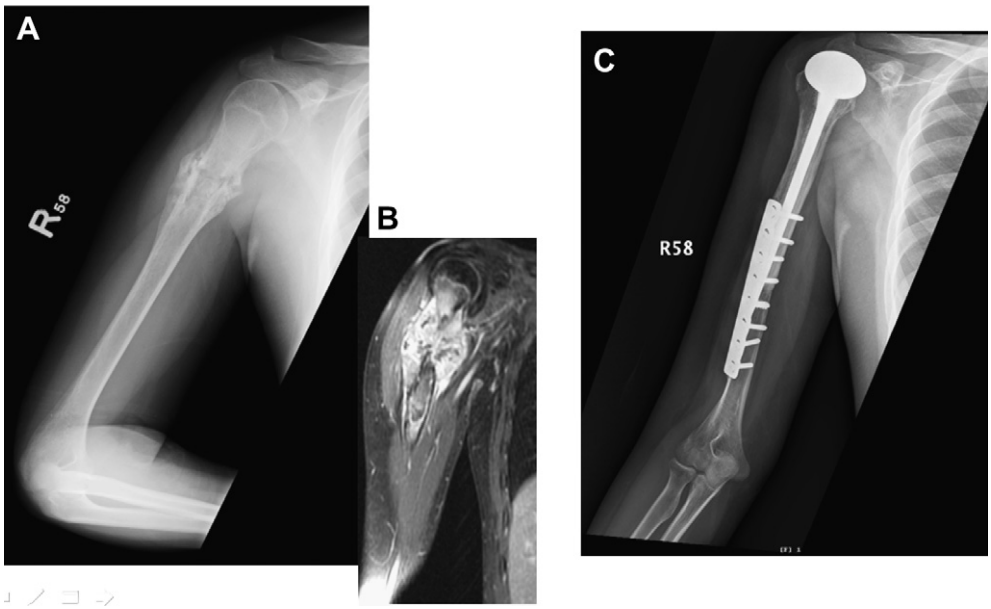

Fig. 1. A 15-year-old boy (case 9) with Ewing sarcoma of the right proximal humerus received wide excision surgery with allograft-prosthesis composite reconstruction. (A) Plain radiograph showing a heterogeneous lesion with cortex disruption and periosteal reaction of the right upper humerus; (B) magnetic resonance imaging revealed an osteodestructive lesion with soft tissue invasion of the right upper humerus; (C) plain radiograph of the right humerus after wide excision surgery with allograft-prosthesis composite reconstruction.

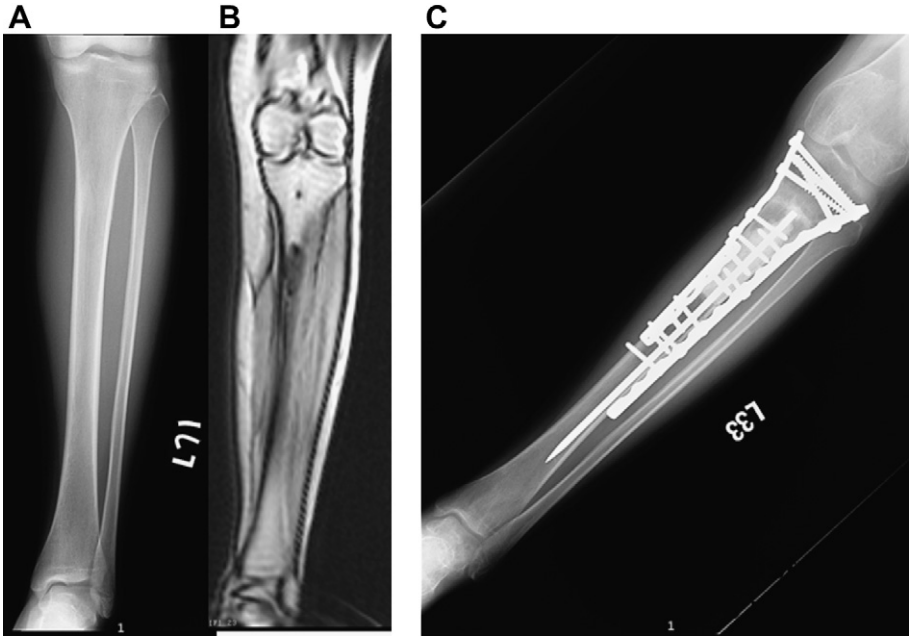

Fig. 2. A 23-year-old woman (Case 10) with Ewing sarcoma of the left tibia received wide excision surgery with recycled autograft reconstruction. (A) Plain radiograph showing an osteolytic lesion with cortex invasion of the left tibia; (B) magnetic resonance imaging revealed an osteolytic lesion of the left proximal tibia; (C) plain radiograph of the left tibia after wide excision surgery and recycled autograft reconstruction.

The data collected and analyzed included gender, age, tumor size and site, local recurrence, and distant metastasis. A survival analysis was conducted by the Kaplan-Meier method. A p-value <0.05 was considered significant. The cut-off point of a patient's age and tumor volume were calculated by a receiver operating characteristic curve. The study was approved by the Institutional Review Board of our hospital; the requirement for informed consent was waived because of the retrospective nature of the study.

3. Results

The median of the follow-up survival time was 33 months (range, 9–84 months). Of the twelve patients, six (50%) died of the disease, and the remaining six patients were disease-free at the time of the last follow-up. The 2-year and 3-year overall survival (OS) rates were 45.5% and 22.7%, respectively. The 2-year OS of the patients without metastasis was 100%, while that of patients with metastasis was only 16.7% ($p = 0.014$) (Fig. 3).

In addition to the two patients with distant metastases at diagnosis, four patients (40.0%) developed distant metastases within a mean follow-up period of 19 months. Of the six patients with distant metastases, three had metastases to the lungs, two to the vertebral bodies, and one patient had metastases to both locations. Interestingly, the 2-year OS rates of the patients with lung metastasis and those without lung metastasis were 0% and 42.9%, respectively ($p = 0.021$). The 2-year OS rates of patients with and without distant bone metastases were not significantly different ($p = 0.103$).

The results of the univariate analyses of clinical variables and OS are presented in Table 2. Sex, age ($\geq$ 22 years), primary tumor site (trunk/limb; pelvis/extra-pelvic), tumor size (>8 cm), treatment-related variables, or necrosis rate (>90%) did not significantly influence OS. The only factor that was significantly associated with OS was the presence of distant metastases. In addition, metastasis to the lungs was a more significant predictive of poor outcome as compared with metastasis to distant bones.

4. Discussion

Ewing sarcoma is relatively rare in black populations and in Eastern and Southeastern Asians.[1] While many articles discuss the genetic predispositions, prognostic factors, treatments, and clinical outcomes in Western populations, there are

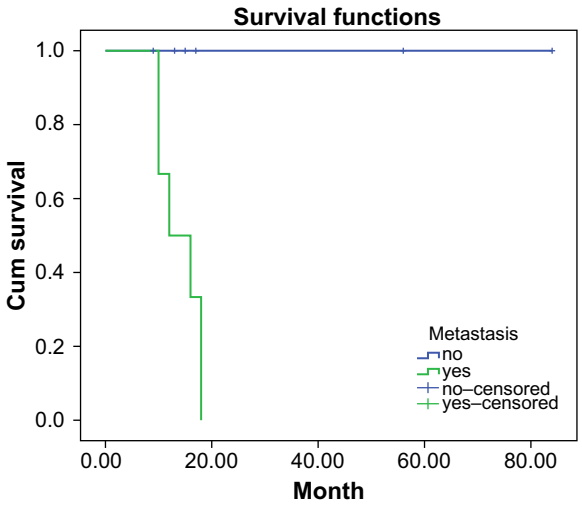

Fig. 3. Kaplan-Meier analysis for overall survival rate with and without metastasis.

Table 2
Univariate analysis of factors associated with overall survival ($n = 12$).

Variable	No. patients	2-y overall survival (%)	p
Sex			
Male	7	44.3	0.608
Female	5	53.3	
Tumor size (cm)			
≥8	8	44.4	0.301
<8	4	53.3	
Age at diagnosis (y)			
≥22	6	53.3	0.855
<22	6	44.4	
Histological response to chemotherapy			
Grade 3–2 (necrosis ≥ 90%)	4	31.3	0.487
Grade 1–0 (necrosis ≤ 90%)	8	0	
Primary tumor site			
Trunk	7	41.7	0.777
Extremities	5	60.0	
Primary tumor site			
Pelvic	3	46.9	0.852
Extra-pelvic	9	50.0	
Disease extension			
Localized	6	100	0.014
Metastatic	6	16.7	
Disease extension (lung metastasis)			
Lung metastasis	4	0	0.021
Non-lung metastasis	8	42.9	
Disease extension (bone metastasis)			
Bone metastasis	3	0	0.103
Non-bone metastasis	9	25	

few reports regarding these factors in Asian populations because of the extreme rarity of the disease.

In our study, we found that the 2-year OS of patients with Ewing sarcoma was 45.5%, which is quite dismal compared with that reported in other major series.[3–6] However, in our cohort, two patients (16.7.0%) had metastases at diagnosis, and seven patients (58.3%) had the trunk as their primary tumor sites. The statistical power of our analyses, however, is severely limited by the small population.

Several prognostic factors of Ewing sarcoma have been confirmed in large series. [3,6–8] However, in our study, the only statistically significant factor which influenced survival was the presence of a distant metastasis ($p = 0.014$). Other factors were not associated with survival in our series. It has previously been reported that patients with metastases limited to the lungs seem to have better OS than those with metastases to other sites. [9–11] However, our data did not support the same conclusion; we found that the presence of lung metastasis was more significantly predictive of poor OS as compared with metastasis to other sites ($p = 0.021$).

It has been shown that up to 85% of patients with Ewing sarcoma have the chromosomal translocation t(11;22)(q24:q12). [12] The t(11;22)(q24:q12) translocation was present in all 12 patients in our study (Fig. 4).

Due to the low incidence of Ewing sarcoma in Asian populations, and the small population of Taiwan, Ewing sarcoma is quite rare in our country. Because of the small number of cases in this report, the statistical power is limited. Nevertheless, we confirmed that distant metastases are highly predictive of a poor outcome, and found that the t(11;22)(q24:q12) translocation was present in all of our patients. We believe that study of innovative gene therapies, targeted therapies, and immunotherapies can improve the survival rate of patients with Ewing sarcoma.

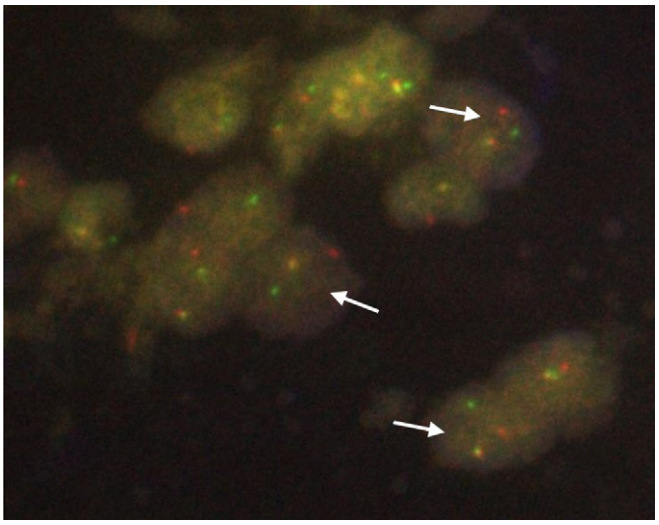

Fig. 4. Ewing sarcoma: fluorescence *in situ* hybridization-positive case with *EWS* gene break apart. Instead of the normal fused red and green signals (sometimes become yellow), arrows point to the separated *EWS* gene signal.

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