Original Article

Effects of different treatments and other factors on the prognosis of patients with ewing sarcoma

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Background: Ewing sarcoma is a small round cell tumor of bone or soft tissue originating from the neuroectoderm. Aggressive and highly malignant are the main pathological features of the tumor. Studying the effects of different treatments and other factors on prognosis will help us to understand the disease more deeply and find a way to actively deal with it.

Methods: Through the search of the National Cancer Institute database, ewing sarcoma patients registered between January 1, 2004 and December 31, 2015 were selected as research goals. Summarize the basic information of patients included in the study, including demographics, tumor pathology and treatment. Kaplan–Meier survival curves and log-rank test were used to analyze the overall survival (OS) and ewing sarcoma-specific survival (ESSS) of each prognostic factor and categorical variable. Multivariate Cox regression analysis was used to analyze all-cause mortality (ACM) and ewing sarcoma-specific mortality (ESSM) for each prognostic factor and categorical variable.

Results: A total of 837 ewing sarcoma patients were included in this article. Patients receiving chemotherapy (CT), radiotherapy (RT) or surgery were 804 (96.1%), 414 (49.5%), and 524 (62.6%). The mean age and median age of 837 patients were 19.92 and 16 years, respectively. The mortality rate gradually increased with the increase of the age at diagnosis (ACM: 50.6% *vs.* 45.3% *vs.* 25.7%, P<0.001; ESSM: 44.0% *vs.* 43.0% *vs.* 25.1%, P<0.001). Married patients' mortality was significantly higher than unmarried patients (ACM: 53.2% *vs.* 31.2%, P<0.001; ESSM: 29.8% *vs.* 48.5%, P<0.001). CT combined surgery achieved the highest OS and ESSS. Observing clinical pathology data, the primary site of the tumor located in pelvic bones, sacrum coccyx and associated joints, which had the highest mortality (ACM: 45.3%; ESSM: 43.9%). The mortality of tumors classified as American Joint Committee on Cancer (AJCC) III–IV stage was significantly higher than that of AJCC IIA and AJCC IIB stage, and the mortality increased with the higher AJCC stage (ACM: 53.0% *vs.* 31.3% *vs.* 21.0%, P<0.001; ESSM: 51.2% *vs.* 30.1% *vs.* 18.6%, P<0.001). The mortality of T2–T3 stage was significantly higher than that of T0–T1 stage (ACM: 40.7% *vs.* 27.0%, P<0.001; ESSM: 39.1% *vs.* 24.8%, P<0.001). N1 stage was significantly higher than N0 (ACM: 49.2% *vs.* 32.8%, P=0.008; ESSM: 49.2% *vs.* 30.7%, P=0.002). M1 stage was significantly higher than M0 stage (ACM: 56.8% *vs.* 25.5%, P<0.001; ESSM: 55.2% *vs.* 23.5%, P<0.001). Compared with other treatments, patients who received CT and surgery had the lowest ACM (21.7%) and ESSM (20.9%), and the mean survival (59.90±39.24 months) and median survival (53 months) were the longest.

Conclusions: From the demographic and tumor pathology data, the older patients at the age of diagnosis, married, the primary sites in the pelvic bones, sacrum coccyx and associated joints, American Joint Committee on Cancer (AJCC) III–IV, T2–T3, N1 and M1 stage tumors are all prompted to patients' poor prognosis. Compared with CT, CT and RT, or CT and RT and surgery, ewing sarcoma patients receiving CT combined with surgery have the longest median survival, the lowest mortality, and the best prognosis.

Keywords: Ewing sarcoma; chemotherapy; radiotherapy; surgery; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Ewing sarcoma is a small round cell tumor of bone or soft tissue originating from the neuroectoderm (1). Aggressive and highly malignant are the main pathological features of the tumor (1). Mainly due to the translocation of chromosome 11 and chromosome 22, the ews-fli1 fusion gene was formed, which led to the formation of ewing sarcoma (2,3). ES is the second common primary bone malignancy in children and adolescents. It is rare in adults and the incidence ratio is about 1.5:1 (4). In primary tumors, ewing sarcoma accounts for 6–8%, and occurs in the pelvis and limbs. It is rare in the spine (1,5). The disease has a high degree of malignancy, short course of disease, rapid metastasis, simple surgery, radiotherapy (RT), single-agent chemotherapy (CT), the effect is not very satisfactory, the vast majority of patients died within 2 years, 5 years survival rate does not exceed 10 % (1,5).

In the past, surgery was the main measure to treat this disease (6). With the improvement of the efficacy of RT and CT and the countermeasures for the side effects caused by it, the number of patients treated with surgery alone is decreasing (6,7). But so far, surgical amputation or removal is still one of the treatments for this disease. The principle of surgery was to completely remove the tumor to maximize effective local control, prevent and reduce tumor metastasis. Ewing sarcoma is extremely sensitive to RT and is the main treatment. Generally, a small dose (3,000–4,000 rad) is irradiated, which can rapidly reduce the tumor and reduce or disappear the local pain (7,8). However, the long-term effect of simple RT is very poor. In terms of CT, the drugs currently considered effective for ewing sarcoma include cyclophosphamide, doxorubicin, dactinomycin, vincristine, and carban mustard (9). Because most of the disease occurs within 2 years, it is generally recommended that CT should last for 2 years. Combined with a variety of treatments, the disease-free survival rate of ewing sarcoma patients has risen from less than 20% to 70–75% (1).

To date, few clinical retrospective studies have compared the efficacy of combination therapy in patients with ewing sarcoma. In addition, the demographic and tumor pathology features are summarized to see if the above characteristics have changed in recent years. Therefore, this study aimed to investigate which combination of treatments can improve the prognosis of patients with ewing sarcoma and identify factors that influence the prognosis of patients.

Methods

Data collection

Surveillance, Epidemiology, and End Results (SEER) database covers about 28 percent of the population of the United States and collects data on cancer patients from 18 tumor registration centers. The latest data for the (1973–2016 varying) database released in November 2018 was obtained using SEER stat special software (version 8.3.5), and data acquisition was done in client–server mode. A total of 837 patients with ewing sarcoma in the United States diagnosed between January 1, 2004 and December 31, 2015. Exclusion criteria include: unknown survival time, vital status, American Joint Committee on Cancer (AJCC) stage and TNM stage.

Inclusion codes and criteria

The main end points of the study were overall survival (OS) and ewing sarcoma-specific survival (ESSS). In this study, we classified patients according to the following factors, such as age (0–18, 19–40, >40), gender (male, female), race (White, others), marital status (yes, no) and state (West, East, South, North).

For the tumor , The tumors were classified according to the main location (upper limb, scapula and long bone of related joints; lower limb and long bone of related joints; rib, sternum, clavicle and associated joints; pelvic bones, sacrum coccyx and associated joints; other), grade (I, II, III, IV, Unknown), AJCC (IIA, IIB, III–IV), T (T0–T1,T2–T3), N (N0, N1) and M (M0, M1).

Statistical analysis

The χ^2 test was used to compare the basic clinical features of the patients included in the study and whether ewing sarcoma patients received CT, RT, or surgery. Kaplan–Meier survival curves and log-rank test were used to analyze the OS and ESSS of each prognostic factor and categorical

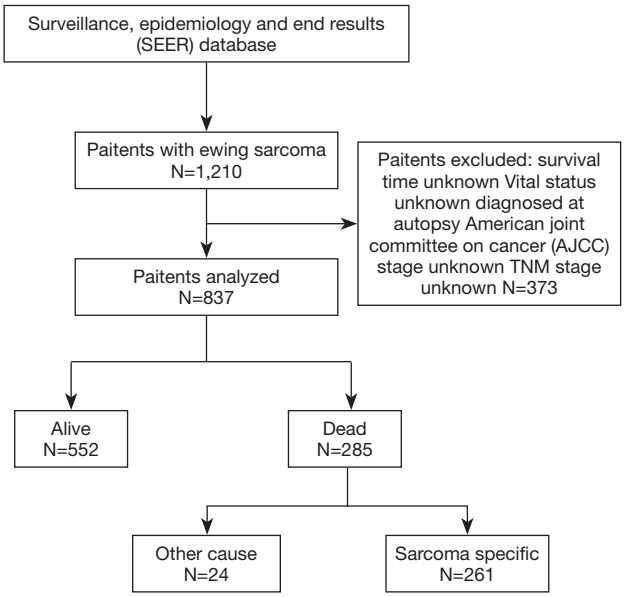


Figure 1 Flowchart of patients identification and selection.

variable. Multivariate Cox regression analysis was used to analyze all-cause mortality (ACM) and ewing sarcoma-specific mortality (ESSM) for each prognostic factor and categorical variable. Moreover, the hazard ratios (HR) and 95% confidence intervals (CI) for all strata of each factor are also calculated. The P value <0.05 is considered statistically significant. All statistical analysis is completed by Statistical package for the social sciences (version 23.0 USA).

Results

Demographic and tumor pathological features of ewing sarcoma patients

The specific screening process was shown in *Figure 1*. Between Jan 1, 2004 and Dec 31, 2015, 837 ewing sarcoma patients were included in this article. Patients receiving CT, RT or surgery were 804 (96.1%), 414 (49.5%), and 524 (62.6%), respectively (1). From 2004 to 2015, the number of patients receiving CT was basically stable, and the proportion of patients receiving RT was also stable, while the proportion of patients undergoing surgery decreased to a certain extent, but there was no significant difference in the decline.

The mean age and median age of 837 patients were 19.92 and 16 years, respectively. The majority of the categorical variables in this study were 0–18 years old (60.3%), unmarried (87.0%), white (89.2%), male (62.2%), diagnosed in the West (49.6%) and the primary site in long bones of lower limb and associated joints (28.9%). The categorical variables of age at diagnosis, primary site, tumour grade, AJCC stage and T stage were associated with CT. The categorical variables of state, primary site, AJCC stage, T stage and M stage were associated with RT. The categorical variable associated with surgery include age at diagnosis, primary site, tumor grade, AJCC stage and TNM stage. All variables had significant differences (χ^2 test: P value <0.05). The demographic and tumor pathological information of the patients was presented in *Table 1*.

The impact of different variables on ACM and ESSM

Among all 873 patients, 285 (34.1%) patients with all-cause mortality, while 261 (31.2%) died of ewing sarcoma (*Figure 1*, *Table 2*). Observing the demographic data, mortality was significantly higher in patients over 40 years compared with patients under 40 years, and the mortality rate gradually increased with the increase of the age at diagnosis (ACM: 50.6% *vs.* 45.3% *vs.* 25.7%, P<0.001; ESSM: 44.0% *vs.* 43.0% *vs.* 25.1%, P<0.001). Married patients' mortality was significantly higher than unmarried patients (ACM: 53.2% *vs.* 31.2%, P<0.001; ESSM: 29.8% *vs.* 48.5%, P<0.001). In addition, gender, ethnicity, and diagnostic areas had no significant effect on mortality.

Observing clinical pathology data, the primary site of the tumor located in pelvic bones, sacrum coccyx and associated joints, which had the highest mortality (ACM: 45.3%; ESSM: 43.9%). The mortality of tumors classified as AJCC III–IV stage was significantly higher than that of AJCC IIA and AJCC IIB stage, and the mortality increased with the higher AJCC stage (ACM: 53.0% *vs.* 31.3% *vs.* 21.0%, P<0.001; ESSM: 51.2% *vs.* 30.1% *vs.* 18.6%, P<0.001). The mortality of T2–T3 stage was significantly higher than that of T0–T1 stage (ACM: 40.7% *vs.* 27.0%, P<0.001; ESSM: 39.1% *vs.* 24.8%, P<0.001). N1 stage was significantly higher than N0 (ACM: 49.2% *vs.* 32.8%, P=0.008; ESSM: 49.2% *vs.* 30.7%, P=0.002). M1 stage was significantly higher than M0 stage (ACM: 56.8% *vs.* 25.5%, P<0.001; ESSM: 55.2% *vs.* 23.5%, P<0.001).

Observed treatment data showed that patients receiving CT had significantly improved ACM (33.2% *vs.* 54.5%, P<0.001), but ESSM was not statistically significant (31.6% *vs.* 46.4%, P=0.098). The ACM and ESSM of patients receiving RT was significantly higher (ACM: 40.6% *vs.* 27.7.%, P<0.001; ESSM: 38.3% *vs.* 26.1%, P<0.001).

Table 1 Characteristics for ewing sarcoma patients stratified by chemotherapy (CT), radiotherapy (RT) and surgery χ^2 test

Characteristics	Total	CT					Surgery					Surgery				
		CT		No CT		P	RT		No RT		P	Surgery		No surgery		P
		N	%	N	%		N	%	N	%		N	%	N	%	
Total	837	804	96.1	33	3.9		414	49.5	423	50.5		524	62.6	313	37.4	
Year of diagnosis						0.351					0.744					0.074
2004–2006	159	154	96.9	5	3.1		79	49.7	80	50.3		104	65.4	55	34.6	
2007–2009	187	180	96.3	7	3.7		86	46.0	101	54.0		126	67.4	61	32.6	
2010–2012	225	219	97.3	6	2.7		115	51.1	110	48.9		144	64.0	81	36.0	
2013–2015	266	251	94.4	15	5.6		134	50.4	132	49.6		150	56.4	116	43.6	
Age at diagnosis						<0.001					0.71					0.019
0–18	505	494	97.8	11	2.2		244	48.3	261	51.7		335	66.3	170	33.7	
19–40	247	239	96.8	8	3.2		127	51.4	120	48.6		143	57.9	104	42.1	
>40	85	71	83.5	14	16.5		43	50.6	42	49.4		46	54.1	39	45.9	
Sex						0.593					0.809					0.291
Male	521	499	95.8	22	4.2		265	50.9	256	49.1		319	61.2	202	38.8	
Female	316	305	96.5	11	3.5		158	50.0	158	50.0		205	64.9	111	35.1	
Race						0.978					0.221					0.054
White	747	717	96.0	30	4.0		364	48.7	383	51.3		476	63.7	271	36.3	
Other	90	87	96.7	3	3.3		50	55.6	40	44.4		48	53.3	42	46.7	
Marital status						0.181					0.097					0.185
Yes	109	102	93.6	7	6.4		62	56.9	47	43.1		62	56.9	47	43.1	
No	728	702	96.4	26	3.6		352	48.4	376	51.6		462	63.5	266	36.5	
State						0.143					0.019					0.17
West	415	393	94.7	22	5.3		217	52.3	198	47.7		243	58.6	172	41.4	
East	186	181	97.3	5	2.7		74	39.8	112	60.2		126	67.7	60	32.3	
South	109	108	99.1	1	0.9		53	48.6	56	51.4		64	58.7	45	41.3	
North	127	122	96.1	5	3.9		70	55.1	57	44.9		91	71.7	36	28.3	
Primary site						0.003					<0.001					<0.001
Long bones of upper limb, scapula and associated joints	105	102	97.1	3	2.9		43	41.0	62	59.0		69	65.7	36	34.3	

Table 1 (*Continued*)

Table 1 (*Continued*)

Characteristics	Total	CT					Surgery					Surgery				
		CT		No CT		P	RT		No RT		P	Surgery		No surgery		P
		N	%	N	%		N	%	N	%		N	%	N	%	
Long bones of lower limb and associated joints	242	233	96.3	9	3.7		71	29.3	171	70.7		186	76.9	56	23.1	
Rib, sternum, clavicle and associated joints	110	105	95.5	5	4.5		53	48.2	57	51.8		87	79.1	23	20.9	
Pelvic bones, sacrum coccyx and associated joints	201	200	99.5	1	0.5		146	72.6	55	27.4		59	29.4	142	70.6	
Other	179	164	91.6	15	8.4		101	56.4	78	43.6		123	68.7	56	31.3	
Grade						0.009					0.281					0.002
I–III	58	52	89.7	6	10.3		24	41.4	34	58.6		42	72.4	16	27.6	
IV	161	159	98.8	2	1.2		86	53.4	75	46.6		117	72.7	44	27.3	
Unknown	618	593	96.0	25	4.0		304	49.2	314	50.8		365	59.1	253	40.9	
American joint committee on cancer AJCC						0.042					< 0.001					<0.001
IIA	333	313	94.0	20	6.0		134	40.2	199	59.8		251	75.4	82	24.6	
IIB	240	233	97.1	7	2.9		109	45.4	131	54.6		164	68.3	76	31.7	
III, IV	264	258	97.7	6	2.3		171	64.8	93	35.2		109	41.3	155	58.7	
T-stage						0.039					0.001					<0.001
T0, T1	411	389	94.6	22	5.4		186	45.3	225	54.7		290	70.6	121	29.4	
T2, T3	426	415	97.4	11	2.6		228	53.5	198	46.5		234	54.9	192	45.1	
N-stage						0.166					0.457					0.022
N0	774	741	95.7	33	4.3		380	49.1	394	50.9		493	63.7	281	36.3	
N1	63	63	100.0	0	0.0		34	54.0	29	46.0		31	49.2	32	50.8	
M-stage						0.228					<0.001					<0.001
M0	608	581	95.6	27	4.4		261	42.9	347	57.1		439	72.2	169	27.8	
M1	229	223	97.4	6	2.6		153	66.8	76	33.2		85	37.1	144	62.9	

Table 2 Univariate survival analyses of ewing sarcoma patients according to various clinicopathological variables

Characteristics	All cause					Ewing sarcoma-specific				
	Dead		Alive		P	Dead		Alive		P
	N	%	N	%		N	%	N	%	
Total	285	34.1	552	65.9		261	32.1	552	67.9	
Age at diagnosis					<0.001					<0.001
0–18	130	25.7	375	74.3		126	25.1	375	74.9	
19–40	112	45.3	135	54.7		102	43.0	135	57.0	
>40	43	50.6	42	49.4		33	44.0	42	56.0	
Sex					0.149					0.072
Male	187	35.9	334	64.1		175	34.4	334	65.6	
Female	98	31.0	218	69.0		86	28.3	218	71.7	
Race					0.305					0.323
White	250	33.5	497	66.5		229	31.5	497	68.5	
Other	35	38.9	55	61.1		32	36.8	55	63.2	
Marital status					<0.001					<0.001
Yes	58	53.2	51	46.8		48	48.5	51	51.5	
No	227	31.2	501	68.8		213	29.8	501	70.2	
State					0.203					0.33
West	145	34.9	270	65.1		132	32.8	270	67.2	
East	56	30.1	130	69.9		52	28.6	130	71.4	
South	45	41.3	64	58.7		40	38.5	64	61.5	
North	39	30.7	88	69.3		37	29.6	88	70.4	
Primary site					0.002					0.002
Long bones of upper limb, scapula and associated joints	27	25.7	78	74.3		26	25.0	78	75.0	
Long bones of lower limb and associated joints	73	30.2	169	69.8		70	29.3	169	70.7	
Rib, sternum, clavicle and associated joints	35	31.8	75	68.2		28	27.2	75	72.8	
Pelvic bones, sacrum coccyx and associated joints	91	45.3	110	54.7		86	43.9	110	56.1	
Other	59	33.0	120	67.0		51	29.8	120	70.2	
Grade					0.913					0.811
I–III	21	36.2	37	63.8		20	35.1	37	64.9	
IV	57	35.4	104	64.6		52	33.3	104	66.7	
Unknown	207	33.5	411	66.5		189	31.5	411	68.5	

Table 2 (*Continued*)

Table 2 (*Continued*)

Characteristics	All cause					Ewing sarcoma-specific				
	Dead		Alive		P	Dead		Alive		P
	N	%	N	%		N	%	N	%	
American joint committee on cancer (AJCC)					<0.001					<0.001
IIA	70	21.0	263	79.0		60	18.6	263	81.4	
IIB	75	31.3	165	68.8		71	30.1	165	69.9	
III, IV	140	53.0	124	47.0		130	51.2	124	48.8	
T-stage					<0.001					<0.001
T0–T1	111	27.0	300	73.0		99	24.8	300	75.2	
T2–T3	174	40.8	252	59.2		162	39.1	252	60.9	
N-stage					0.008					0.002
N0	254	32.8	520	67.2		230	30.7	520	69.3	
N1	31	49.2	32	50.8		31	49.2	32	50.8	
M-stage					<0.001					<0.001
M0	155	25.5	453	74.5		139	23.5	453	76.5	
M1	130	56.8	99	43.2		122	55.2	99	44.8	
Chemotherapy (CT)					0.011					0.098
Yes	267	33.2	537	66.8		248	31.6	537	68.4	
No	18	54.5	15	45.5		13	46.4	15	53.6	
Radiotherapy (RT)					<0.001					<0.001
Yes	168	40.6	246	59.4		153	38.3	246	61.7	
No	117	27.7	306	72.3		108	26.1	306	73.9	
Surgery					<0.001					<0.001
Yes	148	28.2	376	71.8		135	26.4	376	73.6	
No	137	43.8	176	56.2		126	41.7	176	58.3	
Treatment method					<0.001					<0.001
No CT and no RT and no surgery	6	50.0	6	50.0		4	40.0	6	60.0	
CT	38	42.2	52	57.8		36	40.9	52	59.1	
RT	2	66.7	1	33.3		1	50.0	1	50.0	
Surgery	6	50.0	6	50.0		4	40.0	6	60.0	
CT and RT	91	43.8	117	56.3		85	42.1	117	57.9	
CT and surgery	67	21.7	242	78.3		64	20.9	242	79.1	
RT and surgery	4	66.7	2	33.3		4	66.7	2	33.3	
CT and RT and surgery	71	36.0	126	64.0		63	33.3	126	66.7	

Surgery improved ACM (28.2% *vs.* 43.8%, P<0.001) and ESSM (26.4% *vs.* 41.7%, P<0.001). CT combined surgery achieved the lowest ACM (21.7%) and ESSM (20.9%).

Survival

We plotted Kaplan–Meier survival curves based on patient OS and ESSS for some factors that were statistically different in *Table 2*, including age at diagnosis, marital status, primary site, AJCC stage, TNM stage and treatment method (*Figure 2*).

The median survival and survival month are shown in *Table 3*. Overall median survival was 42.0 months. Patients with a diagnosis of 0–18 years of age had significantly better survival months (57.54±39.83 *vs.* 46.81±37.03 *vs.* 39.05±35.97 months) and median survival (47 *vs.* 36 *vs.* 24 months). The number of months of unmarried patients was significantly longer (54.35±39.69 *vs.* 40.14± 32.95 months) and median survival (43 *vs.* 28 months). Among the primary sites, the longest survival months were long bones of lower limb and associated joints (56.19± 39.17 months), while the highest median survival time was rib, sternum, clavicle and associated joints (51 months). In the AJCC staging, patients with stage IIA had the longest survival (61.18±41.49 *vs.* 57.36±39.24 *vs.* 37.13± 30.75 months) and median survival (51 *vs.* 47 *vs.* 28 months). In TNM staging, T0–T1 stage, N0 stage and M0 stage were significantly longer (56.82±40.81 *vs.* 48.33±37.05; 53.62±39.48 *vs.* 38.76±32.04; 59.21±40.30 *vs.* 34.68± 29.27 months, respectively) and median survival (46 *vs.* 37 months; 43 *vs.* 32 months; 49 *vs.* 26 months, respectively).

Patients with CT or surgery have achieved the longest survival (53.43±39.10 *vs.* 29.88±33.75 months; 59.95±39.86 *vs.* 41.70±35.45 months) and median survival (43 *vs.* 18 months; 49 *vs.* 30 months). The mean survival (49.89±37.97 *vs.* 55.04±40.16 months) and median survival (37 *vs.* 47 months) of patients receiving RT decreased. CT combined surgery achieved the longest mean survival (59.90±39.24 months) and median survival (53 months) (*Table 3*). Patients who underwent CT or received CT combined with RT had close median survival (32 *vs.* 30 months).

Multivariate Cox regression of prognostic factors in ewing sarcoma patients

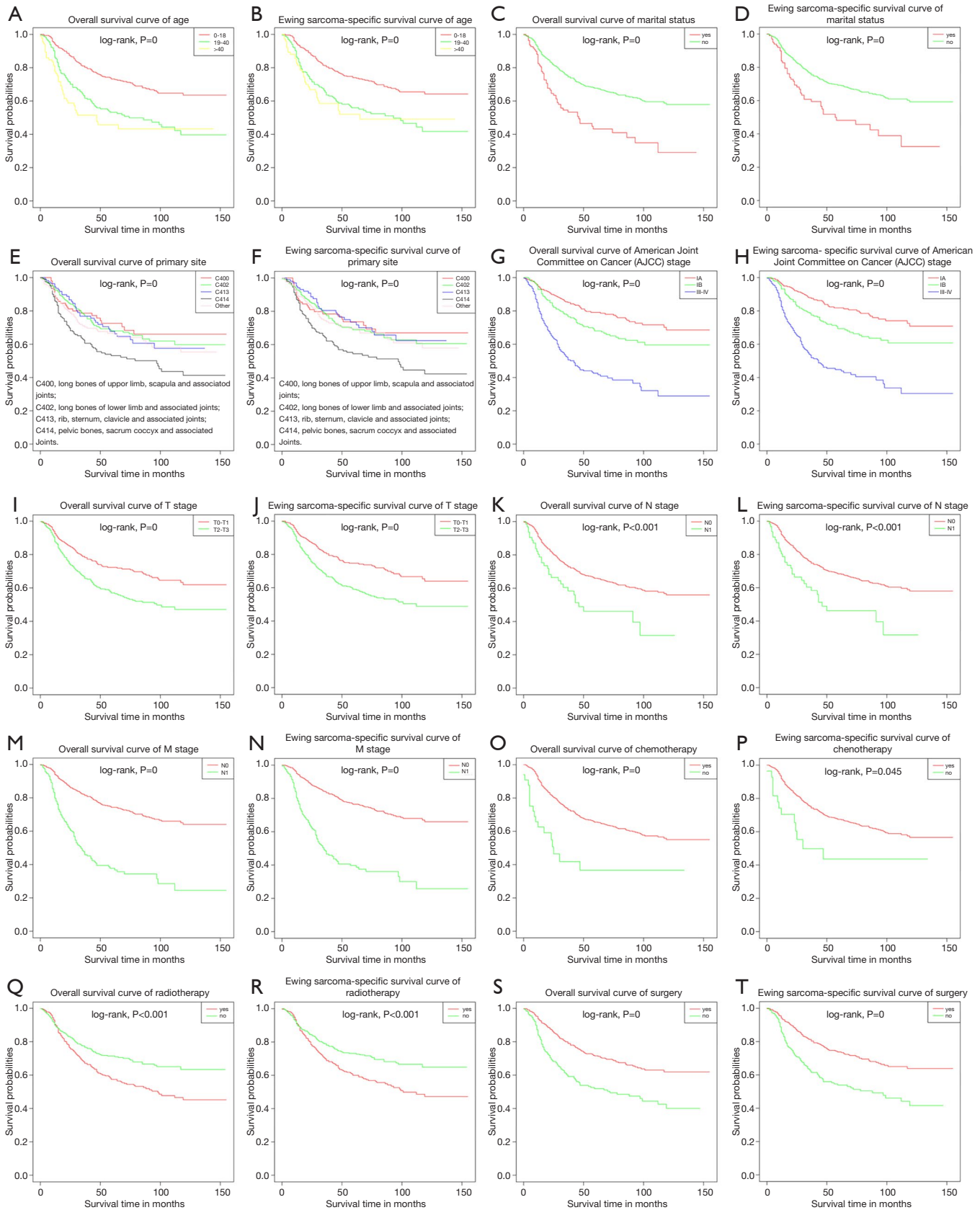
Multivariate Cox regression analysis of factors such as age, race, marital status, sex, primary site, state, grade, AJCC, TNM stage and treatment methods (*Table 4*). Using age at diagnosis 0–18 years as a reference, patients with 19–40 years and >40 years had increased risk of ACM ACM (19–40 years, HR =1.793; >40 years, HR =2.179) and ESSM (19–40 years, HR =1.714; >40 years, HR =1.866). Using married as a reference, unmarried patients had decreased risk of ACM (unmarried, HR =0.624) and ESSM (unmarried, HR =0.869). Using AJCC stage IIA as a reference, IIB and III–IV stage patients had increased risk of ACM (IIB, HR = 1.758; III–IV, HR =1.189) and ESSM (IIB, HR =1.967; III–IV, HR =1.047).

Using received CT as a reference, unreceived CT patients had increased risk of ACM (no CT, HR =3.120) and ESSM (no CT, HR =2.685). Using received surgery as a reference, unreceived surgery patients had increased risk of ACM (no surgery, HR =1.305) and ESSM (no surgery, HR =1.283). Using received RT as a reference, unreceived RT patients had decreased risk of ACM (no RT, HR =0.870) and ESSM (no RT, HR =0.878).Using only CT treatment as a reference, CT combined surgery had achieved the best prognosis (ACM: HR =0.391; ESSM: HR =0.393) , CT combined with RT and surgery also achieved a good prognosis (ACM: HR =0.652; ESSM: HR =0.620).

Discussion

Ewing sarcoma is mainly found in bones and muscles, and is also found in soft tissues (10). The disease is more common in men, and there are differences in species, which are common in white people, and Asians and Africans are rare. Early ewing sarcoma has a single treatment and a poor prognosis (11). In recent years, with the deepening of research and the improvement of medical treatment methods, the OS rate of ewing sarcoma patients has been significantly improved (12).

CT is considered to be a widely accepted treatment, which is well documented in our study, regardless of the number of patients receiving CT (6,9,13). Still from the perspective of survival rate, CT is undoubtedly the best solution. Current research focuses on the choice of CT protocol (14-18). Bacci *et al.* (19) retrospectively analyzed the situation of 579 patients with ewing sarcoma admitted from 1972 to 1998. All patients underwent CT. Not only the number of CT drugs was different, but also the time distribution difference in the choice of chemotherapy regimen. In this study, it was found that with the increase in the number of chemotherapy drugs



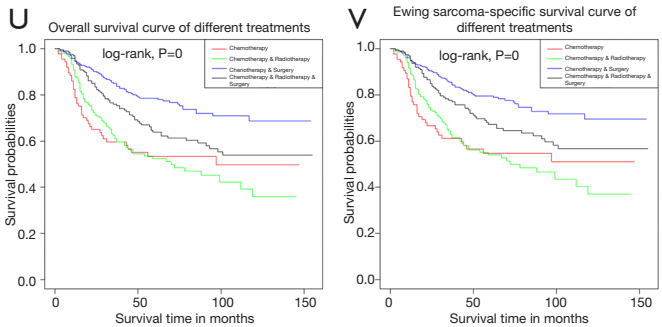


Figure 2 Survival curves in ewing sarcoma patients according to different treatments and other factors.

Table 3 Median and mean survival months of ewing sarcoma patients

Characteristics	Patients, N	Median survival (mean survival), months
Age at diagnosis		
0–18	505	47 (57.54±39.83)
19–40	247	36 (46.81±37.03)
>40	85	24 (39.05±35.97)
Marital status		
Yes	109	28 (40.14±32.95)
No	728	43 (54.35±39.69)
Primary site		
Long bones of upper limb, scapula and associated joints	105	43 (53.42±41.65)
Long bones of lower limb and associated joints	242	45 (56.19±39.17)
Rib, sternum, clavicle and associated joints	110	51 (54.48±33.80)
Pelvic bones, sacrum coccyx and associated joints	201	34 (48.38±40.51)
Other	179	39 (50.36±38.98)
American Joint Committee on Cancer (AJCC)		
IIA	333	51 (61.18±41.49)
IIB	240	47 (57.36±39.24)
III, IV	264	28 (37.13±30.75)
T-stage		
T0–T1	411	46 (56.82±40.81)
T2–T3	426	37 (48.33±37.05)
N-stage		
N0	774	43 (53.62±39.48)
N1	63	32 (38.76±32.04)

Table 3 (*Continued*)

Table 3 (*Continued*)

Characteristics	Patients, N	Median survival (mean survival), months
M-stage		
M0	608	49 (59.21±40.30)
M1	229	26 (34.68±29.27)
Chemotherapy (CT)		
Yes	804	43 (53.43±39.10)
No	33	18 (29.88±33.75)
Radiotherapy (RT)		
Yes	414	37 (49.89±37.97))
No	423	47 (55.04±40.16)
Surgery		
Yes	524	49 (59.95±39.86)
No	313	30 (41.70±35.45)
Treatment method		
CT	90	30 (45.46±40.62)
CT and RT	208	32 (41.58±33.18)
CT and surgery	309	53 (59.90±39.24)
CT and RT and surgery	197	48 (59.81±40.63)

Table 4 Multivariate Cox regression analysis for all-cause mortality and ewing sarcoma-specific mortality in patients with different treatments and other factors

Characteristics	All-cause mortality		Ewing sarcoma-specific mortality	
	Hazard ratios (95% confidence intervals)	P	Hazard ratios (95% confidence intervals)	P
Age at diagnosis				
0–18	1.000 (reference)		1.000 (reference)	
19–40	1.793 (1.364–2.357)	<0.001	1.714 (1.291–2.275)	<0.001
>40	2.179 (1.383–3.432)	<0.001	1.866 (1.138–3.060)	0.013
Sex				
Male	1.000 (reference)		1.000 (reference)	
Female	0.911 (0.705–1.179)	0.479	0.869 (0.663–1.139)	0.309
Race				
White	1.000 (reference)		1.000 (reference)	
Other	1.398 (0.964–2.025)	0.077	1.378 (0.935–2.033)	0.106

Table 4 (*Continued*)

Table 4 (*Continued*)

Characteristics	All-cause mortality		Ewing sarcoma-specific mortality	
	Hazard ratios (95% confidence intervals)	P	Hazard ratios (95% confidence intervals)	P
Marital status				
Yes	1.000 (reference)		1.000 (reference)	
No	0.634 (0.436–0.920)	0.017	0.624 (0.418–0.932)	0.021
State				
West	1.000 (reference)		1.000 (reference)	
East	0.921 (0.669–1.267)	0.612	0.952 (0.683–1.325)	0.769
South	1.335 (0.940–1.896)	0.106	1.324 (0.914–1.919)	0.138
North	1.053 (0.731–1.518)	0.781	1.094 (0.749–1.595)	0.643
Primary site				
Long bones of upper limb, scapula and associated joints	1.000 (reference)		1.000 (reference)	
Long bones of lower limb and associated joints	1.150 (0.734–1.802)	0.543	1.142 (0.722–1.805)	0.571
Rib, sternum, clavicle and associated joints	1.154 (0.686–1.941)	0.589	1.043 (0.600–1.813)	0.881
Pelvic bones, sacrum coccyx and associated joints	1.458 (0.933–2.279)	0.098	1.416 (0.897–2.235)	0.135
Other	1.265 (0.776–2.062)	0.347	1.198 (0.722–1.988)	0.485
Grade				
I–III	1.000 (reference)		1.000 (reference)	
IV	1.103 (0.649–1.874)	0.718	1.061 (0.612–1.839)	0.833
Unknown	1.041 (0.654–1.658)	0.865	1.001 (0.619–1.620)	0.996
American joint committee on cancer (AJCC)				
IIA	1.000 (reference)		1.000 (reference)	
IIB	1.758 (1.063–2.901)	0.028	1.967 (1.166–3.318)	0.011
III, IV	1.189 (0.532–2.656)	0.673	1.047 (0.438–2.504)	0.918
T-stage				
T0, T1	1.000 (reference)		1.000 (reference)	
T2, T3	1.061 (0.693–1.490)	0.935	0.960 (0.645–1.430)	0.842
N-stage				
N0	1.000 (reference)		1.000 (reference)	
N1	1.469 (0.939–2.298)	0.092	1.625 (1.038–2.544)	0.034
M-stage				
M0	1.000 (reference)		1.000 (reference)	
M1	3.131 (1.522–6.441)	0.002	3.969 (1.801–8.746)	< 0.001

Table 4 (*Continued*)

Table 4 (*Continued*)

Characteristics	All-cause mortality		Ewing sarcoma-specific mortality	
	Hazard ratios (95% confidence intervals)	P	Hazard ratios (95% confidence intervals)	P
Chemotherapy (CT)				
Yes	1.000 (reference)		1.000 (reference)	
No	3.120 (1.826–5.329)	< 0.001	2.685 (1.452–4.966)	0.002
Radiotherapy (RT)				
Yes	1.000 (reference)		1.000 (reference)	
No	0.870 (0.672–1.126)	0.29	0.878 (0.671–1.150)	0.346
Surgery				
Yes	1.000 (reference)		1.000 (reference)	
No	1.305 (0.985–1.729)	0.064	1.283 (0.954–1.726)	0.01
Treatment method				
CT	1.000 (reference)		1.000 (reference)	
CT and RT	1.034 (0.707–1.511)	0.864	1.023 (0.693–1.513)	0.908
CT and surgery	0.391 (0.263–0.583)	<0.001	0.393 (0.261–0.591)	<0.001
CT and RT and surgery	0.652 (0.439–0.966)	0.033	0.620 (0.412–0.935)	0.022

and the continuous update of chemotherapy regimens, 5-year disease-free survival increased, which means that researchers have deepened their understanding of ewing sarcoma, and targeted treatment is widely used. Abou Ali *et al.* (17) reviewed 42 ewing sarcoma patients admitted to the institution from 1999 to 2012. All patients underwent CT, and the CT regimen was well tolerated. A research cooperation group in Brazil to determine the effect of alternating VDC (vincristine, doxorubicin, cyclophosphamide) with ICE (ifosfamide, carboplatin and etoposide) as a first-line treatment for newly diagnosed Ewing sarcoma family tumors (ESFT) patients, institutional patients with 0–30 years of histologically confirmed ESFT were selected in the study and found that carboplatin did not appear to increase the prognosis of patients identified as high risk, on the contrary, the toxicity was more significant. The group believes that the addition of carboplatin can produce significant toxicity and has no significant improvement in prognosis (20). A large clinical trial comparing the efficacy of cyclophosphamide or ifosfamide in ewing sarcoma patients who were identified as standard risk, which suggests that cyclophosphamide can replace the standard risk of ewing sarcoma with ifosfamide. However, compared with VAI (vincristine, dactinomycin, and ifosfamide), there are still some uncertainties in the non-inferiority of VAC (vincristine, dactinomycin, and cyclophosphamide), and volunteers are still needed to conduct long-term renal and gonadal toxicity studies (21).

Local treatment is also an important step, surgery and radiotherapy are currently widely accepted local treatments (22). The effective resection of the primary lesion by surgery is considered to be an important factor affecting the prognosis. However, sometimes the patient's own condition or disease cannot be operated, and RT is needed to treat the local part. Casey *et al.* (8) performed RT on 22 patients with ewing sarcoma bone metastases between 1999 and 2013. The study found that radiotherapy for the metastatic site and the primary site can improve the survival rate of patients. Similarly, it is clear that the therapeutic dose range of the primary site of treatment can be applied to the treatment of the metastatic site. European Ewing Sarcoma Research Group reported an observational study in 2016 to determine whether the presence of postoperative RT is significant in the local standard risk ewing sarcoma (7). The study included a total of 599 patients, of whom 142 (24%) received postoperative RT (median dose: 45 Grays),

and received surgery combined with RT had a significantly lower local recurrence rate than simple surgery (HR =0.43). RT appears to be an effective local treatment, especially when surgery cannot be completely removed or CT cannot effectively reduce tumor volume. One of the challenges of using RT to treat pediatric ewing sarcoma, the use of high-RT doses, while achieving good therapeutic results, can have a devastating effect on the surrounding tissue. In order to balance this relationship, Talleur *et al.* (23) suggested adopting protective measures and dose control for larger tumors to solve the radiotherapy dilemma of pediatric ewing sarcoma, and confirmed the method to increase the dose of radiation by reviewing 45 patients. A good prognosis is achieved without increasing the risk at the standard dose.

In our study, age and gender were also considered to be important factors influencing the prognosis of ewing sarcoma patients. As the age increased, the risk of death increased. In addition, male mortality was higher than female. In addition to being an independent prognostic factor, treatment options are also closely related to age and gender (11,24,25). Paioli *et al.* (26) studied the relationship between CT-related toxicity and gender and age in non-metastatic ewing sarcoma. This study found that the hematological toxicity of CT drugs did not differ between children and adults; in women with ewing sarcoma, CT-related blood. The incidence of learning toxicity is higher. National Cancer Registry of Australia has reported that young male ewing sarcoma patients aged 15 to 30 years after CT have a higher mortality rate than children (24).

We demonstrate that CT combined surgery or CT combined with RT can significantly improve prognosis compared with simple CT. Compared with CT alone, CT combined with RT may not help to increase median survival (30 *vs.* 32 months), also does not help to reduce ACM (HR =1.034) and ESSM (HR =1.023). This study found that the increase in age, primary site in pelvic bones, sacrum coccyx and associated joints, AJCC stage rise and TNM stage rise were risk factors for ewing sarcoma patients with unsatisfactory prognosis. For the treatment of ewing sarcoma patients, we recommend to develop a treatment plan based on individual differences based on comprehensive treatment.

Limitations

This study is based on a retrospective study conducted by the SEER database. Due to the limitations of the data included in the database itself, more detailed patient information is not available. We are unable to obtain specific indicators such as lactate dehydrogenase (LDH), whether it is neoadjuvant CT and standard CT, the number of RT, and the specific method of each irradiation dose and surgical treatment, which limits our further evaluation. The relationship between treatment and prognosis. In addition, this article does not summarize the transfer situation. After we conducted preliminary statistics, the database ewing sarcoma patient transfer situation could not get complete information. In addition, due to the limited overall sample size, the number of metastases patients could not reach our ideal number. This limits our detailed analysis of metastatic cases.

Conclusions

From the demographic and tumor pathology data, the older the patients at the age of diagnosis, married, the primary sites in the pelvic bones, sacrum coccyx and associated joints, AJCC III–IV, T2–T3, N1 and M1 stage tumors are all prompted to patients' poor prognosis. Multiple methods of integrated therapy have become the consensus of most cancer treatments. This study includes four treatments, CT combined surgery is the best treatment option, ewing sarcoma patients can get the longest median survival and the highest survival rate. Compared with CT, CT and RT, or CT and RT and surgery, ewing sarcoma patients receiving CT combined with surgery have the longest median survival, the lowest mortality, and the best prognosis.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.02.08). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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