International Journal of Clinical Oncology (2019) 24:863–870
https://doi.org/10.1007/s10147-019-01422-0

ORIGINAL ARTICLE

Long-term outcomes and prognostic factors of pulmonary metastasectomy for osteosarcoma and soft tissue sarcoma

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Received: 27 September 2018 / Accepted: 21 February 2019 / Published online: 26 February 2019

Abstract

Background The prognostic factors of pulmonary metastasectomy in patients with osteosarcoma and soft tissue sarcoma remain controversial. The purpose of our analysis was to explore the prognostic factors and outcomes of patients with osteosarcoma and soft tissue sarcoma who underwent pulmonary metastasectomy at our institution.

Methods We reviewed the data of 44 patients who underwent resection of pulmonary metastases from 1996 to 2016 at our institution. The Kaplan–Meier method, log-rank test and multivariate Cox hazard model were used for comparison and survival analyses.

Results There was no perioperative mortality. The median post-metastasectomy overall survival was 24.8 months, and the 5-year overall survival rate of all patients was 43.5%. The 5-year survival rate of the patients who underwent repeat thoracotomies was 60.0%. Incomplete resection, a largest tumor size > 2 cm and a disease-free interval < 12 months were associated with poor survival in multivariate analyses. Among eight patients, who underwent repeat pulmonary resection, two remain alive with no evidence of disease. These patients had the longest DFI and DFI-2 (time from first pulmonary metastasectomy to the diagnosis of recurrent pulmonary metastasis), respectively.

Conclusion The survival of patients with a relatively long disease-free interval, small tumor size and complete resection was favorable following the treatment of osteosarcoma and soft tissue sarcoma with pulmonary metastasectomy. Repeat pulmonary metastasectomies also provide favorable prognosis in select patients.

Keywords Osteosarcoma · Soft tissue sarcoma · Pulmonary metastasectomy

Introduction

Osteosarcoma (OS) and soft tissue sarcoma (STS) are rare malignant neoplasms that develop in mesenchymal tissue. Many patients with sarcoma undergo curative resection for the primary tumor; however, approximately 20% of patients diagnosed with STS and 40% of those with OS will develop isolated pulmonary metastases at some point in the clinical course of their disease [1, 2]. Although there are no randomized controlled trials to guide the management of patients with potentially resectable pulmonary metastases from OS and STS, evidence from a retrospective study series supports the view that patients should be considered for pulmonary metastasectomy when complete resection is possible [3].

Previous reports have shown 5-year survival rates ranging from 15 to 52% in patients selected to undergo pulmonary resection [2, 4–15], which compares favorably with the poor survival of patients with non-operative therapy [1, 16]. Nowadays, pulmonary metastasectomy for sarcoma is an established treatment option in the multidisciplinary management. Various factors, including the disease-free interval (DFI), completeness of resection, number of pulmonary nodules, tumor size and laterality have been reported as prognostic factors in pulmonary metastasectomy; however, controversy remains regarding the influence of these factors.

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We, therefore, retrospectively reviewed our experience with PM performed for OS and STS at our institution to analyze the prognostic factors associated with the overall survival in select patients.

Patients and methods

From January 1996 to December 2016, 44 patients underwent pulmonary resection at Osaka University Hospital to treat pulmonary metastases originating from orthopedic sarcomas. The study protocol was approved by the Ethical Review Board for Clinical Studies at Osaka University (control number 18,225). Patients who underwent a surgical biopsy were excluded from this study. Preoperative diagnoses of the pulmonary nodules were made based on the radiological findings of chest computed tomography (CT). In all patients, the primary tumors were pathologically diagnosed prior to pulmonary resection and the primary tumor was treated by radical resection or chemotherapy. In all cases, the lung specimens were histologically evaluated, and metastatic osteosarcoma or soft tissue sarcoma metastases were diagnosed by pathologists. Clinical information was collected from the medical records in our hospital.

Patients underwent resection of pulmonary metastases generally after meeting the following criteria [16] : (1) complete resection of the pulmonary metastasis (or metastases) was considered to have been achieved; (2) the metastatic lesions were limited to the lungs, or extra-pulmonary distant metastases was already controlled or controllable if present; (3) the patient's primary tumor was already controlled or controllable; (4) lymph node metastasis from the pulmonary lesion was determined to be absent by a preoperative evaluation; (5) the general condition of the patient was good, and the patient's respiratory function was sufficient to tolerate pulmonary resection; and (6) secondary spontaneous pneumothorax caused by pulmonary metastases was not controlled.

The disease-free interval (DFI) was defined as the time from treatment of primary disease to the diagnosis of the first metastatic pulmonary lesion. The DFI was considered to be 0 for patients who presented with primary metastatic disease at the initial diagnosis. DFI-2 was defined as the time from the first pulmonary metastasectomy to the diagnosis of recurrent pulmonary metastasis. Complete resection was defined as follows: no tumor cells at the surgical margin of the resected lung macroscopic and histological examination. All visible and palpable pulmonary nodules were resected during surgery. Repeat pulmonary resection was also performed if the patient met the criteria for the first pulmonary resection. The type of resection and surgical approach were selected according to the size and location of the recurrent pulmonary metastatic lesions.

The indications for perioperative chemotherapy and the timing of chemotherapy were determined by the orthopedic surgeons in charge after considering the extent of the disease and the general condition of the patient.

Patient follow-up

Follow-up was generally based on chest X-ray or chest CT, a physical examination and blood chemistry performed every 6–12 months after the first pulmonary metastasectomy. The overall survival was the primary end point defined as the time interval between the date of pulmonary resection and death or the last follow-up for surviving patients. The median follow-up time in the present study was 130 months (range 31–275 months).

Statistical analyses

Statistical analyses were performed using the JMP Pro 14 software program (SAS Institute, Berkley, CA, USA). Differences in the clinical variables of the two groups were evaluated using Student's *t* test or Fisher's exact test. The overall and disease-free survival after pulmonary resection were analyzed using the Kaplan–Meier method. The significance of differences between subgroups was calculated using the log-rank test. A multivariate analysis of prognostic factors was performed using the Cox multivariate proportional hazard model. A p value less than 0.05 was considered to indicate statistical significance. The data are expressed as the mean ± standard deviation or median values.

Results

The characteristics of the 44 patients are shown in Table 1. A majority of the patients were male and had STS ($n = 28$, 64%) with the remaining had a bone primary tumor ($n = 16$, 36%). One patient was not treated with primary surgery but received chemotherapy for the primary tumor. One patient underwent first pulmonary resection due to secondary spontaneous pneumothorax induced by metastatic sarcoma. The median age at the time of first pulmonary resection was 54 years (range 11–85 years). The median DFI was 13.2 months (range: 0-120.5 months), including 5 synchronous cases (11.4%). Nine patients had bilateral metastatic lesions, two underwent simultaneous resection of both sides of pulmonary metastases and seven underwent two-stage bilateral thoracotomy.

The surgical factors are shown in Table 2. During surgery, wide wedge resection was the most frequently performed PM procedure (72.7%). Video-assisted thoracic surgery was introduced in 23 patients (52.3%), and the rest underwent open thoracotomy (47.7%). While complete

Table 1 Patient characteristics

Variable	Number of patients (%)
Sex	
Male	26 (59)
Female	18 (41)
Age (years)	
Median/Range	54/11–85
Type of sarcoma	
OS	16 (36)
STS	28 (64)
Location of primary tumor	
Extremities	25 (57)
Trunk	19 (43)
Histology	
Osteosarcoma	12 (27)
Synovial sarcoma	6 (14)
MFH	5 (11)
ESFT	3 (7)
Myxofibrosarcoma	2 (5)
Rhabdomyosarcoma	3 (5)
MPNST	2 (5)
Others	11 (27)
Time of detection of PM	
Synchronous	5 (11)
Metachronous	39 (89)
Disease-free interval	
Median/Range	13.2/0–120.5
Distribution of disease	
Unilateral	35 (80)
Bilateral	9 (20)
Preoperative chemotherapy	
Yes	22 (50)
No	22 (50)
Repeat resection	
Yes	8 (18)
No	36 (82)

OS osteosarcoma, *STS* soft tissue sarcoma, *MFH* malignant fibrous histiocytoma, *ESFT* Ewing sarcoma family of tumor, *MPNST* malignant peripheral nerve sheath tumor, *PM* pulmonary metastasectomy

Table 2 Operation-related factors

Variable	Number of patients (%)
Approach	
VATS	23 (52)
Open	21 (48)
Type of resection	
Lobectomy	6 (14)
Segmentectomy	6 (14)
Wide wedge resection	32 (72)
Largest resected tumor size(cm)	
Median/Range	1.6/0.4–11.5
Number of resected tumors	
Solitary	28 (64)
Multiple	16 (36)
Median/Range	1/1–18
Completeness of resection	
Complete resection	38 (86)
Incomplete resection	6 (14)

VATS video-assisted thoracic surgery

resection was accomplished in 38 cases (86.4%), the surgical procedure resulted in incomplete resection in 6 cases (13.6%). The reasons for incomplete resections were as follows; unexpected pleural dissemination was observed in two patients, and unresectable multiple pulmonary metastases observed at surgery in four patients. There was no perioperative mortality for pulmonary resection. The median number of resected tumors was 1 (range 1–18). The median largest resected tumor size was 1.6 cm, with a mean of 2.5 ± 2.3 cm (range 0.4–11.5 cm).

In terms of the long-term outcomes, the median length of survival was 28.7 months. The 5-year survival rate of all patients was 43.5% (Fig. 1a). The 5-year survival rate of the 8 patients who underwent repeat pulmonary resection was 60.0% (Fig. 1b). The following factors were selected for the univariate analysis of the survival: sex, age, DFI, number of resected tumors, laterality, diameter of the largest resected pulmonary metastases, type of surgical procedure, surgical approach, and completeness of resection. The results of the univariate analysis are shown in Table 3. Significant relationships were found between the following factors and the survival: the largest size of the pulmonary metastases, approach, completeness of resection, DFI, and number of resected tumors. A multivariate analysis was performed using the same factors selected for the univariate analysis described in Table 4. The largest size of the pulmonary metastases, the completeness of resection and the DFI were independent prognostic factors, while the number of resected pulmonary metastases and surgical approach were not significant.

The clinical courses after the first pulmonary metastasectomy are shown in Fig. 2. Of the 38 patients who underwent the complete resection of pulmonary metastases, 12 survived and were free of disease after the first PM. Twenty-six patients experienced recurrence. Among them, the initial site of recurrence after pulmonary metastasectomy was the lung in 19 patients and second pulmonary resection was performed in 8 patients. All repeat pulmonary resections were complete resections. The details of the patients who underwent repeat pulmonary metastasectomy are shown in Table 5. No major operative morbidity,

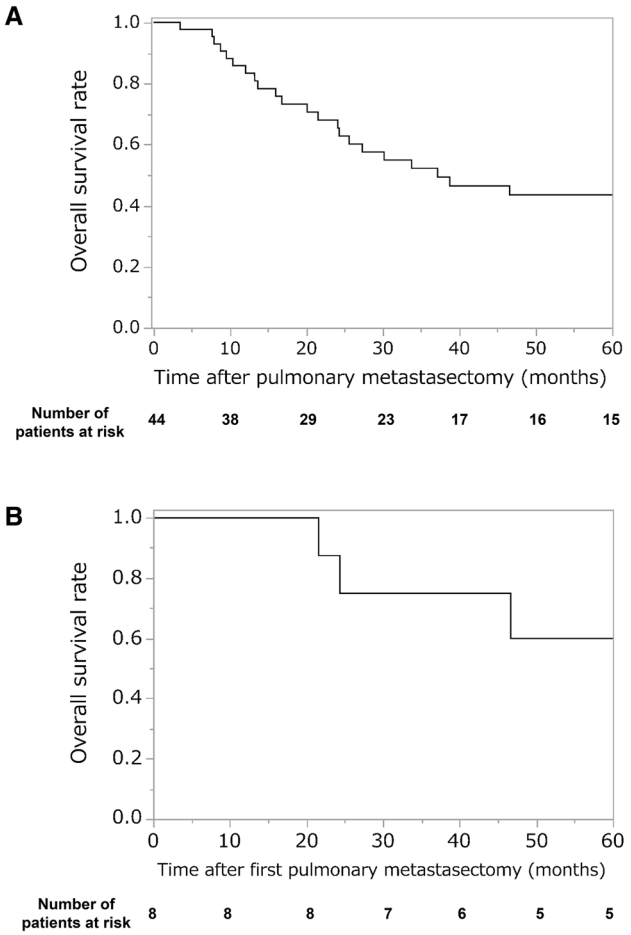

Fig. 1 The clinical course after the first pulmonary metastasectomy in all patients. *NED* no evidence of disease, *DOD* died of disease, *AWD* alive with disease, *DOAD* died of another disease

mortality, or respiratory dysfunction were observed after surgery in any of the patients. Of the eight patients who underwent repeat pulmonary resection, six underwent wide-wedge resection for the first and second operations (cases 1, 2, 4, 6, 7, and 8). One patient underwent wide wedge resection for the first operation and segmentectomy for the second operation (case 3). One patient underwent lobectomy for the first operation and wide wedge resection for the second operation (case 5). Two out of three patients, who had no recurrence of the disease after second pulmonary resection, died due to other causes, one died of myelodysplastic syndrome (case 7), the other case was an accidental death (case 6). Disease recurrence was observed again in 5 patients and a third resection was performed for all 5 patients (case 1, 2, 3, 4 and 5). All five underwent wide wedge resection. Thus far, two patients remain alive with no evidence of disease with a long survival time and had the longest DFI and DFI-2, respectively (cases 5, 8). The number of metastases did not seem to be associated with long-term survival.

Table 3 Univariate analyses of the factors associated with the overall survival after pulmonary metastasectomy

Variable	5-year survival (%)	*p* value
Sex		
Male	32.3	
Female	58.0	0.267
Type of tumor		
OS	44.6	
STS	42.7	0.877
Age (year)		
< 50	50.4	
≧ 50	39.5	0.910
Time of detection of PM		
Synchronous	20	
Metachronous	46.9	0.069
DFI (months)		
≦ 12	23.7	
> 12	56.3	0.008
Distribution of disease		
Unilateral	45.6	
Bilateral	37.5	0.277
Preoperative chemotherapy		
Yes	43.2	
No	42.7	0.817
Site of primary tumor		
Extremity	44.1	
Trunk	42.7	0.637
Largest resected tumor size (cm)		
≦2	69.3	
> 2	6.8	< 0.0001
Number of resected tumors		
Solitary	58.3	
Multiple	9.9	0.009
Type of resection		
Lobectomy	16.7	
Segmentectomy	62.5	
Wedge	47.5	0.554
Approach		
VATS	60.2	
Open	23.8	0.012
Complete resection		
Yes	49.8	
No	0	0.001
Repeat resection		
Yes	39.5	
No	60.0	0.377

PM pulmonary metastasectomy, *DFI* disease-free interval, *VATS* video-assisted thoracic surgery

Table 4 Multivariate analyses of the factors associated with the overall survival rate after the first pulmonary metastasectomy

Variables	Hazard ratio	95% Confidence interval	*p* value
DFI	4.521	1.674–13.271	0.004
Approach	2.450	0.778–8.258	0.135
Largest tumor size	5.113	1.725–16.748	0.004
Number of tumors	2.052	0.822–5.115	0.118
Complete resection	4.199	1.304–11.708	0.009

DFI disease-free interval

Discussion

In the present study, OS and STS patients who underwent pulmonary resection in our hospital were evaluated retrospectively. We showed that, in select patients, pulmonary metastasectomy can achieve a favorable prognosis, and repeat pulmonary metastasectomies also resulted in a favorable survival. Previous reports have shown 5-year survival rates of 15–52% in patients selected to undergo pulmonary resection (Table 6) [2, 4–14]. The long-term outcomes of pulmonary metastasectomy in the present study (a 5-year overall survival rate of 43.4%) were similar to those reported in previous studies.

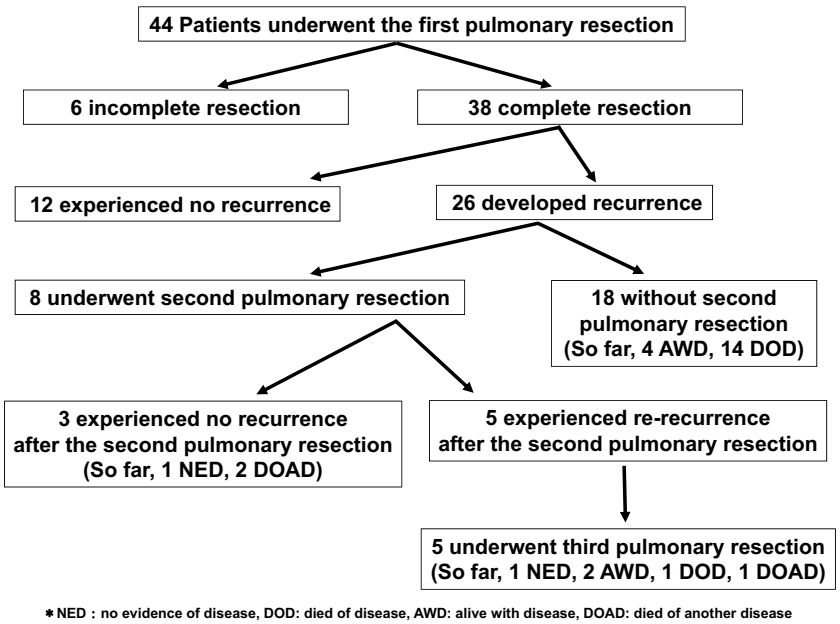

Fig. 2 **a** The survival rate after pulmonary metastasectomy of all patients. The 5-year survival rate of all patients was 43.5%. **b** The survival rate after the first pulmonary metastasectomy of the patients who underwent repeat thoracotomies. The 5-year survival rate was 60.0%

Table 5 Details of patients who underwent repeat pulmonary metastasectomy

Case	Age/sex	Type of tumor	Solitary or multiple	DFI (month)	DFI-2 (month)	Treatment for second relapse	Outcome/survival after first pulmonary metastasectomy (month)
1	11/M	OS	Solitary	49	2	Repeat resection	DOAD/24
2	25/M	OS	Multiple	7	5	Repeat resection and chemotherapy	AWD/31
3	58/F	STS	Solitary	9	6	Repeat resection	DOD/21
4	59/F	STS	Multiple	118	7	Repeat resection	AWD/110
5	36/M	STS	Solitary	120	9	Repeat resection	NED/64
6	63/M	STS	Solitary	6	16	No recurrence	DOAD/46
7	41/M	OS	Solitary	0	20	No recurrence	DOAD/130
8	47/M	STS	Solitary	12	27	No recurrence	NED/106

DFI, disease-free interval (time from treatment of primary disease to the diagnosis of the first metastatic pulmonary lesion), *DFI-2* disease-free interval (time from first pulmonary metastasectomy to the diagnosis of recurrent pulmonary metastasis), *OS* osteosarcoma, STS, soft tissue sarcoma, *DOAD* died of another disease, *AWD* alive with disease, *DOD* died of disease, *NED* no evidence of disease

Table 6 Studies on pulmonary metastasectomy for sarcoma

Author	Year	Number of patients	Histology	5-year survival rate (%)	Prognostic factors
Ueda	1993	23	STS	25	Histology, histologic grade Metastatic localization
Temeck	1995	152	OS STS	35	Complete resection, histology, number
Choong	1995	274	STS	40	Size, number, DFI
van Geel	1996	255	STS	38	Complete resection, age, DFI
Chen	2008	23	OS	31	Number
Chen	2009	23	STS	43	–
Smith	2009	94	STS	15	Complete resection, DFI
Garcia- Franco	2010	52	OS	31	DFI
Kim	2011	97	OS STS	50	Complete resection, DFI, number, laterality
Dear	2012	114	OS STS	43	Complete resection, DFI, SIZE
Mizuno	2013	52	OS STS	51	Complete resection, number
Dossett	2015	120	OS STS	44	DFI
Present study	2018	44	OS STS	44	Complete resection, DFI, size

DFI disease-free interval

Complete resection has been shown to be an important favorable prognostic factor after pulmonary resection in OS and STS [6–11]. The importance of compete resection is obvious in our analysis as well. Taken together, these present and previous findings suggest that patients with residual disease are unlikely to be cured. Suzuki et al. reported that the 5-year survival rate in patients who underwent incomplete resection was 8.3% [17], and another report showed that no patients survived after 5 years [8]. There were no 3-year survivors among our 6 cases of incomplete resection. Our analysis also showed that a DFI of more than 12 months was a significant prognostic factor. Several reports [8, 10, 14, 18] support our analysis and suggest that patients with oligo-metastatic disease and a DFI > 12 months be considered for surgical metastasectomy [14]. While, the largest size of pulmonary metastases was also a significant prognostic factor in our study, it has been found to be prognostic indicator of survival less frequently than other factors. However, a previous report published from the Mayo clinic in one of the largest populations to date similarly found that, the strongest prognostic importance for the post-thoracotomy survival was the size of the largest pulmonary metastasis [11].

The relationship between the overall survival and the surgical approach was significant in the univariate analysis; however, it was not significant in the multivariate analysis. This likely represents a bias toward patients with a smaller tumor size and solitary pulmonary metastases being selected for the VATS approach. Indeed, the selection of the surgical approach depends on the tumor characteristics, and VATS resection itself was not suggested to improve the survival in the present study. Whether or not a less invasive approach affects the outcome remains an issue that future studies should explore. The number of metastases has been shown to be a prognostic factor in several studies [5, 8, 10–12]. However, in our multivariate analysis, the number of metastases had no prognostic impact. The limited number of patients in the present study might have affected the results of the multivariate analysis. Further samples are needed to analyze the clinical significance of the number of pulmonary metastases.

Repeat pulmonary metastasectomies are reported to be beneficial for patients with pulmonary metastasis from various organs [19, 20]. Furthermore, repeat pulmonary metastasectomy has recently been considered to be a useful treatment for subsequent pulmonary re-recurrence in patients with OS or STS [12, 21, 22]. Most series report that repeat resection is associated with a favorable prognosis in both OS and STS. Indeed, in STS a 5-year survival rates of 36% and median survival time of 32.4 months has been reported [23]. A similar survival rate was reported in OS [12]. The findings in our present study are consistent with those showing a favorable prognosis in patients undergoing repeat resection (5-year overall survival rate: 60.0%). Half of the patients who underwent repeat pulmonary resection survived for more than 5 years after first pulmonary metastasectomy (cases 4, 5, 7 and 8). Patients with a longer DFI-2 who underwent repeat pulmonary metastasectomies had a relatively longer survival time. Furthermore, no patients with DFI-2 > 12 months experienced second recurrence. Some reports have demonstrated that the prognosis of patients with a longer DFI-2 was better than that of patients with a shorter DFI-2 [19, 21, 24]. It is possible that a longer DFI might reflect less aggressive tumor behavior. However, the accumulation of more cases and a longer follow-up period are required to discuss the outcomes of long-term survivors. It was also previously reported that complete resection is the

most important prognostic factor after repeat pulmonary metastasectomies [13, 21, 23]. All of the tumors in these patients were resected with a negative margin. Thus, the first treatment of choice should be surgical resection when complete resection is deemed to be achievable based on a preoperative radiologic examination.

Secondary spontaneous pneumothorax (SSP) caused by metastases account for less than 2% of all spontaneous pneumothorax cases. Approximately 80% of SSP cases are associated with metastatic sarcoma, and OS was the most commonly encountered (31.4%) [25]. SSP due to metastatic sarcoma is often associated with advanced disease or systemic chemotherapy; consequently, the prognosis is generally poor [26]. On reviewing 153 cases of SSP complicated sarcoma by Hoag et al. [25], chest tube placement was performed most commonly followed by thoracic surgery, pleurodesis and aspiration. In our case, a solitary pulmonary mass with cavity and pneumothorax was detected on chest CT, and a chest tube was placed. However, air leak was prolonged and required thoracic surgery. Based on the tumor location and size, we performed right lower lobectomy via open thoracotomy without any complications. After surgery, recurrence of pneumothorax was not observed, and anti-cancer therapy was effectively carried out, resulting in an improved quality of life for the patient.

Several limitations associated with the present study warrant mention. First, we had a small sample size due to the rarity of these diseases, and our data were necessarily derived from a single institution, limiting the power of our statistical findings. Second, because of the long period of this study, the diagnostic modalities changed with the introduction of positron emission tomography. Advancements in radiologic examination techniques might have affected the patient selection. In addition, the retrospective design introduces inevitable selection bias.

In conclusion, our data demonstrated that pulmonary metastasectomy results in good long-term outcomes in select patients. Our data also showed that the patients with a relatively long DFI, and metastasis size ≦ 2 cm should be carefully considered, and strong efforts for complete resection should be made in these patients. Furthermore, even if patients who undergo pulmonary metastasectomy to treat OS and STS experience recurrent in the lungs, aggressive repeat pulmonary metastasectomies in selected patients improve the survival.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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