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ORIGINAL ARTICLE

Treatments and outcomes of spinal metastasis from thymic epithelial tumors: 10-year experience with 15 patients in a single center

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Abstract

Purpose Although thymic epithelial tumors (TETs) are rare, their spinal metastases are even rarer, and they have only been described in a few case reports. The aim of the present study is to discuss the possible treatments and outcomes of patients with spinal metastasis from TETs.

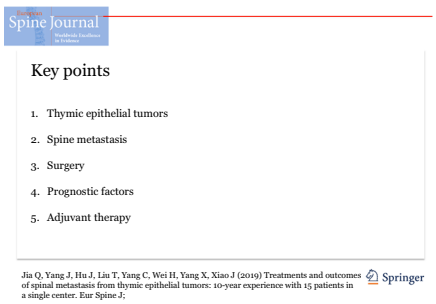
Methods Included in this retrospective study were 15 patients with metastasis of TETs who received either radical or debulking surgery plus radiochemotherapy as adjuvant therapy in our center between 2007 and 2017. Possible prognostic factors for progression-free survival (PFS) and overall survival (OS) were analyzed by log-rank analysis.

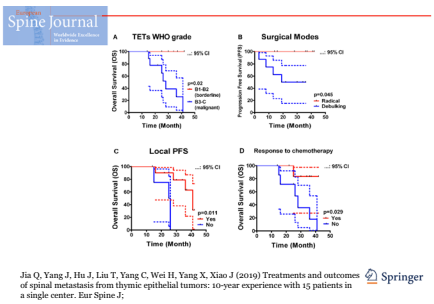
Results Our series comprised seven men and eight women, with a median age of 52 years. The period from the primary diagnosis to spinal metastasis varied from 0 to 16 months. The metastatic lesions were mainly located in the thoracic spine ($n=11$; 73.3%), followed by the cervical and lumbar spine ($n=2$; 13.3%, respectively). The median follow-up period was 28 months. Local tumor progression was detected in four patients (26.7%), and seven patients (46.7%) died of the disease during the follow-up period. Log-rank analysis indicated that radical resection was associated with longer PFS, whereas PFS, response to systemic chemotherapy and WHO *B*1–*B*2 were favorable factors of OS for patients with spinal metastatic TETs.

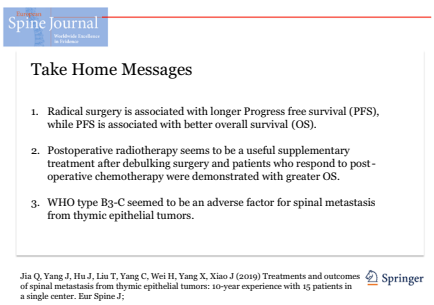
Conclusions Radical surgery is associated with longer PFS, while PFS is associated with better OS. Postoperative radiotherapy seems to be a useful supplementary treatment after debulking surgery, and patients who respond to postoperative chemotherapy were demonstrated with greater OS. WHO type *B*3–*C* seemed to be an adverse factor for spinal metastasis from TETs.

Graphical abstract

These slides can be retrieved under Electronic Supplementary Material.







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Keywords Thymic epithelial tumors · Spine metastasis · Surgery · Prognostic factors · Adjuvant therapy

Introduction

Although rare, thymic epithelial tumors (TETs) are the most common primary neoplasms in the anterior mediastinum, with an overall annual incidence of approximately 1.3–3.2 per million [1, 2]. According to the World Health Organization (WHO) classification [3], TETs can be stratified into thymoma (types *A*, *AB*, *B*1, *B*2 and *B*3) and thymic carcinoma (TC, type *C*) on the basis of the morphology of epithelial cells and the lymphocyte-epithelial cell ratio. Kondo et al. [4] further categorized TETs as benign (*A* and *AB*), borderline (*B*1 and *B*2) and malignant types (*B*3 and *C*) to reflect their oncologic behaviors.

Although metastasis from TETs to the pleural space and regional lymph nodes is somewhat common, metastasis to distant lymph nodes, the liver, skeletal muscle and bone is rare, occurring in only 1–15% patients with TETs, especially in those with TC [2, 4–6]. Spinal metastasis is very rare and only sporadically reported in the English literature (Supplementary Table 1) [2, 5–13]. Vladslav et al. [5] reported the largest case series with distant metastasis from TETs, while spinal metastasis occurred in only three of their 35 patients (8.6%). Jee et al. [6] reported the first case series involving TC spinal metastasis, but only seven patients were included. As a result, the probable epidemiological features of spinal metastases from TETs remain unclear and treatment recommendations largely depend on that limited number of sporadic case reports [2, 5–13].

In this study, we report our experience with 15 consecutive patients with spinal metastasis from TETs who received surgical treatment and adjuvant therapies, in an attempt to illustrate the clinical features, systemic treatments and outcomes of this rare disease.

Materials and methods

Patient selection

We retrospectively reviewed 15 patients with spinal metastasis from TETs who received treatment in a large tertiary center in Eastern China from January 2007 to December 2017. The histological type of all the metastatic lesions was confirmed by two independent pathological experts according to the WHO (2004) classification [3, 4]. Relevant clinical data were obtained through a review of the medical records. This study was approved by the ethics committee of the hospital, and informed consent was obtained from the surviving patients or the family members of those who had passed away. This study was carried out according to STROBE statement.

All patients were radiographically evaluated by plain radiography, CT and MRI of the spine. PET-CT and chest and abdominal CT scans were performed to evaluate systemic metastasis. Tumor markers were assayed by chemiluminescence immunoassay in all patients. The preoperative and postoperative neurological status at 3 months after surgery was assessed according to the Frankel score [14]. The quality of life (QoL) of all patients was assessed by the Eastern Cooperative Oncology Group performance score (ECOG-PS) [15]. Surgery was performed in all patients using debulking or radical surgery according to Weinstein–Boriani–Biagini system [16] and Tomita score [17, 18] by the same surgery team. Radical surgery was usually selected as the principal treatment of choice and debulking surgery was employed when radical surgery was unfeasible. Patients with a spinal instability neoplastic score > 7 were considered unstable and thus underwent spinal stabilization using the screw-rod system [19]. Systemic chemotherapy was recommended in all patients, usually for at least six cycles of combination of etoposide, ifosfamide and cisplatin (VIP) after surgery. In our study, MRI or CT scan was repeated after postoperative chemotherapy to evaluate the response: Response to the chemotherapy includes complete remission or partial remission. Complete remission means the complete disappearance of the tumor mass and partial remission was defined as a decrease of 50% or more in the size of the tumor [20]. We focused on the local tumor progression-free survival (PFS) and overall survival (OS) after the initial surgery.

Regular radiographic assessment (X-ray, CT or MRI) was performed at 3, 6, and 12 months after surgery, every 6 months for the next 2 years, and then annually for life. Follow-up data were obtained from office visits and telephone interviews. Three months after surgery, QoL was re-assessed based on ECOG-PS. The follow-up period was defined as the interval from the date of surgery to death, or until September 2018 for patients alive.

Statistical analyses

The log-rank test was used for univariate analysis to identify possible factors that could influence local progression and OS. The patient factors were: age, gender, visceral metastasis, primary TETs treatments, primary TETs to metastasis, duration of symptoms, ECOG score and preoperative Frankel score. The treatment factors were surgical mode, intraoperative blood loss, chemotherapy and radiotherapy. The tumor factors were location, WHO grade and tumor markers.

Statistical analysis was supported by IBM SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA). Factors with $P \leq 0.05$ were accepted as statistically significant.

Results

Patient features

Included in this study were seven men and eight women, with a median age of 52 (range 34–64) years (Table 1). Of these patients, 13 (86.7%) patients were younger than 60 years. The lesions were mainly located in the thoracic spine in 11 (73.3%) cases, cervical spine in two cases (13.3%) and lumbar spine in 2 cases (13.3%). In addition, 14 (93.3%) patients suffered from multiple spinal metastases and only one had a solitary spinal lesion. Multiple extraspine metastases including the lung, liver, rib, lymph node, pleura or other soft tissues occurred in 12 (80%) patients. Localized pain was the most consistent complaint, with a median duration of 9 (range 1–24) months. Neurological symptoms, varying from simple and slight radicular pain to paraparesis, occurred in all patients. Additional symptoms included myasthenia gravis in one patient (case 5). With respect to tumor markers, CA125 was positive in eight (53.3%) patients (median 56.98; range 37.21–74.3; reference 0–35 U/ml), and CEA72-4 was increased in three (20%) patients (median 17.38; range 8.95–23.51; reference < 8.2 U/ml).

There was no perioperative mortality. Evaluation of the neurological status and QoL at 3 months after surgery showed that both were the same or improved by 1–2 grades. The median follow-up period was 28 (range 14–42) months. Local tumor progression was detected in four (26.7%) patients, with the median time from surgery to local progression being 10.5 (range 3–19) months. Of the 15 included patients, seven (46.7%) died of the disease in a median period of 26 (range 15–41) months.

Treatment of primary TETs

Before admission into our center, 12 (80%) patients had been previously diagnosed with TETs and three were discovered at the initial presentation. Ten (66.7%) patients received total resection of the primary tumors with or without adjuvant therapy [stereotactic radiotherapy (SRT) and systemic chemotherapy], and two (13.3%) patients only received SRT and chemotherapy (Supplementary Table 2).

Pathologic study

In all 15 cases, the histology of the metastatic lesions was the same as that of the primary tumors. According to the WHO classification, five patients belonged to borderline types ($B1 = 1$; $B2 = 4$), while ten belonged to malignant types ($B3 = 5$; $C = 5$). The period from the primary diagnosis of TETs to spinal metastases varied widely (range 2 years-16 years, $n = 12$) with a median of 6.5 years (Supplementary Table 2). The mean interval of spinal metastasis for WHO type *B*2, *B*3 and C lesions was 12.3, 4.8 and 2.4 years. Surprisingly, spinal metastasis occurred 2 years after primary diagnosis in one patient with *B*1. The median OS was 25.5 months for WHO *B*3–*C* and 34.0 months for WHO *B*1–*B*2. Log-rank analysis illustrated that WHO *B*3–*C* tumors were associated with decreased OS ($p = 0.02$, Fig. 1a, Table 2).

Radiologic study

The plain radiographic features were nonspecific, and compression fracture was uncommon ($n = 3$; 20.0%) in our series (Fig. 2a). CT scans usually showed osteoblastic and osteolytic changes in the lesions ($n = 11$; 73.3%) (Fig. 2b). MRI demonstrated extradural lesions with severe narrowing of the spinal canal and compression of the dura mater, as well as involvement of the paravertebral muscle in eight patients ($n = 8$; 53.3%) (Fig. 3). After gadolinium administration, tumors showed strong enhancement in most cases.

Treatment and survival analysis

Survival analysis of the clinical factors is shown in Table 2. Postoperative local tumor progression was somewhat common in our series ($n = 4$; 26.7%), and the OS rate was 53.3% ($n = 8$).

Surgery was performed in all cases including debulking resection in eight cases and radical resection in seven cases. Out of eight patients who underwent debulking resection, four had PFS (50.0%), while out of seven patients who had radical resection, all had PFS. Therefore, PFS rate was significantly higher in patients who underwent radical resection compared to those who had debulking ($p = 0.045$, Fig. 1b). And local progression was found to be an adverse factor for OS ($p = 0.011$, Fig. 1c). Postoperative SRT was performed 4–6 weeks after surgery in six patients at a median dose of 45 Gy (range 40–55). Debulking surgery + SRT (1/4; 25.0%) seems to lower the progression rate than debulking surgery only (3/4; 75.0%). The median intraoperative blood loss was 1200 (range 500–3200) ml.

Although systemic chemotherapy was recommended for all patients, four of ten patients (40%) with WHO *B*3–*C* type and four of the five patients (80%) with WHO *B*1–2 type responded well to chemotherapy, showing an overall response rate of 53.3% ($n = 8$). The median OS was 32.0 months for the patients who responded to systemic chemotherapy, and 26.0 months for the patients who failed

Table 1 Demographics, clinical and surgical parameters of 15 patients with spinal metastasis from TETs

No.	Age/gender	Location	Symptoms/DS (m)	Pre/post ECOG	Pre/post F-S	Surgical modes	Intrableeding	Postoperative AT	WHO grade	Local progression (m)	FU time (m)/Last status
1	59/M	T10–T11	Back pain/6; paraparesis/1	3/2	*C*/*D*	Debulking	800	CT + RT	*B*2	No	30/AWD
2	63/F	T10–T12	Back pain/24; paraparesis/0.5	4/2	*B*/*D*	Debulking	2000	No	*B*3	Yes(3)	26/DEAD
3	34/M	T9–T11	Back pain/2; lower extremities pain/1	2/1	*D*/*E*	Radical	3200	CT	*B*2	No	37/AWD
4	52/F	T5–7	Thoracic back pain and zonesthesia/12; paraparesis/1	3/2	*C*/*D*	Radical	1200	No	*C*	No	36/DEAD
5	49/M	T9–11	Thoracic back pain and paraparesis/1	4/2	*B*/*D*	Debulking	500	CT	*B*3	No	22/AWD
6	37/F	T8–10	Thoracic back pain/1	2/1	*D*/*E*	Debulking	1200	RT	*B*1	Yes(19)	25/AWD
7	59/M	L2–3	Back pain/1	2/1	*D*/*E*	Radical	1000	CT + RT	*B*3	No	14/NED
8	41/F	T2–3	Thoracic back pain/12; paraparesis/0.5	3/1	*C*/*E*	Debulking	2400	No	*C*	Yes(8)	15/DEAD
9	59/M	C3	Cervical pain/18; deteriotation/1	2/1	*D*/*E*	Radical	600	No	*C*	No	41/DEAD
10	50/F	T11–12	Thoracic back pain/18; deteriotation/1	2/2	*D*/*D*	Radical	1600	No	*B*3	No	28/DEAD
11	46/F	T3–5	Thoracic back pain/9; paraparesis/0.5	3/1	*C*/*E*	Debulking	1200	RT + CT	*B*2	No	34/AWD
12	43/M	C5–6	Cervical pain/13; movement restriction/1	2/1	*D*/*E*	Debulking	1600	CT	*C*	Yes(13)	25/DEAD
13	54/M	T4–5	Thoracic back pain/11; paraparesis/0.5	4/2	*B*/*D*	Radical	800	CT	*B*2	No	42/AWD
14	56/F	T5–7	Thoracic back pain/6	2/1	*D*/*E*	Radical	2500	RT	*C*	No	16/DEAD
15	64/F	L1–3	Back pain/4; lower extremities pain/1	3/2	*C*/*D*	Debulking	3100	CT + RT	*B*3	No	36/AWD
X	51.1		9.2				1580				28.5

TETs thymic epithelial tumors, *X* mean, *M* male, *F* female, *C* cervical, *T* thoracic, *L* lumbar, *m* month, *ECOG* Eastern cooperative oncology group, *pre* preoperation, *post* postoperation, *F-S* Frankel score, *CT* chemotherapy, *RT* radiotherapy, *DS* duration of preoperative symptom, *FU* follow-up, *NED* no evidence of disease, *AWD* alive with disease

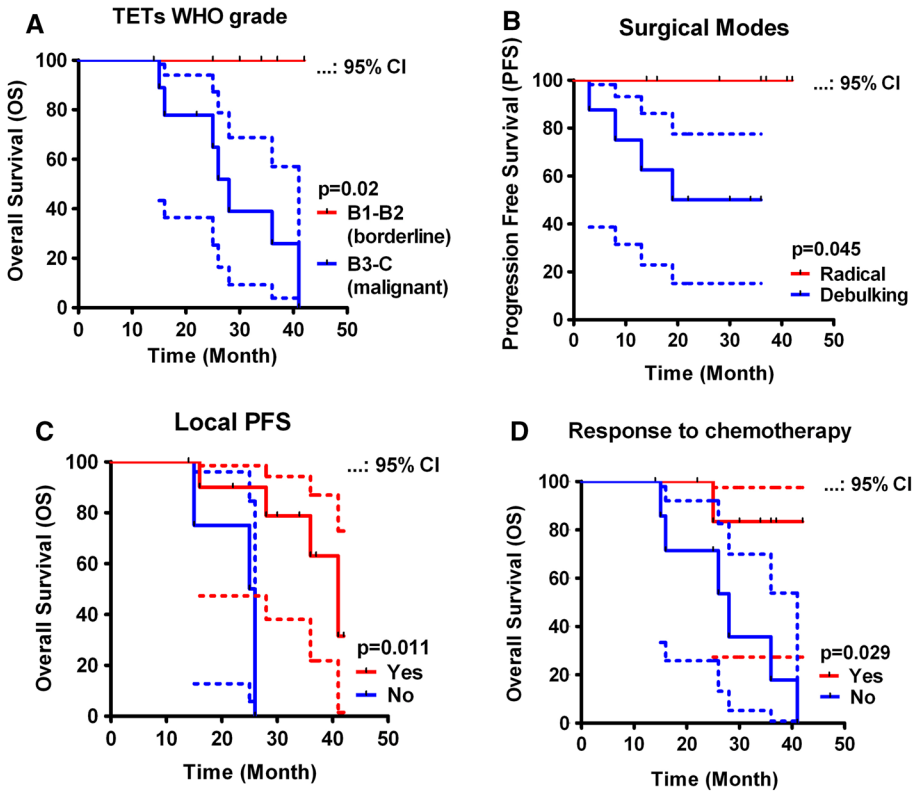

Fig. 1 Kaplan–Meier curves of overall survival for **a** thymic epithelial tumors (TETs) WHO grade, **c** local PFS and **d** response to chemotherapy; Kaplan–Meier curves of local progression-free survival (PFS) for **b** surgical modes

Table 2 Log-rank analysis of prognostic factors affecting PFS and OS of spinal metastasis from TETs

Factors	*n*	PFS			OS		
		Median (m)	Percentage	*p* values	Median (m)	Percentage	*p* values
Age, > 50/≤ 50	8/7	33.0/22.0	87.5%/57.1%	0.283	33.0/25.0	50.0%/57.1%	0.563
Gender, F/M	8/7	23.5/30.0	62.5%/85.7%	0.314	27.0/30.0	37.5/71.4	0.12
Location, C/T/L	2/11/2	27.0/28.0/25.0	50.0%/72.7%/100.0%	0.623	33.0/28.0/25.0	0.0/54.5/100.0	0.610
Visceral meta, yes/no	12/3	25.0/34.0	75.0%/66.7%	0.689	26.5/34.0	50.0%/66.7%	0.391
WHO grade, *B3–C/B1–B2*	10/5	19.0/34.0	70.0%/80.0%	0.553	25.5/34.0	30.0/100.0	0.02*
Primary treatments, surgery/nonsurgery	10/5	26.0/28.0	80.0%/60.0%	0.401	27.5/28.0	80.0%/0.0%	0.108
Pri-TETs to meta, ≥ 7/< 7 ys	7/8	29/16.5	100.0%/50.0%	0.134	30.0/25.5	71.4%/37.5%	0.176
DS, 6/≤ 6 ms	8/7	31.0/22.0	62.5%/85.7%	0.314	31.0/25.0	25.0%/85.7%	0.253
ECOG-PS, 3-4/1-2	8/7	32.0/19.0	75.0%/71.4%	0.924	32.0/25.0	62.5%/42.9%	0.42
PreFrankel, D-E/A-C	7/8	19.0/32.0	71.4%/75.0%	0.924	25.0/32.0	42.9%/62.5%	0.42
Tumor marker, positive/negative	9/6	22.0/34.0	55.6%/100.0%	0.087	26.0/35.0	55.6%/50.0%	0.908
Surgical modes, debulking/radical	8/7	20.5/32.0	50.0%/100.0%	0.045*	25.5/36.0	62.5%/42.9%	0.782
Bleeding, > 2000/≤ 2000	4/11	26.0/28.0	75.0%/72.7%	0.984	26.0/28.0	50.0%/54.5%	0.686
Chemotherapy, yes/no	8/7	32.0/19.0	87.5%/57.1%	0.18	32.0/26.0	87.5%/14.3%	0.029*
Radiotherapy, yes/no	6/9	28.0/28.0	100.0%/55.6%	0.087	30.0/27.0	71.4%/37.5%	0.422
Local progression	4/11	/	/	/	25.0/34.0	25.0%/63.6%	0.011*

TETs thymic epithelial tumors, *PFS* progression-free survival, *OS* overall survival, *M* male, *F* female, *C* cervical, *T* thoracic, *L* lumbar, meta metastasis, *Pri-TETs* primary TETs, *ys* years, *DS* duration of symptoms, *ECGO* Eastern cooperative oncology group

*p value less than 0.05

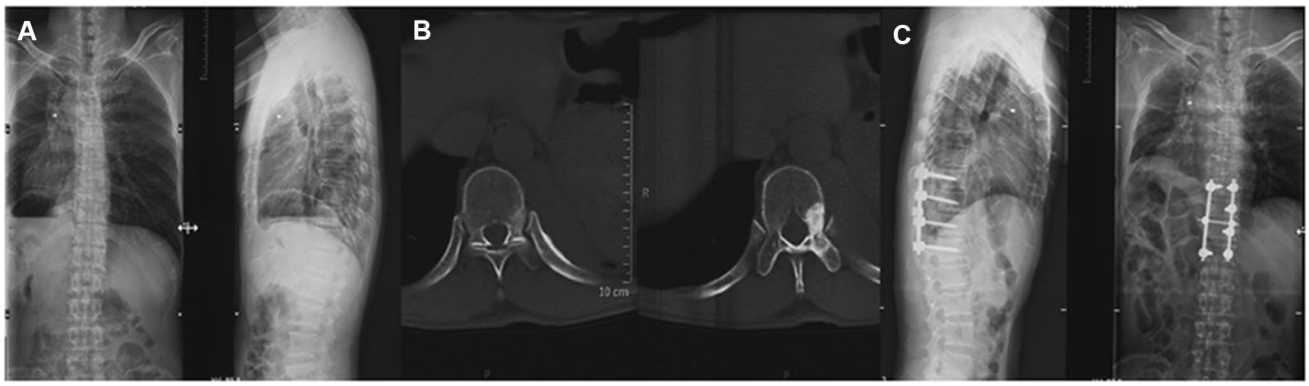

Fig. 2 A 59-year-old man (case 1, WHO grade *B*2) **a** preoperative X-ray of whole spine; **b** transverse plane of the T11 level showing the osteoblastic lesion (CT imaging); **c** postoperative X-ray showing instrumentation

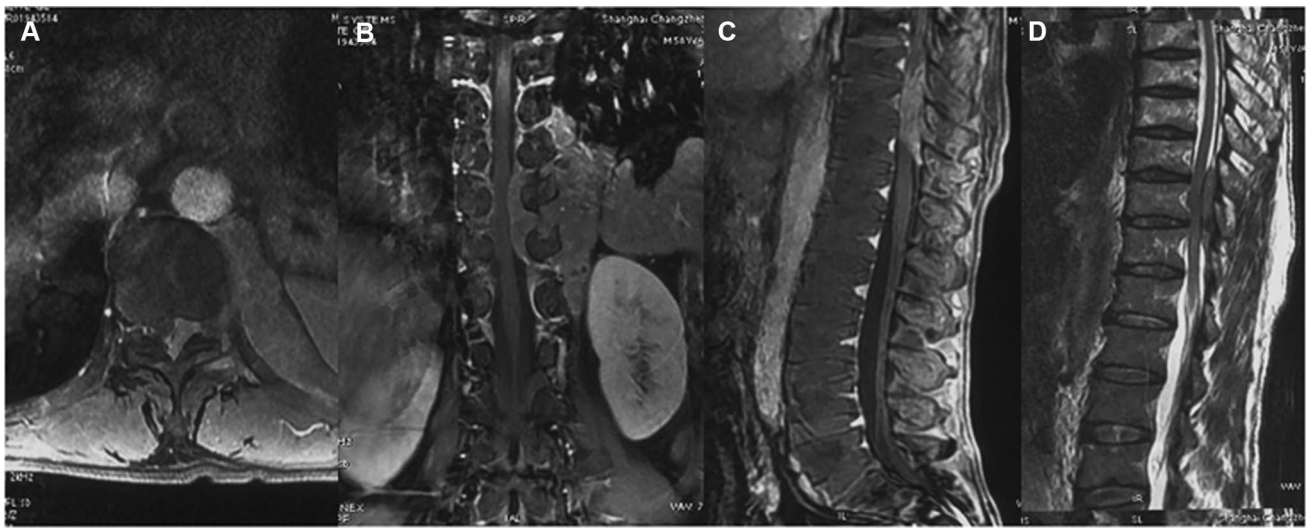

Fig. 3 A 59-year-old man (case 1, WHO grade *B*2). MRI images: **a** transverse plane of the T11 level showing that the lesion extends through the left intravertebral foramen to the spinal canal; **b** coronal plane of the thoracic segments showing a giant lesion; **c**, **d** sagittal plane of the thoracic segments showing the compression of spinal cord

Table 3 Details about treatments and outcomes of 15 patients with WHO type *B*1–*B*2 and *B*3–*C*

WHO subtypes	Treatments	*N*	PFS/% (%)	OS/% (%)
*B*3–*C* (*n* = 10)	RS + CT	1	1/100	1/100
	DS + CT	3	2/66.7	2/66.7
	RS	4	4/100	0/0
	DS	2	0/0	0/0
*B*1–*B*2 (*n* = 5)	RS + CT	2	2/100	2/100
	DS + RT + CT	2	2/100	2/100
	DS + RT	1	0/0	1/100

RS radical surgery, *DS* debulking surgery, *CT* chemotherapy, *RT* radiotherapy, *PFS* progression-free survival, *OS* overall survival

to respond to chemotherapy. There was a statistical difference in OS between the two groups of patients ($p = 0.029$, Fig. 1d). Table 3 shows the treatments and outcomes of the 15 patients with WHO type *B*1–*B*2 and *B*3–*C*.

Complications

Pleural damage was noticed in two (13.3%) patients (case 4 and 8), in whom pleurocentesis and drainage were performed to diminish the postoperative pleural effusion. Radiation pneumonia occurred in two (13.3%) patients after radiotherapy of the primary TETs (case 1 and 14).

Discussion

Thymic epithelial tumors are one of the most common neoplasms arising in the thymus [1, 2, 21, 22]. However, rare literature [6, 23] has focused on the treatment and prognostic prediction of their spinal metastasis. In this study, we performed univariate analyses to investigate the possible variables that could influence local progression and OS of spinal metastasis from TETs. The present study is the first study to report that radical resection was associated with longer PFS, while PFS, response to systemic chemotherapy and WHO *B*1–*B*2 were favorable factors of OS for patients with spinal metastasis from TETs.

The previous studies reported that the male-to-female ratio in patients with distant metastases from TETs was 1.35–2:1 [5, 23], but we found no significant gender difference in patients with spinal metastases. It was reported that primary TETs usually occurred in patients older than 60 years of age [21, 22], but our study showed that 13 (86.7%) patients were younger than 60 years old, which is in line with the previous literature about spinal metastasis from TETs [2, 7–10]. This result seems to indicate that spinal metastasis from TETs is more likely to occur in young patients. With respect to tumor location, the thoracic spine was more likely to be infringed by metastatic TETs [2, 5], which is similar to spinal metastasis from other solid cancers [24]. The time of spinal metastasis after the initial presentation varied widely, with a median interval of 6.5 years in our study, which is the same with other reports [2, 5]. It was found that type C had the shortest duration between the primary lesion to the occurrence of metastasis, followed by *B*3 and *B*2, which is in accordance with the aggressive behavior of WHO classification [3–5].

The WHO histological subtype was found to be well correlated with the invasion of primary TETs [3–5]. However, there was no study examining the difference in outcomes of spinal metastasis between different WHO subtypes. The previous study [23] about prognostic factors of survival in metastatic TETs showed that TC was associated with lower OS than thymoma, but they did not study the difference between subtypes of thymoma. This study illustrated an even distribution of type C, *B*3 and *B*1–*B*2 for spinal metastasis, and the log-rank analysis showed type *B*3–*C* was associated with a lower OS ($p = 0.02$) than type *B*1–*B*2 lesions, which may be due to the aggressive behavior of type *B*3–*C* lesion.

Generally, most lesions showed both osteoblastic and osteolytic lesions in a CT scan [6, 25]. MRI, especially with gadolinium enhancement, remains an important choice for better definition of lesions and for evaluating relations with the thecal sac, spinal nerves and major vessels [1, 24]. Although compression fracture was uncommon on X-ray, extradural lesions with a narrowing of the spinal canal and compression of the dura mater were common in MRI imagings [6, 9–12].

Given the intractable pain, spinal instability and increasing neurological deficits [26], surgery is usually indicated for spinal metastasis of TETs [2, 5–12]. Surgical treatment has a positive effect on the improvement in the neurological status and QoL of patients with spinal metastases [2]. In our study, radical resection has a positive impact on PFS ($p = 0.045$), while PFS is a favorable factor for OS ($p = 0.011$). Thus, for spinal metastasis from TETs, we recommend radical tumor resection when feasible to achieve complete spinal cord decompression and thus maximize the likelihood of neurologic improvement.

Thymic epithelial tumors are known as relatively radiosensitive tumors; however, whether the addition of SRT after surgery is associated with a reduction in mortality has been controversial for invasive and metastatic TETs. The previous studies [5–12] about spinal metastasis from TETs indicated that most patients received postoperative adjuvant therapy with chemotherapy, radiation, or a combination of them, but no research confirmed the effectiveness of SRT in improving local control and survival. Additionally, Kondo and associates [25] showed that adjuvant radiotherapy did not improve the prognosis of invasive and metastatic TETs. There was no significant difference in PFS and OS between patients who received postoperative SRT and those who did not. However, SRT after debulking surgery seemed to increase PFS as compared with debulking surgery alone (75% vs. 25%). Therefore, postoperative SRT is recommended as a supplementary treatment after debulking surgery.

There has been a consensus that systemic chemotherapy is important in the treatment of metastatic TETs because this rare malignancy has been thought of as being chemosensitive [23, 25, 27]. However, systemic chemotherapy was reported to produce a durable remission rate between 32% and 77% in patients with metastatic TETs [28, 29]. In our study, a combination of VIP was employed, achieving a response rate of 53.3%, which is within the acceptable range. Additionally, our study further showed that type *B*3–*C* lesions appeared to be less sensitive to chemotherapy than *B*1–*B*2 type lesions, which is similar to the previous results [27–29]. There was also a significant difference in survival between patients who responded to chemotherapy and those who failed to respond to chemotherapy.

Strengths and limitations

We acknowledge several limitations in our study. Firstly, it is retrospective in nature, and the number of patients included is small, which precludes conducting multivariate statistics. Secondly, we only discussed patients undergoing surgical

treatment, which may produce some epidemiological bias. Although the number of patients included in this study seems relatively small ($n = 15$), to the best of our knowledge, it is the largest case series study reported in the literature that focus on surgery-based treatment and prognosis of spinal metastasis of TETs.

Conclusions

Spinal metastasis of TETs is a challenging clinical entity, given the low OS rate and flickering of the time from the initial diagnosis of primary TETs to spinal metastasis. Radical surgery is associated with longer PFS, while PFS is associated with better OS. Postoperative radiotherapy seems to be a useful supplementary treatment after debulking surgery, and patients who responded to postoperative chemotherapy were demonstrated with greater OS. WHO type *B*3–*C* seemed to be an adverse factor for spinal metastasis from TETs.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflicts of interest.

Ethical standards This research was approved by the hospital ethics committee of the hospital, and written informed consent was obtained from patients or their legal guardians.

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