·Clinical Research·

Efficacy and survival of 92 cases of Ewing's sarcoma family of tumor initially treated with multidisciplinary therapy

Rou-Jun Peng,[1,2] Xiao-Fei Sun,[1,2] Xiao-Juan Xiang[1,2], Zi-Jun Zhen,[1,2] Jia-Yu Ling,[1,2]
Gang-Ling Tong,[1,2] Yi Xia,[1,2] Guang-Chuang Xu[1,2] and Wen-Qi Jiang[1,2]

[1]State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, 510060, P. R. China; [2]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, P. R. China

[Abstract] Background and Objective: Ewing's sarcoma family of tumor (ESFT) is aggressive. The optimal therapy modality for ESFT is still to be found. This study was to explore the clinical characteristics and therapy for ESFT. **Methods:** Ninety-two cases of ESFT were collected from January 1995 to April 2008 in Sun Yat-sen University Cancer Center and analyzed retrospectively. **Results:** Of 92 cases, 23 were Ewing's sarcoma of bone, 21 extraosseous Ewing's sarcoma, 43 peripheral primitive neuroectodermal tumor, and 5 Askin tumor. Median follow-up time was 31.5 months (range, 10–137 months). Thirty-eight patients received multidisciplinary therapy and 19 single model therapy in non-metastasis group. Three-year overall survival (OS) and event-free survival (EFS) were significantly different between non-metastatic multidisciplinary therapy group and non-metastatic single model group (63% vs. 20%, 46% vs. 18%, respectively, $P<0.001$). The patients who received surgery plus chemotherapy and plus radiation or not had longer survival than those treated with chemotherapy plus radiation in non-metastatic multidisciplinary therapy group ($\chi^2=7.591$, 9.212; $P=0.006$, 0.002). CAV/IE alternative regimen was superior to other regimens in event-free survival, but not in overall survival ($\chi^2=6.950$, 3.530; $P=0.008$, 0.06). Cox regression analysis suggested therapy model and response to treatment were independent prognostic factors for ESFT. **Conclusions:** Our studying showed multidisciplinary therapy could significantly improve non-metastatic ESFT patients' survival. Chemotherapy plus surgery and plus radiation or not were superior to chemotherapy plus radiation in local control for the non-metastatic ESFT. Therapy model and response were independent prognostic factors.

Key words: Ewing's sarcoma family of tumor, Ewing's sarcoma, primitive neuroectodermal tumor, Askin tumor, multimodal therapy, survival analysis

Ewing's sarcoma family of tumors (ESFT) is a common malignant tumor in adolescents that mostly occurs in the bones and soft tissues in 10–20-year-old adolescents. The cell origin of ESFT has always been controversial. Currently, it is considered that ESFT is originated from neuroectoderma, and includes primitive neuroectodermal tumor (PNET), Ewing's sarcoma and Askin tumor.[1] ESFT is highly malignant and extremely prone to develop recurrence and metastasis.[2] Ever since 1960s, chemotherapy as postoperative adjuvant therapy has significantly improved the overall survival of ESFT patients, and thereby the concept of multiple-discipline treatment is gradually developed.[3-5] However, in China, no systemic report regarding ESFT is seen yet. In this study, we retrospectively analyzed the treatment for and efficacy on 92 cases of ESFT treated in the Sun Yat-sen University Cancer Center from January 1995 to April 2008.

Data and Methods

General data

A total of 105 patients were diagnosed with ESFT from January 1995 to April 2008 in Sun Yat-sen University Cancer Center. Excluding nine patients with tumors primarily originating from the central nerve, three with recurrent tumors and one who was still undergoing treatment, a total of 92 patients fulfilled the inclusion criteria. General features, treatment profile, short-term efficacy and long-term survival of the 92 patients are shown in Table 1. Of them, 61 were men and 31 were women, aged 1–72 years, with a median of 16 years, and those at the age of 10–20

Correspondence to: Xiao-Fei Sun; Tel: +86-20-87343347; Email: gzsunxf@ yahoo .com.cn

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Table 1 Characteristics of 92 cases of Ewing's sarcoma family of tumor (ESFT)

Item	Mutiple disciplines therapy [number (%)]		Single therapy [number (%)]		Total (number)
	Non-metastasis	Metastasis	Non-metastasis	Metastasis	
Gender					
Male	27(29.3)	10(10.9)	13(14.1)	11(12.0)	61
Female	11(12.0)	8 (8.7)	6 (6.5)	6 (6.5)	31
Age (years)					
<10	8 (8.7)	1 (1.1)	4 (4.3)	1 (1.1)	14
10–20	23(25.0)	9 (9.8)	6 (6.5)	10(10.7)	48
>20	7 (7.6)	8 (8.7)	9 (9.8)	6 (6.5)	30
Pathological subtype					
ETB	12(13.0)	5 (5.4)	3 (3.3)	3 (3.3)	23
EOE	14(15.2)	1 (1.1)	3 (3.3)	3 (3.3)	21
Askin tumor	1 (1.1)	2 (2.2)	2 (2.2)	0 (0.0)	5
PNET	11(12.0)	10(10.9)	11(12.0)	11(12.0)	43
PS					
0–1	26(28.3)	6 (6.5)	11(12.0)	4 (4.3)	47
2	12(13.0)	9 (9.8)	8 (8.7)	9 (9.8)	38
⩾3	0 (0.0)	3 (3.3)	0 (0.0)	4 (4.3)	7
LDH					
Normal	24(26.1)	8 (8.7)	10(10.9)	4 (4.3)	46
Elevated	14(15.2)	10(10.9)	9 (9.8)	13(14.1)	46
Location					
Limb	14(15.2)	1 (1.1)	4 (4.3)	2 (2.2)	21
Central line	10(10.9)	7 (7.6)	8 (8.7)	12(13.0)	37
Pelvis	4 (4.3)	4 (4.3)	1 (1.1)	3 (3.3)	12
Chest wall	4 (4.3)	4 (4.3)	3 (3.3)	0 (0.0)	11
Head & neck	6 (6.5)	2 (2.2)	3 (3.3)	0 (0.0)	11
Total	38	18	19	17	92

ETB, Ewing's sarcoma of bone; EOE, extraosseous Ewing's sarcoma; PNET, peripheral primitive neuroectodermal tumor; PS, performance status; LDH, lactate dehydrogenase.

years accounted for 52.2% of all patients; 23 had Ewing's sarcoma of the bone, 21 had extraosseous Ewing's sarcoma, 43 had peripheral PNET and five had Askin tumor; 57 had non-metastatic disease and 35 had metastatic disease. The most common primary sites were structures that distributed along the medial line, including the spine, vertebrae, para-vertebral structures, abdominal cavity, thoracic cavity and mediastinum in 37 (39.8%) patients, followed by the extremities in 21 (22.6%) patients, including 11 cases in proximal extremities.

Pathologic diagnosis and staging criteria

Small blue round cells were observed in typical ESFT tissues under microscope. ESFT showed no specific immune phenotype. A relatively specific marker was positive periodic acid-Schiff's staining (PAS); 90% of ESFTs expressed CD99, and 80%–90% of them were Vimentin-positive. In addition, they also expressed NSE and S100.[6]

Currently, no TNM staging system for ESFT is available. Thus, ESFT was classified as non-metastatic or metastatic according to the existence of distant metastasis and/or non-regional lymph node metastasis.

Evaluation criteria for efficacy

Spiral plain and contrast CT scanning was performed for efficacy evaluation. Response Evaluation Criteria in Solid Tumor (RECIST) were used to assess short-term efficacy. Overall survival (OS) was defined as the time span between the date of diagnosis and the date of death or last visit, while event-free survival (EFS) as the time span between the start date of treatment and the date of adverse event or last visit. Adverse events included disease progression, occurrence of a second tumor and death.

Treatment profile

Multiple-discipline treatment schemes included surgery plus chemotherapy and radiotherapy, surgery plus chemotherapy, and radiotherapy plus chemotherapy; sole treatment schemes included local surgery plus radiotherapy, surgery alone, radiotherapy alone and chemotherapy alone (Table 2).

A total of 75 patients received systemic chemotherapy with alternative CAV (CTX plus VCR and ADM) and IE (IFO plus VP-16) scheme, IFO plus ADM based schemes, anthracyclines (mostly CAV and CAP) based schemes, or high-dose IFO scheme; other chemotherapy schemes included interventional therapy, MMC, DTIC, CTX, and so on; on the basis of multiple-discipline treatment, three patients underwent super-high-dose chemotherapy with blood stem cell transplantation (Table 2). Chemotherapy lasted for 1–12 cycles, averagely 6 cycles. Till the last visit, 60 patients had recurrence or metastasis, and 54 died of tumor.

Follow-up

The patients were followed up till July 2008 via telephone call or clinic visit. Follow-up duration ranged from 10 to 137 months, with a median of 31.5 months. The follow-up rate was 78%.

Statistical analyses

SPSS13.0 was used for the statistical analyses. Survival analysis was conducted with Kaplan-Meier method, and statistical

Table 2 Treatments and regimens of patients with different stages of ESFT

Therapy	Non-metastasis [number (%)]	Metastasis [number (%)]	Total
Treatment			
Resection + RT + CT	19(20.7)	3 (3.3)	22
Resection + CT	11(12.0)	7 (7.6)	18
CT + RT	8 (8.7)	8 (8.7)	16
Resection + RT	5 (5.4)	1 (1.1)	6
Resection	7 (7.6)	3 (3.3)	10
RT	1 (1.1)	0 (0.0)	1
CT	6 (6.5)	13(14.1)	19
Regimen			
CAV/IE alternatively	27(29.3)	8 (8.7)	35
IFO+ADM based	5 (5.4)	13(14.1)	18
ADM based	9 (9.8)	6 (6.5)	15
IFO based	1 (1.1)	2 (2.2)	3
Others	2 (2.2)	2 (2.2)	4

CT, chemotherapy; RT, ratdiotherapy; C, cyclophosphamide; A/ADM, adriamycin; V, vincristine; I/IFO, ifosfamide; E, etoposide, VP-16.

test performed using log-rank method. Multivariate analysis was conducted using Cox regression hazard model (inclusion and exclusion criteria were 0.05 and 1.00, respectively).

Results

Treatment efficacy and survival profile

Among the 57 patients with non-metastatic disease, 38 were included into multi-discipline treatment group and 19 into sole treatment group; as for the 35 patients with metastatic disease, 18 were included into multi-discipline treatment group and 17 into sole treatment group. The short-term efficacy, median OS, 3-year OS rate, median EFS, 3-year EFS rate of these groups are shown in Tables 3 and 4. Due to the small number of patients with metastatic disease and imbalanced patient distribution among all groups, we merely conducted efficacy and survival observation, rather than statistical analysis on the differences.

Among the patients with non-metastatic disease, the short-term efficacy and long-term survival were better in multi-discipline treatment group than in sole treatment group (P<0.05) (Tables 3 and 4, Figs. 1 and 2).

Efficacy of local treatment on non-metastatic disease

For the 30 patients who received surgery plus chemotherapy and/or radiotherapy and the eight patients who received radiotherapy plus chemotherapy, the median survival durations were 108 months and 22.4 months, respectively; the 3-year OS rates were 74% and ⩽15%, respectively; the median EFS were 108 months and 12 months, respectively; the 3-year EFS rates were 53% and 33%, respectively, with significant differences between these two groups (χ^2=7.591, 9.212, P=0.006, 0.002) (Figs. 3 and 4).

Table 3 Response of patients with ESFT

Response	Non-metastasis group (number)		χ^2	P	Metastasis group (number)	
	Multiple group	Single group			Multiple group	Single group
CR+PR	34	14	23.991	<0.001	10	7
SD+PD	4	5			8	10

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table 4 Survival analysis of patients with ESFT

Survival	Non-metastasis group		χ^2	P	Metastasis group	
	Multiple group	Single group			Multiple group	Single group
OS[months(%)]	66.7 (63)	20.7 (20)	17.597	<0.001	19.4 (27)	11.3 (9)
EFS[months(%)]	40.9 (46)	8.8 (18)	17.799	<0.001	9.0 (21)	6.8 (0)

OS, overall survival; EFS, event-free survival.

Comparisons on the efficacies of different chemotherapy schemes

A total of Among the 56 patients who received multi-discipline treatments, 27 of the 38 patients with non-metastatic disease were treated with CAV/IE schemes and 11 with non-CAV/IE schemes; of the 18 group, three of the 18 patients with metastatic disease were treated with and 15 with non-CAV/IE schemes. Survival statuses of these groups are shown in Table 5, Figures 5 and 6. Likewise, only the survival of the patients with non-metastatic disease was analyzed. The results revealed that alternative CAV/IE schemes prolonged EFS of those received multi-discipline treatment (χ^2=6.950, P=0.008), but the difference in OS was not significant (χ^2=3.530, P=0.06).

Multivariate analyses on prognosis

Multivariate analysis on factors including gender, age, tumor location, pathologic type, clinical stage, tumor volume, LDH, serum albumin concentration, treatment pattern and efficacy showed that treatment pattern and efficacy were independent prognostic factors (P<0.001).

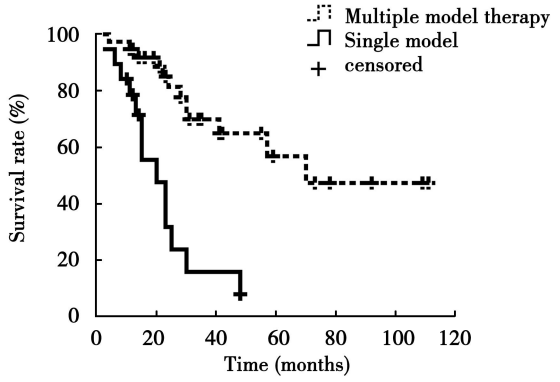

Figure 1 Overall survival curves of patients in non-metastasis group treated with different therapy models

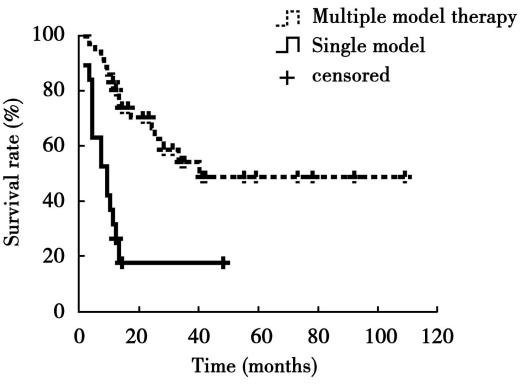

Figure 2 Event-free survival curves of patients in non-metastasis group treated with different therapy models

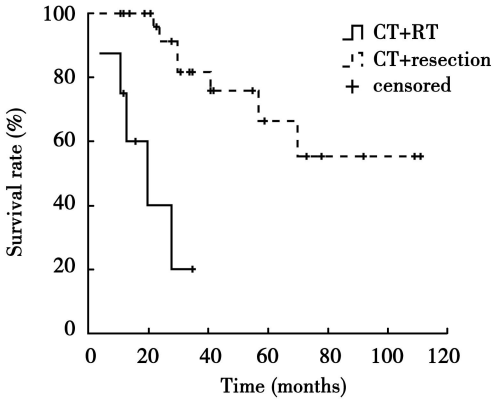

Figure 3 Overall survival curves of patients in non-metastasis group treated with different local controls combining with chemotherapy

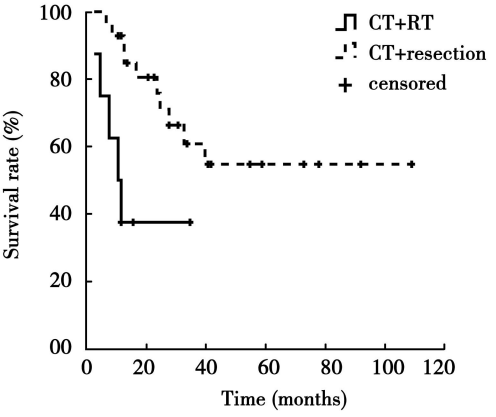

Figure 4 Event-free survival curves of patients in non-metastasis group treated with different local controls combining with chemotherapy

Table 5 Survival analysis of patients with ESFT in different stage after treatment with different chemotherapy regimens

Survival	Non-metastasis group		χ^2	*P*	Metastasis group	
	CAV/IE[a] group	non-CAV/IE group			CAV/IE group	non-CAV/IE group
Total	27	11			3	15
OS[months(%)]	66.6 (69)	52.5 (54)	3.530	0.060	18.0 (0)	7.5 (≤20)
EFS [months(%)]	72.0 (56)	29.7 (33)	6.950	0.008	0	0

[a]C, cyclophosphamide; A, adriamycin; V, vincristine; I, ifosfamide; E, etoposide. Other abbreviations as in Table 4.

Discussion

ESFT is highly malignant but sensitive to chemotherapy and radiotherapy. In most patients, micro-metastatic lesions have already been developed when they are diagnosed, and the survival rate of those treated with surgical resection or radiotherapy alone were less than 10%.[7] In 1974, Rosen *et al.*[8] reported that the 5-year EFS rate was increased to 75% in 20 patients with Ewing's sarcoma of bone who were treated by radiotherapy plus VACD (VCR, ADM, Act-D and CTX) chemotherapy. Thereby, VACD had been widely used as the standard chemotherapy scheme, and the survival benefits for patients with varied risk factors were increased from 20% to 40% -60% . On the other hand, clinical trials CESS-86 and ET-2 started to use IFO instead of CTX in treating high risk ESFT and achieved increased survival rates.[9,10] Clinical trial INT-0091 used IFO plus VP-16 scheme and VACD scheme alternatively to treat ESFT, and selected local treatment after chemotherapy based on primary site; it was found that the addition of IFO plus VP-16

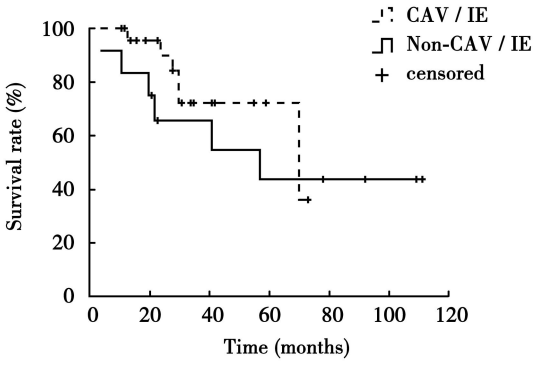

Figure 5 Overall survival curves of patients in non-metastasis group treated with different chemotherapy regimens based on multidisciplinary therapy

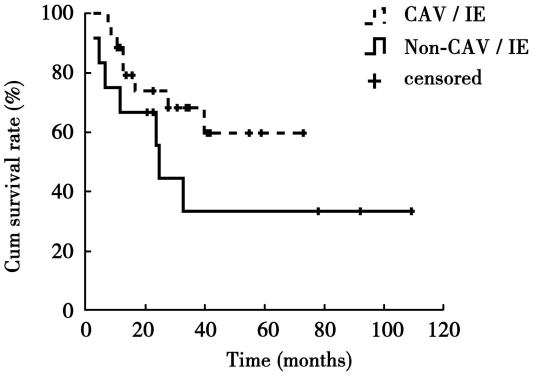

Figure 6 Event-free surviral curves of patients in non-metastasis group treated with different chemotherapy regimens based on multidisciplinary therapy

scheme increased 5-year EFS to 69% in patients with non-metastatic disease.[11] Thereby, the efficacy of alternative IFO plus VP-16/VACD scheme on non-metastatic ESFT was confirmed. Many international multi-center trials have demonstrated that multi-discipline treatment could significantly improve EFS and OS of the patients with non-metastatic ESFT, but had little effect on the survival of those with metastatic ESFT.

Our study also demonstrated that multi-discipline treatment had significantly improved short-term efficacy and long-term survival of patients with non-metastatic ESFT as compared with sole treatment. On the basis of systemic chemotherapy, the addition of surgical resection with or without radiotherapy could better improve survival rate as compared with chemotherapy plus radiotherapy. This is generally consistent with the results reported in literature.[12] Theoretically, surgical resection removes primary tumor lesion and regional draining lymph nodes completely, promotes the growth of residual tumor and improves the sensitivity to chemotherapy. Evaluation of short-term efficacy after treatment is important for long-term survival prediction. The patients with complete remission (CR) and partial remission (PR) have longer survival than those with stable disease (SD) and progressive disease (PD). Moreover, available results also confirm that post-chemotherapy efficacy evaluation is an important predictor for prognosis.[13] We also found that treatment pattern and efficacy were also independent prognostic factors, but stage, primary site and tumor volume were not predictors for long-term survival; controversially, chemotherapy prolonged EFS of the patients with non-metastatic ESFT who received multi-discipline treatment, but the difference in OS was not significant. The survival duration of our patients was shorter than those reported in other countries. The possible reasons were as follows: 1) Most of our patients had primary tumors in midline structures, and thus did not receive radical resection. 2) The number of chemotherapy cycles was generally small, averagely 6 cycles; while in other countries, the patients generally received 12-18 cycles of chemotherapy. In addition, dose intensity of chemotherapeutic agents was also lower than that in other countries. 3) CAV/IE scheme was put into clinical use since January 2001 in our center, therefore, the patients were followed for a short time; furthermore, with a small number of patients, the survival benefit of the scheme was not fully revealed. 4) As a retrospective analysis, our study had selection bias and data bias. 5) Since ESFT is rare, and systemic chemotherapy was used in China in 1990s, therefore, our study included patients from across a long period of time and the follow-up rate in our study was relatively low. More follow-up and survival data should be collected in further clinical observation and multi-center randomized controlled trials.

Our results suggest that multi-discipline treatment including systemic chemotherapy and surgery could prolong survival in patients with non-metastatic ESFT; alternative CAV/IE scheme might be better than other chemotherapy schemes; short-term efficacy evaluation is important for long-term survival prediction.

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