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An analysis of extraskeletal osteosarcoma based on the literature

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Extraskeletal osteosarcoma (ESOS) is a very rare malignant tumor. This study aimed to provide more evidence about the natural history and clinical features of ESOS, and clarify the impact of chemotherapy (CT) and radiotherapy (RT) on patient survival and postoperative recurrence for the sake of gaining a better understanding about the disease. Patient/tumor characteristics, recurrence, treatment, and follow-up durations were collected by searching studies in PubMed, Web of Science, Ovid, Elsevier, SpringerLink, Chinese National Knowledge Infrastructure (CNKI), and WAN FANG Data before June 30, 2023. Data were analyzed by SPSS-26. Altogether 1287 patients diagnosed with ESOS were retrieved from the literature. Of them, follow-up data were available in 981 patients, in whom 78 patients (7.6%) had metastases and 730 patients (74.5%) had localized disease at the time of diagnosis. Of the 730 patients with localized disease, 682 (93.4%) received surgical resection. The 5-year OS in all 981 patients, 78 metastatic patients, and 682 patients with localized disease was 33.40%, 4.9% and 41.1%, respectively. Of the 682 surgical patients, 367 patients underwent surgical resection alone, 170 received surgical resection + CT, 82 patients received surgical resection + RT, and 58 patients received both adjuvants. In addition, 348 (51%) of the 682 patients developed recurrence, including local recurrence ($n = 102$), metastasis ($n = 130$), and both ($n = 116$). Univariate analysis of 5-year PFS and 5-year OS showed that age, tumor size, CT, metastasis, and local recurrence were significant prognostic factors in the 682 patients with localized disease. There was no significant difference in 5-year OS between osteosarcoma-type and soft tissue-type regimens ($P = 0.273$). Multivariate analysis of 431 patients showed that postoperative recurrence and metastasis were significant prognostic factors for survival, and CT was not a significant prognostic factor, though CT decreased the incidence of local recurrence in ≤ 45-year age group ($P = 0.047$). RT reduced the incidence of local recurrence in patients ≤ 45years ($P = 0.035$) and patients with tumors > 5 cm ($P = 0.044$). So, we recommend that CT should be used for patients aged ≤ 45years, and RT can be used for patients ≤ 45years or those with tumors > 5 cm for the sake of decreasing the incidence of local recurrence, which we believe would indirectly benefit the survival of ESOS patients.

Keywords Extraskeletal osteosarcoma, Chemotherapy, Radiotherapy

Extraskeletal osteosarcoma (ESOS) is a rare malignant tumor that produces bone matrix and/or chondroid material without direct attachment to bone or periosteum[1], which was firstly reported by H. Wilson in 1941[2].The occurrence of ESOS is very rare accounting for 0.38-1% of soft tissue sarcomas and 4% of all osteosarcomas[3–6]. According to the predominant morphologic component, ESOS is classified into six subtypes: osteoblastic, fibroblastic, chondroblastic, malignant fibrous histiocytic, telangiectatic, and small cell[7].

Compared with primary osteosarcoma, the median age of primary ESOS at diagnosis is usually between 50 and 60 years of age[8]. The common locations of primary ESOS are the extremities, abdomen/retroperitoneum and chest[8,9], and the common sites of metastasis are the lung, lymph node and bone[8,9]. Exposure to radiation and trauma are perceived as important triggers. Patient age, tumor size, and surgical type and margins are main prognostic factors for ESOS[8]. Surgical resection is the standard treatment for ESOS. However, it is not clear whether chemotherapy (CT) and radiotherapy (RT) are beneficial for ESOS.

Since the first report of ESOS in 1941, only sporadical cases or relatively large series studies involving more than 40 patients have been reported in the literature[4,8–17]. For this reason, the natural history and clinical features

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of ESOS remain elusive. The aim of the present study was to provide more evidence about the natural history, clinical features, and treatment of ESOS by reviewing ESOS cases reported in the literature.

Materials and methods

The study has been registered at PROSPERO (ID = CRD42024586013). We searched PubMed, Web of Science, Ovid, Elsevier, SpringerLink, Chinese National Knowledge Infrastructure (CNKI) and WAN FANG DATA using the terms of "extraskeletal osteosarcoma", "extraskeletal osteogenic sarcoma", "extraosseous osteosarcoma", "extraosseous osteogenic sarcoma", and "primary osteosarcoma" before June 30, 2023 (Fig. 1). We also reviewed the references cited by the reports in the databases in order to find missing reports. We collected the data of ESOS patients provided by the case reports and serial studies, but as some patients and tumor information were incomplete, we performed the analysis based on the data currently available.

Overall survival (OS) was defined as the period from diagnosis to death or last follow-up. Progression-free-survival (PFS) was defined as the period from the date of resection or conservative treatment to disease progression or last follow-up. Osteosarcoma-type chemotherapy was defined as doxorubicin with either cisplatin and/or methotrexate, and soft tissue sarcoma-type chemotherapy was defined as doxorubicin with or without ifosfamide and any agent other than cisplatin and methotrexate. The low-grade histology subtype contains abundant bone deposited in well-formed trabeculae, surrounded by a minimally atypical spindle cell component similar to parosteal osteosarcoma. Compared with low-grade histology subtype, the tumor cells of high-grade histology subtype have obvious atypia. Recurrence refers to the reappearance of tumor cells after treatment, occurring either in the original site or other locations. Metastasis indicates that the primary tumor cells spread to other parts of the body through blood circulation, lymphatic system or other ways, where new tumors form. The recurrence and metastasis of patients in our article were confirmed by image modalities or biopsy. According to the WHO age segmentation method (2002 edition), we divided the patients into two groups at the age of 45 (≤45years are young people,>45years are middle-aged and elderly people). According to previous literature[17],

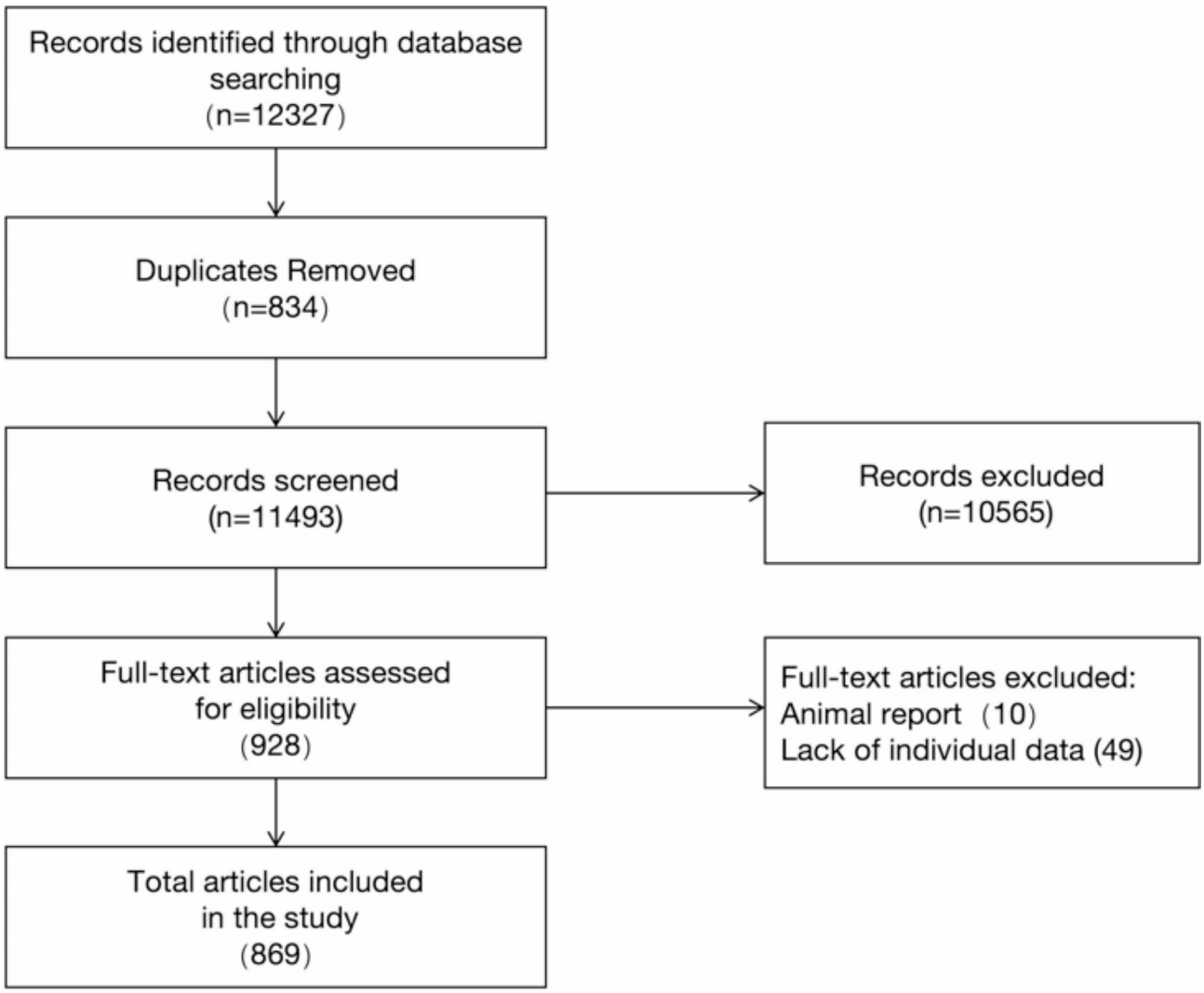

Fig. 1. The flowchart depicting search results and article selection.

we divided the patients into two groups at the tumor size of 5 cm (≤5 cm are small tumors, >5 cm are large tumors).

SPSS software (version 26.0) was used for statistical analysis. Categorical variables was summarized by frequency and percentages for patient characteristics, and analyzed by Chi-square test. Median value and 95% confidence intervals (CI) were used to analyze PFS and OS. PFS and OS were estimated by Kaplan-Meier (KM) methods, and Log-rank test was used to compare PFS/OS between groups. The multivariable Cox regression model was used to analyze the statistical significance of each variable. A p-value < 0.05 was considered statistically significant.

Results

Patient and tumor characteristics

A total of 1287 patients diagnosed with ESOS were retrieved from the case reports and serial studies that could provide patient and tumor information. Patient data and tumor characteristics are summarized in Table 1.

	***n* = 1287**
Gender	
Male	667 (52.5%)
Female	603 (47.5%)
Unknown	17
Age group (years)	
≤45	350 (27.6%)
>45	917 (72.4%)
Unknown	20
Site	
Lower extremity	314 (24.4%)
Upper extremity	94 (7.3%)
Spine	108 (8.4%)
Head	97 (7.5%)
Chest	197 (15.3%)
Abdomen/Retroperitoneum	227 (17.7%)
Pelvic cavity	113 (8.8%)
Breast	115 (8.9%)
Others	17 (1.3%)
Unknown	5
Size	
≤5 cm	295 (34.3%)
>5 cm	564 (65.7%)
Unknown	428
Histological classification	
Osteoblastic	110 (43.8%)
Chondroblastic	60 (23.9%)
Fibroblastic	49 (19.5%)
Malignant fibrous histiocytic	2 (0.8%)
Telangiectatic	14 (5.6%)
Small cell	16 (6.4%)
Unknown	1036
Malignancy grade	
Low-grade	23 (18.1%)
High-grade	104 (81.9%)
Unknown	1160
Inducement	
Trauma	31 (7.1%)
Radiation-related	66 (15.2%)
Surgery-related	28 (6.4%)
Others	26 (5.5%)
None	286 (65.8%)
Unknown	852

Table 1. Patient and tumor characteristics.

Information about gender and the incidence of ESOS was available in 1270 of the 1287 patients, indicating a M: F ratio of 1.1:1. Information about age was available in 1267 of the 1287 patients, indicating that the median and mean age at diagnosis was 56 years and 54 (3–96) years respectively. Of the 1267 patients, 350 (27.6%) patients were younger than or equal to 45 years, and 917 (72.4%) were older than 45 years. According to 647 patients with the availability of information about interval time, the median time from symptom onset to diagnosis was 3 (0-480) months.

The primary tumor site was categorized as the lower extremity, upper extremity, spine, head, chest, abdomen/retroperitoneum, pelvic cavity, breast, and others in 1282 patients. The most common primary site of ESOS was the lower extremity (24.4%), followed by the abdomen/retroperitoneum (17.7%), chest (15.3%), breast (8.9%), pelvic cavity (8.8%), spine (8.4%), head (7.5%), upper extremity (7.3%), and others (1.3%). The tumor size was measured in 859 patients, the median tumor size being 7 cm and the mean tumor size being 8.7 cm (range 0.3–40 cm). In the 859 patients, 295 tumors (34.3%) were smaller than or equal to 5 cm in size, and 564 (65.7%) were larger than 5 cm. The histological subtypes were reported in 251 patients, including the osteoblastic type (110/43.8%), chondroblastic type (60/23.9%), fibroblastic type (49/19.5%), small cell type (16/6.4%), telangiectatic type (14/5.6%), and malignant fibrous histiocytic type (2/0.8%). Of the 1287 patients, the pathologic grade was reported in 127 patients, including the high-grade ESOS in 104 patients (81.9%), and the low-grade ESOS in the remaining 23 patients. Contributing factors were reported in 435 patients, including radiation exposure in 66 patients (15.2%), traumatic injuries in the ESOS areas in 31 patients (7.1%). Of the 435 patients, 28 patients (6.4%) underwent surgical treatment in the ESOS field.

Follow-up durations

Of the 1287 patients, information about follow-up durations was available in 981 patients, showing that the median follow-up duration was 36 (0-335) months. Data of these 981 patients are summarized in Table 2. The median PFS (mPFS) and median survival time (mST) of the 981 patients were 21.6months (95% CI 16.6–26.6 months) and 24months (95% CI 20.4–27.6 months), respectively. Their 5-year PFS was 32.20% and 5-year OS was 33.40%. The 981 patients consisted of 509 males and 455 females, and the gander of 17 patients was unknown. The mPFS and 5-year PFS of male patients were 18months (95% CI 13.8–22.2 months) and 28.4% versus 24months (95% CI 14.6–33.4 months) and 34.4% of female patients($P=0.134$). The mST and 5-year OS were 22 months (95% CI 18.4–25.6 months) and 28.5% in male patients versus 29 months (95% CI 21.9–36.5 months) and 37.2% in female patients, respectively ($P=0.177$). Two hundred and fifty-four patients were younger than or equal to 45 years, 707 patients were over 45 years, and 20 patients were unknown. There was a significant difference in mST and 5-year OS between different age groups($P<0.001$), showing that mPFS, 5-year PFS, mST, and 5-year OS were significantly better in younger patients. Tumor size was ≤5 cm in 237 patients,

		Patient number	mPFS (95% CI) (month)	5-year PFS	mST (95% CI) (month)	5-year OS
		981	21.6 (16.6–26.6)	32.2%	24 (20.4–27.6)	33.4%
Gender	Male	509	18 (13.8–22.2)	28.4%	22 (18.4–25.6)	28.5%
	Female	455	24 (14.6–33.4)	34.4%	29 (21.9–36.5)	37.2%
	Unknown	17				
				$P=0.134$		$P=0.177$
Age	≤45years	254	35 (22.5–47.5)	41.4%	43 (26.6–59.4)	43.4%
	>45years	707	16 (12.9–19.1)	27.2%	21 (17.9–24.2)	28.2%
	Unknown	20				
				$P<0.001$		$P<0.001$
Size	≤5 cm	237	48 (23.4–93.9)	46.7%	51 (28.5–73.5)	42.9%
	>5 cm	426	14 (10.2–17.8)	26.5%	18 (13.3–22.7)	29.5%
	Unknown	318				
				$P<0.001$		$P<0.001$
Position	Upper extremity	79	54 (4.0-104.0)	48.4%	76 (11.6-140.4)	51.7%
	Lower extremity	248	31 (25.2–36.8)	37.1%	36 (29.0–42.0)	40.7%
	Head	84	30 (2.5–57.5)	31.6%	30 (7.8–52.2)	24.3%
	Spine	86	12 (9.9–14.1)	31.9%	21 (12.2–29.8)	36.4%
	Pelvic cavity	88	5 (3.5–6.5)	8.1%	7 (5.2–8.8)	13.4%
	Chest	146	9 (5.9–12.1)	24.8%	12 (8.8–15.2)	27.1%
	Abdomen/Retroperitoneum	155	10 (6.8–13.2)	17.8%	13 (10.1–15.9)	20.9%
	Breast	78	99	48.6%	110 (0-259.3)	57.2%
	Others	17				
				$P<0.001$		$P<0.001$

Table 2. mPFS, 5-year PFS, mST and 5-year OS in 981 patients with ESOS. *PFS* progression free survival, *OS* overall survival, *mPFS* median progression free survival, *mST* Median survival time, *ESOS* extraskeletal osteosarcoma.

and larger than > 5 cm in 426 patients, showing that mPFS, 5-year PFS, mST, and 5-year OS were significantly better in patients with smaller tumor sizes ($P < 0.001$). In addition, mPFS, 5-year PFS, MST, and 5-year OS were significantly better in patients with primary tumors arising in the upper extremity and breast as compared with those in patients with primary tumors arising from other parts of the body ($P < 0.001$).

Patients with metastasis at diagnosis

Of the 981 patients with follow-up data available, 78 patients had developed metastases, 730 patients had localized disease, and the other 173 patients were unknown at the time of diagnosis. Of the 78 metastatic patients, 27 were male, 49 were female, and two patients were unknown. The median age of these patients was 56 (12–85) years. Of the 78 patients, 26 patients had multiple metastatic sites, 41 patients had a single metastatic site, and in the remaining 11 patients the metastatic sites were not clearly defined. Lung metastasis was detected in 36 patients. Twenty-six patients received surgery alone, 18 patients received surgery + CT, 3 patients received surgery + RT, 8 patients received surgery + CT and RT, 12 patients did not receive treatment, and the others received other treatments. The median follow-up duration of the 78 patients was 33 (0.1–41) months, and their mPFS, mST, 5-year PFS and 5-year OS were 5 months (95% CI 3.6–6.4), 6.9 months (95% CI 4.7–9.1), 4.6 and 4.9%, respectively.

Patients with localized disease at diagnosis

Of the 730 patients with localized disease at diagnosis, 682 patients received surgical resection, whose data are shown in Table 3. Gender had no significant effect on 5-year OS ($P = 0.099$). The younger the patients, the smaller the tumors, the higher the 5-year OS ($P < 0.01$). Of them, 367 patients (53.8%) underwent surgery alone, 170 patients (24.9%) underwent surgery + CT, 82 patients (12.0%) underwent surgery + RT, 58 patients (8.5%) underwent surgery + CT and RT, 5 patients (0.7%) received other treatments, one patient received surgery + immunotherapy, one patient received surgery + CT + immunotherapy, one patient received surgery + RT + immunotherapy, the other two patients received surgery + targeted therapy, showing significant

		Patient number	mPFS (95% CI) (month)	5-year PFS	mST (95% CI) (month)	5-year OS
		682	34.8 (27.3–42.3)	40.3%	36 (28.4–43.6)	41.1%
Gender	Male	346	24 (18.5–29.5)	34.3%	28(21.1-34.9)	34.4%
	Female	316	43 (31.5–54.5)	43.3%	48 (24.1–71.9)	46.5%
	Unknown	20				
				$P = 0.089$		$P = 0.099$
Age	≤ 45years	200	48 (25.3–70.7)	46.4%	60 (43.6–76.4)	48.4%
	> 45years	468	29.2 (20.3–38.1)	35.3%	30 (24.5–35.5)	35.7%
	Unknown	14				
				$P = 0.008$		$P = 0.009$
Tumor size	≤ 5 cm	195	57 (3.4-110.6)	49.8%	57 (43.9–70.1)	44.7%
	> 5 cm	280	21 (12.9–30.3)	35.8%	26 (16.0–36.0)	38.0%
	Unknown	207				
				$P < 0.001$		$P < 0.001$
Treatment	S	367	30 (21.0–39.0)	32.8%	30 (22.1–37.9)	33.6%
	S + CT	170	49	49.6%	67 (30.9-103.1)	53.1%
	S + RT	82	30 (14.5–45.5)	37.6%	29.2 (18.5–40.0)	37.6%
	S + CT + RT	58	53 (39.5–66.5)	49.2%	76 (14.1-137.9)	53.8%
	Others	5				
				$P = 0.015$		$P = 0.011$
CT	Yes	229	67	50.1%	67(36.5–97.5)	53.5%
	No	453	29.2 (20.9–37.5)	35.3%	30 (23.9–36.1)	36.4%
				$P = 0.001$		$P = 0.001$
RT	Yes	141	36 (24.0–48.0)	41.7%	36 (26.0–46.0)	43%
	No	541	31 (22.3–40.0)	39.9%	36 (26.9–45.1)	40.5%
				$P = 0.634$		$P = 0.424$
Chemo type	Osteo-type	131		57.7%		56.9%
	STS-type	35		53.1%	36	48.3%
	Others or unknown	516				
				$P = 0.276$		$P = 0.273$

Table 3. mPFS ,5-year DFS, mST and 5-year OS in 682 patients with localized ESOS. *PFS* progression free survival, *OS* overall survival, *mPFS* median progression free survival, *mST* Median survival time, *ESOS* extraskeletal osteosarcoma, *S* surgery, *CT* chemotherapy, *RT* radiotherapy, *Osteo-type* Osteosarcoma-type chemotherapy, *STS-type* soft tissue sarcoma-type chemotherapy.

differences in therapeutic modalities between different treatment groups ($P=0.011$). The results showed that the overall survival outcome was better in patients who received surgery + CT or surgery + CT and RT (Fig. 2).

Of the 682 patients who received surgical resection, 229 patients (33.6%) received postoperative chemotherapy, and their 5-year PFS and 5-year OS were 50.1% and 53.5% respectively. So far as the therapeutic regimen was concerned, 131 patients received the osteosarcoma-type regimen. Of the 131 patients, 111 patients received doxorubicin, 113 patients received cisplatin, 56 patients received ifosfamide, and 48 patients received methotrexate. Of the 35 patients who received the soft tissue-type regimen, 28 patients received anthracycline + ifosfamide with or without other agents, 6 patients received anthracycline alone, one patient received the ifosfamide + Dacarbazine, and 11 patients accepted other chemotherapy regimens. In the 229 patient who received postoperative chemotherapy, details of the chemotherapy were not reported in 52 patients. There was no significant difference in survival parameters between the osteosarcoma-type regimen and soft tissue-type regimen ($P=0.273$) (Fig. 3). Of the 682 patients, 453 patients (66.4%) did not receive CT, and their 5-year PFS and 5-year OS were 35.3% and 36.4%, which were significantly worse than those in patients who received CT ($P=0.001$) (Fig. 4).

Of the 682 patients, 141 patients (20.7%) received RT, in whom mPFS and mST were 36 months (95% CI 24.0–48.0) and 36 months (95% CI 26.0–46.0) versus 31 months and 36 months in the other 541 patients who did not receive RT. In addition, 5-year PFS and 5-year OS in these two groups of patients were 41.7 and 43% versus 39.9 and 40.5%, showing no significant difference between patients receiving RT and those without receiving RT ($P=0.424$) (Fig. 5).

For the 682 patients with localized disease, the median follow-up time was 31 (0-335) months, mPFS was 34.8 months (95% CI 27.3–42.3), mST was 36 months (95% CI 28.4–43.6), 5-year PFS was 40.3%, and 5-year OS was 41.1%. mST, mPFS, 5-year DFS and 5-year OS in patients with localized disease were significantly better than those in patients with metastasis at diagnosis ($P<0.001$) (Fig. 6).

Recurrence

Of the 682 patients with localized disease, 273 patients (40%) developed distant metastasis, 383 patients had no distant metastasis, and the remaining 26 patients were unknown. The data about recurrence are shown in Table 4. In the 273 patients with distant metastasis, 156 patients had a single distant metastatic site, 84 patients had multiple distant metastatic sites, and 33 patients were unknown. Of them, 156 patients (57.1%) had pulmonary metastasis, and 178 had the information about the time of metastasis. The median time of distant metastasis was 8 (0.5–168) months. Patients without metastasis had better outcomes in terms of mPFS, 5-year PFS, mST, and 5-year OS ($P<0.001$).

Of the 682 patients with localized disease, 224 patients (32.8%) developed local recurrence, 410 patients (60.1%) were free of local recurrence, and 48 patients were unknown. The local recurrence time was available in 171 of the 224 patients with local recurrence, and the median time of local recurrence was 6 (0.25–90) months.

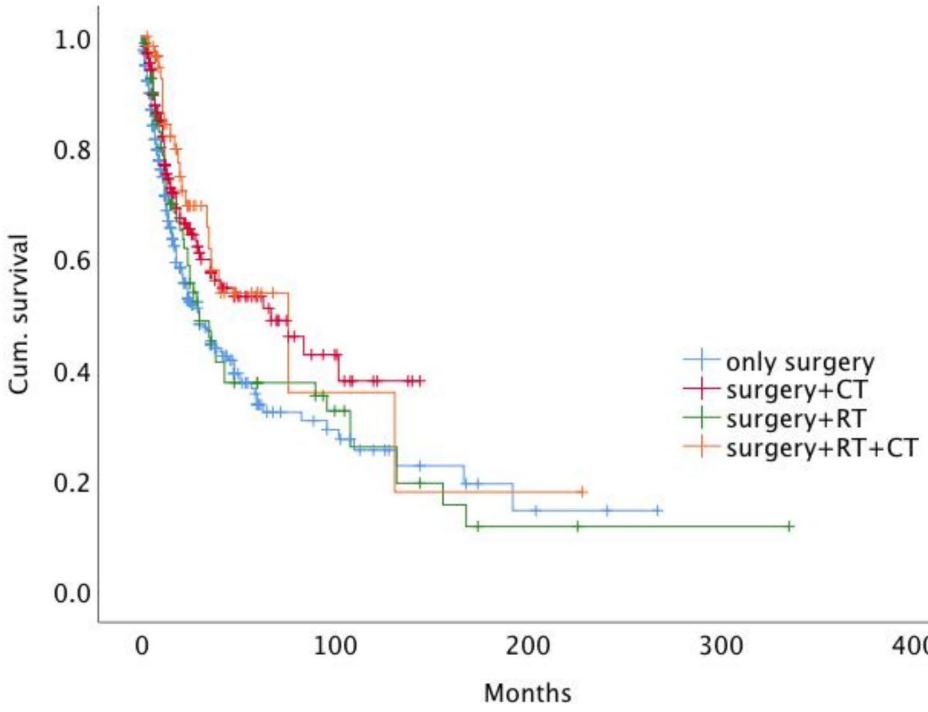

Fig. 2. 5-year overall survival and treatment of patients with localized disease ($P=0.011$).

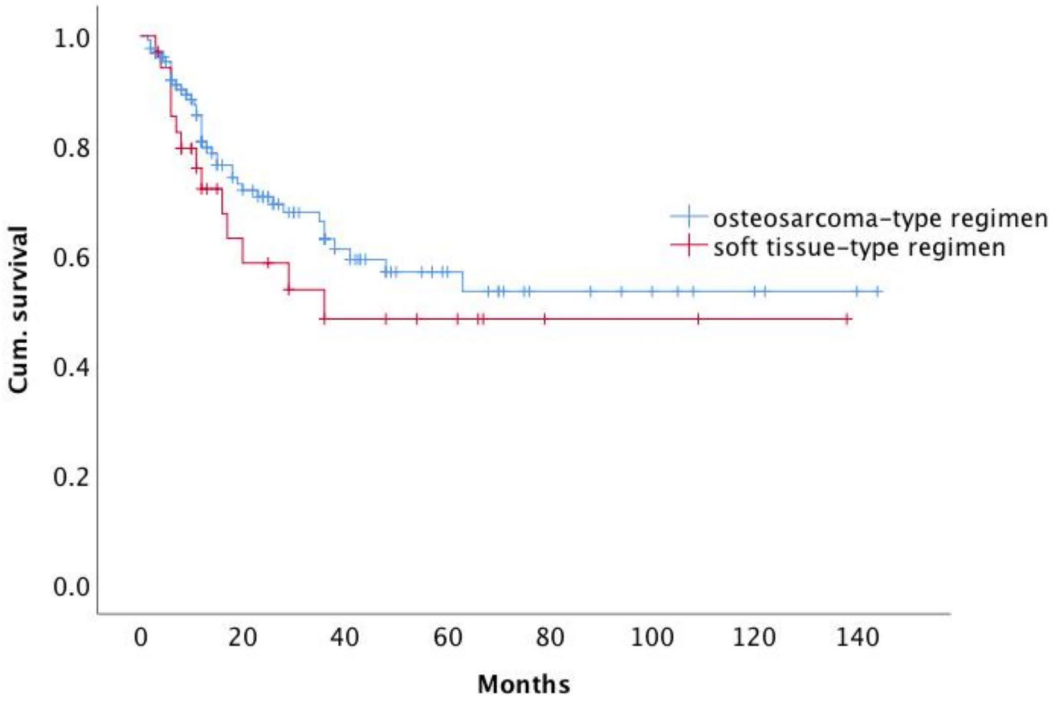

Fig. 3. 5-year overall survival and type of chemotherapy ($P=0.273$).

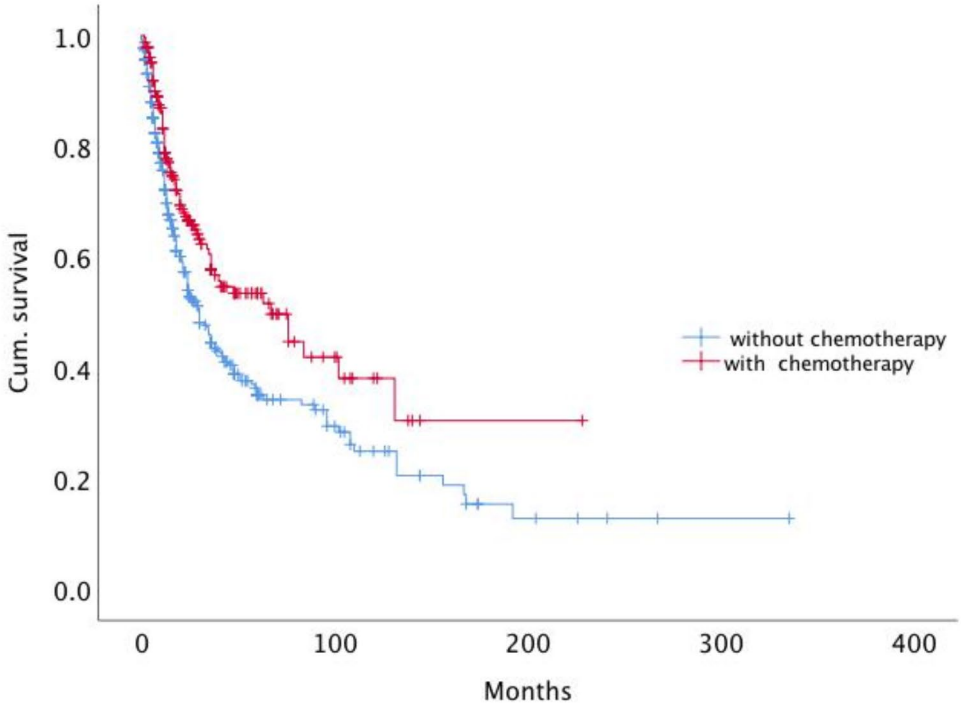

Fig. 4. 5-year overall survival for chemotherapy versus no chemotherapy ($P=0.001$).

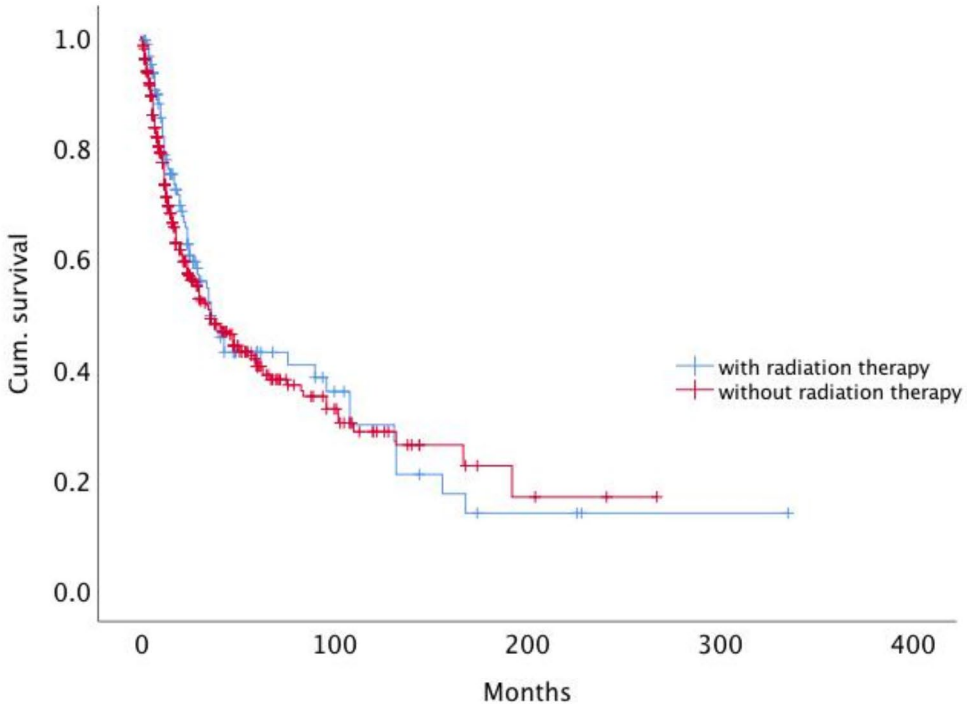

Fig. 5. 5-year overall survival for radiotherapy versus no radiotherapy ($P = 0.424$).

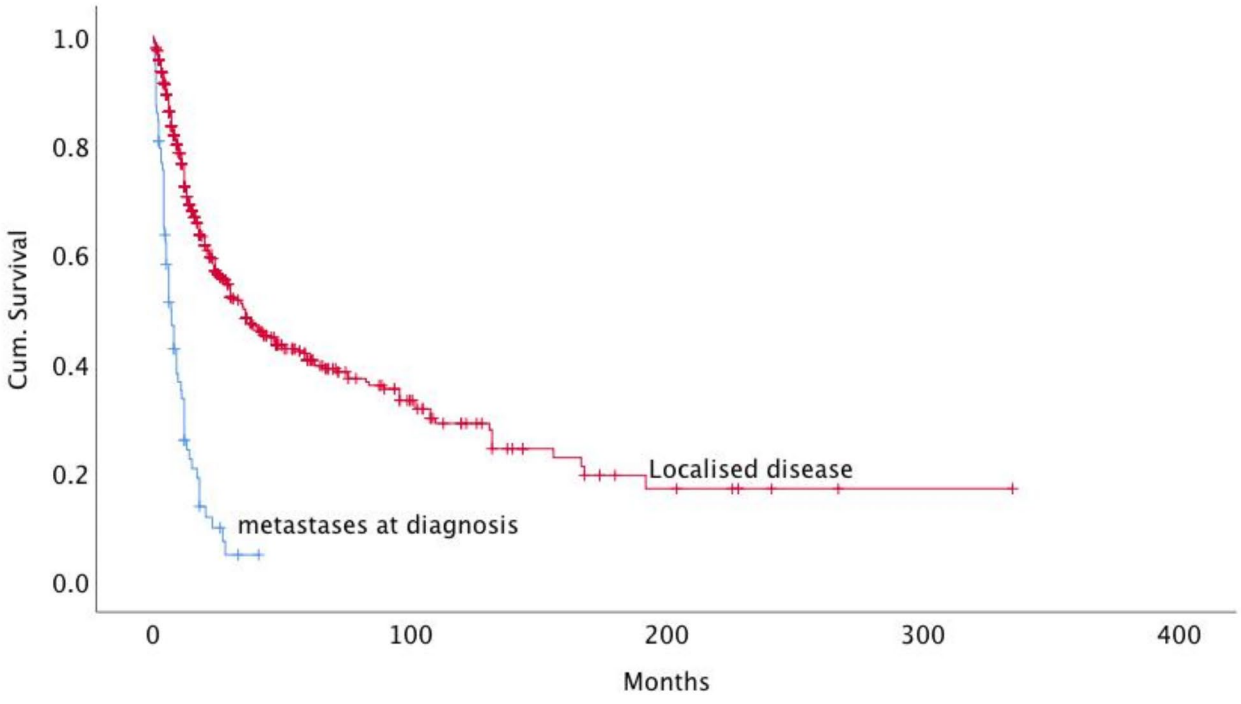

Fig. 6. 5-year overall survival in patients with localized disease versus metastases at diagnosis ($P < 0.001$).

		Patient number	mPFS(95% CI) (month)	5-year PFS	mST(95% CI) (month)	5-year OS
Post-operative metastasis	Yes	273	12 (10.0–14.0)	10.9%	18 (15.3–20.7)	16.3%
	No	383	168 (122.4-213.6)	69.5%	168 (120.6-215.4)	68.4%
	Unknown	26				
				$P<0.001$		$P<0.001$
Post-operative local recurrence	Yes	224	12 (8.8–15.1)	11.8%	21 (16.5–25.5)	20.6%
	No	410	108 (60.6-155.4)	60.1%	108 (78.5-137.5)	60.5%
	Unknown	48				
				$P<0.001$		$P<0.001$
Metastasis and local recurrence	Metastasis with local recurrence	116	9 (5.5–12.4)	6.7%	16 (11.2–20.8)	15.1%
	Metastasis without local recurrence	130	14 (10.2–17.8)	16.1%	18 (15.1–20.9)	20.4%
	Local recurrence without metastasis	102	15 (7.1–22.9)	19.6%	34 (23.7–44.3)	27.1%
	No metastasis and no local recurrence	274		91.3%		91.2%
	Unknown	60				
				$P<0.001$		$P<0.001$

Table 4. Recurrence of 682 patients with localized ESOS. *PFS* progression free survival, *OS* overall survival, *mPFS* median progression free survival, *mST* Median survival time, *ESOS* extraskeletal osteosarcoma.

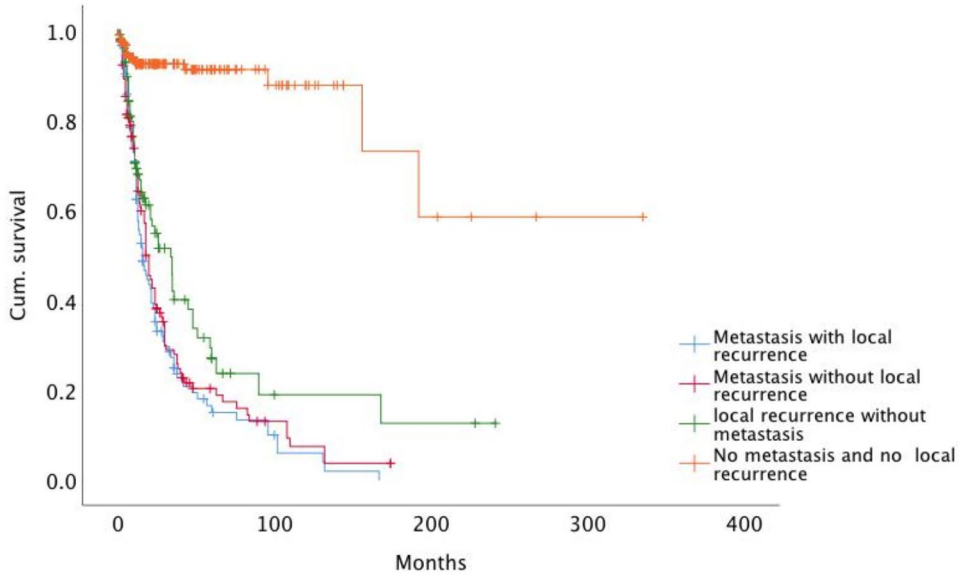

Fig. 7. 5-year overall survival and recurrence ($P<0.001$).

The 5-year PFS and 5-year OS were significantly different between patients with and without local recurrence (both $P<0.001$).

Of the 682 patients with localized disease, 348 patients (51%) had distant metastasis and/or local recurrence, including 116 patients had distant metastasis with local recurrence, 130 patients had distant metastasis without local recurrence, 102 patients with local recurrence but without distant metastasis. In addition, 274 patients (40.2%) neither experienced distant metastasis nor local recurrence. Distant metastasis and/or local recurrence was not reported in 60 (8.8%) of the 682 patients. Patients without distant metastasis and local recurrence had better 5-year OS ($P<0.001$) (Fig. 7).

Chemotherapy, radiotherapy, local recurrence and metastasis

Of the 682 patients with localized disease, 605 patients had complete information about age and recurrence, and 431 patients had complete information about tumor size and recurrence. CT decreased the incidence of local recurrence in patients ≤ 45 years ($P=0.047$). However, CT showed no significant association with metastasis according to the analysis of different age groups. Also, CT could not decrease the incidence of metastasis and local recurrence in all groups of different tumor size (Table 5).

Chemotherapy	Metastasis	No metastasis	*P* value	Local recurrence	No local recurrence	*P* value
With CT for age ≤ 45years	25	57	$P=0.224$	25	57	$P=0.047$
No CT for age ≤ 45years	41	64		47	58	
With CT for age > 45years	54	66	$P=0.447$	36	84	$P=0.370$
No CT for age > 45years	122	176		103	195	
With CT in tumours ≤ 5 cm	15	32	$P=0.556$	9	38	$P=0.067$
No CT in tumours ≤ 5 cm	37	98		45	90	
With CT in tumours > 5 cm	41	59	$P=0.255$	38	62	$P=0.569$
No CT in tumours > 5 cm	72	77		62	87	

Table 5. Chemotherapy, local recurrence and metastasis. *CT* chemotherapy.

Radiation therapy	Metastasis	No metastasis	*P* value	Local recurrence	No local recurrence	*P* value
With RT for age ≤ 45years	12	26	$P=0.591$	9	29	$P=0.035$
No RT for age ≤ 45years	54	95		63	86	
With RT for age > 45years	40	53	$P=0.841$	32	61	$P=0.789$
No RT for age > 45years	136	189		107	218	
With RT in tumours ≤ 5 cm	9	18	$P=0.553$	10	17	$P=0.364$
No RT in tumours ≤ 5 cm	43	112		44	111	
With RT in tumours > 5 cm	20	36	$P=0.099$	16	40	$P=0.044$
No RT in tumours > 5 cm	93	100		84	109	

Table 6. Radiotherapy, local recurrence and metastasis. *RT* radiotherapy.

Variable	Hazard ratio	*P* value
Age		
≤45 yrs	1.308 (95% CI 0.910–1.878)	$P=0.146$
> 45yrs		
Size		
≤5 cm	1.373 (95% CI 0.993–1.899)	$P=0.055$
> 5 cm		
Local recurrence		
Yes	0.516 (95% CI 0.375-712)	$P<0.001$
No		
Metastasis		
Yes	0.270 (95% CI 0.189–0.386)	$P<0.001$
No		
Chemotherapy		
With CT	1.239 (95% CI 0.887–1.730)	$P=0.208$
No CT		

Table 7. Multivariate analysis. *CT* chemotherapy.

RT reduced the incidence of local recurrence in patients ≤ 45years ($P=0.035$) and patients with tumors > 5 cm ($P=0.044$). However, we did not find a relation between metastasis and RT according to the age and tumor size subgroups (Table 6).

Multivariate analysis

For the 682 patients with localized disease, the significant prognostic factors were age, size, CT, metastasis and local recurrence at univariate analysis for 5-year PFS and 5-year OS. Gender, RT and type of chemotherapy were not statistically significant prognostic factors. Multivariate analysis involving 431 patients showed that metastasis and local recurrence were statistically significant prognostic factors. However, age, size and CT were not statistically significant prognostic factors (Table 7).

Discussion

The natural history and clinical features of ESOS remain unclear due to rarity of the disease. In this study, we retrieved the largest series of ESOS patients retrieved from the literature, and analyzed the patient and tumor characteristics which were similar to the previous reports[4,8,11]. The male to female ratio of patients with ESOS is 1:1.4 to 2.6:1 in the previous literature[18,19]. The result showed no significant difference in the incidence of ESOS between men and women in our study. ESOS was most commonly seen in middle-aged and old-age individuals[20]. The median age of ESOS occurrence was 56 years. The most common site of ESOS was the lower extremity[8]. The lower extremity was the primary site of ESOS, accounting for 24.4% in our series. The tumor size was commonly larger than 5 cm. The most common subtype was osteoblastic variant, and high-grade cases were more common[21–23]. Previous RT and trauma were predisposing factors of ESOS[4].

In this study, the 5-year OS in all 981 patients, 78 patients with metastasis at diagnosis and 682 patients with localized disease was 33.40, 4.9, and 41.1%, respectively. The 5-year OS of all 981 patients in this study was lower than 37–66% reported in the previous literature[10,20]. The lowest 5-year OS for ESOS patients was 16%, which was reported by Berner et al. in their study involving 37 patients[24]. The preoperative metastasis rate was 9.7% in our study, which is similar to 7.5–13.9% reported in most previous studies[10,15,17,25–27].However, some studies reported higher preoperative metastasis rates ranging from 18.7 to 22% [8, 11,14,24]. The postoperative metastasis rate in this study was 40%, which is similar to that reported by Longhi et al. (41.7%)[8] and Heng et al. (38%)[17].

The efficacy of adjuvant/neoadjuvant chemotherapy for ESOS is still controversial[3,4,6,8,13–15,17–20,24,26–29]. And for chemotherapeutic regimens, because ESOS is a soft tissue tumor but its histopathologic features are similar to those of osteosarcoma, it is still unclear which the chemotherapeutic regimen (osteosarcoma-type regimen or soft tissue-type regimen) is better for ESOS. These controversial results may be attributed to the extremely low incidence of ESOS, heterogeneity of chemotherapeutic regimens, and dose intensities[29]. Univariate analysis in our study showed that CT had a beneficial effect on 5-year PFS and 5-year OS for ESOS patients, but multivariate analysis showed no statistically significant difference (HR = 1.239; 95% CI 0.887–1.730; $P = 0.208$. It was found in our study that CT could decrease the incidence of local recurrence in patients ≤ 45years ($P = 0.047$). For chemotherapeutic regimens, there was no significant difference between the osteosarcoma-type regimen and soft tissue-type regimen in treatment of ESOS ($P = 0.276$ for 5-year PFS, $P = 0.273$ for 5-year OS). Some studies reported that the osteosarcoma-type regimen was more effective[8,15,26], while other studies[18,24,27] held the opposite view. Wakamatsu et al.[28] proposed that ESOS patients should receive the soft tissue-type chemotherapeutic regimen (doxorubicin and ifosfamide-based) rather than that osteosarcoma-type chemotherapeutic regimen. Tsukamoto et al.[29] analyzed 761 patients with localized ESOS and found that the efficacy of adjuvant chemotherapy on localized ESOS was limited.

There is not much research about the effect of radiotherapy on ESOS[4,6,8,14,17,19,24]. We found no significant difference in 5-year OS between patients who received RT and those without receiving RT ($P = 0.424$), and this finding is similar to that reported by Berner et al.[24] and McCarter et al.[6]. Sordillo et al.[4] reported that the median survival time of ESOS patients who received RT after amputation or wide resection improved from 28 months to 60 months. Wang et al.[14] suggested that RT may improve OS for ESOS patients who could not obtain M0 margins. ln the EMSOS study[8], RT did not reduce the local relapse rate; however, patients with tumors larger than 5 cm ± R0 margins had lower incidences of local relapse after RT. Heng et al.[17] demonstrated that although RT did not improved OS in patients with localized ESOS, it could decrease local recurrences. Although there is no significant difference in 5-year PFS and 5-year OS between RT patients and non-RT patients, we found that RT could reduce the incidence of local recurrence for patients ≤ 45years ($P = 0.035$) and patients with tumor > 5 cm ($P = 0.044$).

As our research data were collected from previous studies in the literature, some data are incomplete compared with other retrospective studies. For example, some studies lacked a clear definition of surgical margins in most patients, did not provide complete information about CT and RT doses, the duration and frequencies of administration. It may be a reason that can explain why univariate analysis of CT is meaningful while multivariate analysis is meaningless. The effectiveness of CT may be related to some factors such as drug resistance, chemotherapeutic regimens, doses, cycles, and frequencies. Multivariate analysis also showed that age and tumor size were not prognostic factors, which may be related to the cut-off point we have chosen at age (45 years) or size (5 cm) for distinguishing the patients. We only selected cases with complete data and removed some cases with incomplete data according to the purpose of our study. As the cases that we collected from the literature, especially the case reports, may have been selected by the original authors, the information that we obtained may not be able to accurately reflect the natural history and the clinical features of ESOS.

Conclusion

The natural history and the clinical features of ESOS are similar with previous studies. Although multivariate analysis showed CT to be ineffective in survival, CT could decrease the incidence of local recurrence in patients ≤ 45years, so we think that CT should be a treatment for patients ≤ 45years. However, which chemotherapeutic regimen is better needs more researches. RT is recommended for patients ≤ 45 years or the patients with tumors > 5 cm to reduce the incidence of local recurrence. Although the roles of CT and RT have not yet been clearly defined, complete surgical resection remains the mainstay of treatment. Due to extreme rarity of ESOS, further multicenter randomized controlled trials are needed to clarify ESOS.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Author contributions

DHW and XZ contributed to designing the study. JLZ, XWF, HQD and YC collected the data. ZFG, DDL and MHC analyzed the data.The final manuscript was written by DHW, JLZ and XZ.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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