

Surgical Management of Metastatic Disease



Emily Z. Keung, MD^a, Mark Fairweather, MD^a, Chandrajit P. Raut, MD, MSc^{a,b,*}

KEYWORDS

- Soft tissue sarcoma • Metastatic sarcoma • Liver metastasis
- Pulmonary metastasis • Metastasectomy

KEY POINTS

- The lung and liver are the most common sites of metastasis in sarcoma.
- First-line treatment of metastatic sarcoma is chemotherapy. In appropriate patients, sarcoma metastasectomy may be considered and may prolong survival in those with good performance status, longer disease-free interval between resection of primary tumor and appearance of metastatic disease, and oligometastasis, and when complete resection can be achieved.
- There is an extensive body of retrospective data on the surgical management of pulmonary sarcoma metastases. There are sparse retrospective data on the surgical management of hepatic sarcoma metastases and there is no consensus on the role of surgery.
- Additional local treatment modalities include radiation therapy and ablative techniques.
- Patients with soft tissue and bone sarcomas should be referred to specialty sarcoma centers and treatment decisions made in conjunction with a multidisciplinary team of medical, radiation, and surgical oncologists who specialize in the care of such patients.

INTRODUCTION

Sarcomas, including soft tissue sarcomas (STSs) and bone sarcomas, are rare cancers of mesenchymal cell origin that include more than 50 histologic subtypes and many more molecularly distinct entities.^{1–3} After gastrointestinal stromal tumors (GISTs), (the management and survival outcomes of which have improved greatly following the introduction of targeted tyrosine kinase inhibitor [TKI] therapies), the next most common subtypes of STS are liposarcoma and leiomyosarcoma. The annual incidence of STS ranges from 2.4 to 3.6 new cases per 100,000 in population-based studies.⁴ The American Cancer Society estimates that 12,310

^a Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA; ^b Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115, USA

* Corresponding author. Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115.

E-mail address: crout@bwh.harvard.edu

new cases of STS will be diagnosed and 4990 patients will die in 2016 in the United States alone.⁵ Despite treatment, approximately 50% of patients with STS are diagnosed with or develop distant metastatic STS (mSTS), reducing their 5-year overall survival (OS) to less than 10% and their median OS to approximately 8 to 15 months.^{2,6}

For primary resectable STS, surgery is the mainstay of treatment. However, for patients with mSTS, systemic therapy with conventional chemotherapy remains the primary treatment modality. Increased OS has been achieved in some patients who receive multimodality therapy, including surgery, for their metastatic disease. Thus, patients with mSTS should be evaluated and managed by a multidisciplinary team of medical, radiation, surgical, thoracic, and orthopedic oncologists specializing in the treatment of STS.

This article provides an overview of the multimodality therapies for metastatic sarcoma, including chemotherapy, radiation therapy, and ablative techniques, with an emphasis on surgical metastasectomy for mSTS.

DIAGNOSIS AND PATTERN OF METASTATIC SOFT TISSUE SARCOMA

The probability of distant metastases from STS depends on primary tumor grade, size, depth of location, and whether it is recurrent disease or not. High-grade STS tends to metastasize more frequently than low-grade tumors and earlier in the clinical course.²

The lungs and liver are by far the most common sites of distant mSTS, with primary STS site influencing the pattern of metastasis.⁷ Jaques and colleagues⁷ reported that the proportion of lung/liver as a site of distant spread from a primary extremity sarcoma is 75:1, in contrast to primary retroperitoneal sarcoma, in which the ratio is 1:1.5, and visceral sarcomas in which the ratio is 1:10.

Leiomyosarcomas tend to show a higher rate of metastasis to the lungs, liver, and soft tissues. Metastases to bone are more often detected in myxoid round cell and metastatic dedifferentiated liposarcoma. Lymph node metastases are rare events, present in only 2.6% to 16% of all patients with STS.⁶ Clear cell sarcoma, epithelioid sarcoma, and synovial sarcoma metastasize to lymph nodes in up to 10% of cases. Soft tissue metastasis usually presents as a late event associated with widely disseminated disease.⁶ Brain metastases are uncommon in adult STS (1%); however, children with Ewing sarcoma or osteosarcoma are more often affected.²

Thus, distant staging of STS should include high-resolution contrast-enhanced chest computed tomography (CT) for moderate and high-grade tumors to evaluate for pulmonary metastases, and abdominal CT to evaluate for intra-abdominal metastases. Paraspinal MRI may be necessary in cases of myxoid liposarcoma because of its tendency to develop extrapulmonary metastases in this area.⁸ PET imaging may be considered to identify additional sites of metastasis outside the lung in specific circumstances.

THE ROLE OF METASTASECTOMY FOR SARCOMA

In select patients with limited metastatic disease, multimodality treatment including surgical metastasectomy has been shown in some retrospective series to offer longer median OS after diagnosis of mSTS (33–39 months) and 5-year OS (30%–50%) compared with historical controls.^{1,3,4,9–12} However, there are no randomized trials or prospective data available to establish standards of care for treatment sequencing in patients with potentially resectable mSTS.¹³ Most studies evaluating the role of metastasectomy in patients with mSTS have focused on pulmonary metastasectomies with limited studies on hepatic resection.

Patient Selection for Metastasectomy

When evaluating patients for potential metastasectomy, several criteria should be met including³:

1. The presence of a controlled or controllable primary tumor
2. The presence of completely resectable metastatic disease
3. The absence of multivisceral metastatic disease
4. A medically fit surgical candidate

Across studies, the most consistent prognostic factor in patients undergoing pulmonary metastasectomy is the ability to achieve a complete (R0) resection. In these patients, median OS is 19 to 33 months compared with 6 to 16 months following incomplete (R1/R2) resection.^{3,14–18} In addition, the decision to perform metastasectomy should factor in the disease-free interval (DFI) between resection of primary tumor and appearance of metastatic recurrence. Longer DFI has been shown to be a positive prognostic factor following metastasectomy for lung resection for metastatic sarcoma.^{6,12,13,19} Other studies have identified additional prognostic factors associated with improved survival in patients undergoing metastasectomy for STS, albeit inconsistently across studies and institutions. These factors include histologic subtype, tumor size, and number of metastatic lesions.^{3,12,20}

Pulmonary Metastasectomy for Sarcoma

Sarcomas show a predilection for metastasis to the lungs. Approximately 20% to 25% of all patients with STS develop pulmonary metastases, and this is the only site of recurrence in more than half of patients with both soft tissue and bone sarcomas who develop distant metastases.² Most patients with sarcoma pulmonary metastases are asymptomatic. Typically, patients initially develop a limited number of pulmonary metastases that are detected during follow-up staging. Most lung metastases are found within the first 2 years following diagnosis.^{15,18,21–23}

The reported median OS for pulmonary metastatic disease with current multidisciplinary treatment of STS is 12 to 14 months.¹⁶ For a small subset of patients with resectable disease and favorable tumor biology, pulmonary metastasectomy has become accepted standard therapy based on an abundance of retrospective and nonrandomized studies showing improved survival with complete resection compared with historical controls without resection (**Table 1**).¹⁶ In an important landmark publication from the International Registry of Lung Metastasectomy, Pastorino and colleagues²⁴ reported a wide difference in 5-year survival among 5206 patients from Europe and North America following pulmonary metastasectomy depending on the type of cancer: 68% for germ cell, 37% for epithelial cancer, 31% for sarcoma, and 21% for melanoma. In more recent studies, 5-year OS following pulmonary metastasectomy for sarcoma have been reported to be as high as 50% (typically ~30%).^{15–17,25,26}

Although pulmonary metastasectomy is now routinely considered for patients with STS, it is important to remember that the published evidence to support this practice consists almost entirely of retrospective studies,^{10–12,14,15,17,18,22–24,27–46} which are inevitably subject to biases, including selection bias. Longer OS rates observed among patient cohorts undergoing pulmonary metastasectomy may be a reflection of patient selection bias rather than a true survival benefit afforded by resection.^{16,21,47–49} Because only 2% to 3% of patients with pulmonary metastases ultimately undergo metastasectomy,⁴⁹ those selected for resection are likely to have more favorable features (including solitary or low number of metastases and long

Table 1
Results of sarcoma pulmonary metastasectomy series

Reference	Institution	Patients Undergoing Metastasectomy (N)	5-y OS (%)	Median OS	Factors Associated with Longer Survival
Soft Tissue Sarcoma: Mixed Histologies					
Van Geel et al, ⁴⁶ 1996	Multi-institutional	255	38	NR	DFI >2.5 y, complete resection, lower tumor grade, age <40 y
Pastorino et al, ²⁴ 1997	Multi-institutional	1917	31	NR	DFI >36 mo, fewer metastases
Billingsley ¹⁸ 1999	Memorial Sloan-Kettering	161	46 (3-y OS)	33 mo	DFI >1 y, complete resection, lower tumor grade, age <50 y
Weiser et al, ¹¹ 2000	Memorial Sloan-Kettering	86 (all underwent multiple pulmonary metastasectomies)	36	42.8 mo	DFI >1 y, complete resection, ≤2 nodules
Canter et al, ³⁰ 2007	Memorial Sloan-Kettering	138	29 (DSS)	30 mo	DFI >1 y, complete resection
Rehders et al, ¹⁴ 2007	Hamburg, Germany	61	25	33 mo	—
Smith et al, ¹⁵ 2009	Roswell Park	94	15	16 mo	DFI >25 mo, complete resection
Stephens et al, ⁴⁴ 2011	MD Anderson	81 (metastasectomy after chemotherapy)	32 vs 0 ^a	35.5 vs 17.2 mo ^a	DFI <2 y, ≤2 nodules, no progression after neoadjuvant chemotherapy
Schur et al, ⁴³ 2014	Vienna, Austria	46	32	45.3 mo	—
Dossett et al, ³⁹ 2015	Moffitt	120	NR	48 mo	—
Lin et al, ⁴⁰ 2015	UCLA	155	34.8	35.4 mo	DFI >1 y, complete resection

Leiomyosarcoma					
Burt et al, ³⁵ 2011	Brigham and Women's Hospital	31	52	69.9 mo	DFI >1 y, age <45 y
Lin et al, ⁴⁰ 2015	UCLA	26	61	NR	Longer DFI
STS/Bone Sarcoma: Mixed Histologies					
Burt et al, ³⁵ 2011	Brigham and Women's Hospital	51	32	23.9 mo	Longer DFI
Kim et al, ¹² 2011	Massachusetts General Hospital	97	50	60.2 mo	DFI ≥1 y, complete resection, unilateral metastatic disease
Mizuno et al, ⁴¹ 2013	Nagoya, Japan	52	50.9	NR	Complete resection, ≤2 nodules
Osteogenic Sarcoma					
Briccoli et al, ³² 2005	Bologna, Italy	127	38	NR	Longer DFI
García Franco et al, ¹⁷ 2009	Pamplona, Spain	52	31	36 mo	Longer DFI
Lin et al, ⁴⁰ 2015	UCLA	21	57	57%	—

Abbreviations: DSS, disease-specific survival; NR, not recorded; UCLA, University of California, Los Angeles.

^a Nonprogressors versus progressors after neoadjuvant chemotherapy.

interoperative interval) associated with longer survival regardless of treatment. Thus, it is difficult to discern how much benefit pulmonary metastasectomy provides.

That the improved survival seen in most reported cohorts of patients undergoing pulmonary metastasectomy may be caused by underlying favorable tumor biology and patient selection bias rather than by surgical resection itself is also suggested by reports from Treasure and colleagues⁴⁵ and Stephens and colleagues.⁴⁴ In 2012, Treasure and colleagues⁴⁵ performed a systematic review of published reports that included survival rates following pulmonary metastasectomy for metastatic sarcoma. Among 1196 patients included in 18 studies, 5-year OS following first pulmonary metastasectomy for osteogenic sarcoma and STS were 34% and 25%, respectively. Compared with 5-year OS among all patients with metastatic sarcoma in the Thames Cancer Registry for 1985 to 1994 and 1995 to 2004 (20% and 25% for bone sarcoma, 13% and 15% for STS), these survival rates were better (*P* values not reported). However, the investigators commented that, "Given that pulmonary metastasectomy is used in a highly selected favorable minority, this suggests that the benefit from metastasectomy cannot be large. Although it is a standard component of sarcoma care, the evidence for benefit is weak."⁴⁵ In 2001, Stephens and colleagues⁴⁴ examined 81 patients with bone and soft tissue sarcoma who underwent pulmonary metastasectomy following neoadjuvant chemotherapy. Patients whose pulmonary metastatic disease progressed as determined by CT imaging following systemic therapy had markedly worse median OS (35.5 vs 17.2 months; *P* > .001) and 5-year survival (0% vs 32%; *P* value not reported) following pulmonary metastasectomy. The survival rates among nonprogressors in this study are comparable with pulmonary metastatic cohorts in other studies despite patients in this study having a higher average number of pulmonary nodules (progressors 5.1, nonprogressors 5.9; *P* value not significant). Clearly, there is a need for randomized trials to determine the true, rather than the perceived, effect of pulmonary metastasectomy in STS and bone sarcoma.

Pulmonary metastasectomy can be performed either via thoracoscopy or thoracotomy for unilateral disease. For bilateral pulmonary metastases, bilateral thoracoscopy/thoracotomy, median sternotomy, or clamshell thoracotomy can be performed. The main principle of pulmonary metastasectomy is complete resection and limiting resection to preserve pulmonary function.²¹

Preoperative planning should include pulmonary function tests (PFTs) and evaluation of the patient's ability to tolerate an operation. Special consideration should be given to patients who received chemotherapeutic agents associated with drug-induced lung disease. Patients should also cease smoking for at least 3 weeks before surgery to decrease the risk of postoperative pneumonia and other complications.²¹

Postoperative follow-up for those with metastatic STS to the lungs (as described by Jaklitsch and colleagues³⁶) includes physical examination and CT scan of the chest every 4 months for 2 years then every 6 months for 6 years. Postoperative follow-up for those with metastatic bone sarcoma to the lungs (as described by Briccoli and colleagues³²) includes physical examination and CT scan of the chest and imaging of primary tumor site every 3 months for 4 years and then every 6 months for 10 years and total-body bone scintigraphy every year.³³

Outcomes following pulmonary metastasectomy for soft tissue sarcoma

Although there are numerous retrospective series reporting outcomes following pulmonary metastasectomy for sarcoma,^{10–12,14,15,17,18,22–24,27–29,31–46} patient cohorts in these studies are highly heterogeneous. These studies not only include patients with primary tumors of mixed STS histologies and primary tumor sites (extremity, trunk, visceral, retroperitoneal), but often also include patients with osteogenic

sarcoma.^{40,41} These studies inconsistently also include patients with synchronous pulmonary metastases, those who received chemotherapy, and/or those who underwent repeated pulmonary resections. Nevertheless, reported 5-year OS rates generally range from 15% to 43% and median OS range from 30 to 48 months in the literature.

The most consistently reported prognostic factor for survival following pulmonary metastasectomy is completeness of resection.^{12,15,18,23,38,41,42,46} Reported median survival ranges from 19 to 33 months for patients who underwent complete resection compared with 6 to 16 months with incomplete resection.^{15,18,22,24,25} Billingsley and colleagues¹⁸ examined 3149 adult patients with STS treated at Memorial Sloan-Kettering Cancer Center from July 1982 and February 1997. Of these, 719 patients either presented with or developed pulmonary metastases. Median OS for all patients from time of diagnosis of pulmonary metastasis was 15 months. Patients who underwent complete resection of pulmonary metastatic disease had a median OS of 33 months, those who underwent incomplete resection had a median OS of 16 months, whereas those treated nonoperatively had a median OS of 11 months ($P < .001$).¹⁸ In a study of 94 patients with mSTS of mixed primary sites, Smith and colleagues¹⁵ reported median OS for R0 resection was 22 months, 11.5 months for R1 resection, and 9.5 months for R2 resection ($P < .0001$). Pogrebniak and colleagues³⁸ similarly reported longer median OS in patients undergoing complete resection of pulmonary metastases compared with those undergoing incomplete resection (25 vs 10 months; $P = .0007$).

Other reported prognostic factors for survival following pulmonary metastasectomy are DFI between resection of primary tumor and appearance of metastatic disease,^{12,15,18,23,24,35,37,39,45,46} number of metastatic pulmonary nodules,^{11,12,24,39,41,45} tumor grade,^{11,18,46} tumor size,^{11,12} and patient age.^{18,23,46} Kim and colleagues¹² reported that DFI greater than or equal to 1 year was associated with improved 5-year OS compared with DFI less than 1 year (65% vs 21%; $P < .0001$).

Several investigators have noted improved survival among patients undergoing pulmonary metastasectomy for leiomyosarcoma.^{35,40} Burt and colleagues³⁵ in 2011 reported longer median OS for patients undergoing repeated pulmonary metastasectomy for leiomyosarcoma compared with other histologies (69.9 vs 23.9 months; $P = .049$) and better 5-year OS (52% vs 32%; $P = .049$). More recently, Lin and colleagues⁴⁰ reported that patients with metastatic leiomyosarcoma ($n = 26$) undergoing pulmonary metastasectomy experienced longer 5-year OS compared with other histologies (61% vs 37%; $P = .02$).

Outcomes following pulmonary metastasectomy for bone sarcoma

Patients with STS are distinct from those with osteogenic sarcoma. Compared with STS, patients with osteogenic sarcoma tend to be younger at diagnosis.^{17,28,29,31–34} Although there are few prospective studies and no randomized trials evaluating pulmonary metastasectomy in patients with osteogenic sarcoma, chemotherapy and pulmonary metastasectomy have transformed metastatic osteosarcoma from a uniformly fatal condition to one with reasonable expectation of survival, with 5-year OS up to 47% with complete resection of pulmonary metastases.²⁸ García-Franco and colleagues¹⁷ examined 52 patients with pulmonary metastases from bone sarcomas, all treated with neoadjuvant chemotherapy before pulmonary metastasectomy. Five-year OS was 31%. In their study of 94 patients with metastatic, Briccoli and colleagues³² reported a 5-year OS from first metastasectomy for osteosarcoma of 38%.⁵⁰

Multiple groups have reported improved survival compared with patients with mSTS to the lungs.^{28,40} Lin and colleagues⁴⁰ reported that patients with osteogenic sarcoma

($n = 21$) undergoing pulmonary metastasectomy experienced longer 5-year OS compared with those with STS (53% vs 37%; $P = .03$). Similar to mSTS, longer DFI, completeness of resection, and number of pulmonary metastases have been shown to be associated with improved survival following pulmonary metastasectomy for osteogenic sarcoma metastasis.^{17,32}

As with mSTS, patients who present with synchronous pulmonary metastasis at the time of the initial sarcoma diagnosis have reported worse OS.^{29,33} Kager and colleagues²⁹ reported outcomes of 202 patients with high-grade osteosarcoma with clinically detectable metastases at initial presentation registered in the neoadjuvant Cooperative Osteosarcoma Study Group before 1999. The most frequent metastatic site was the lung (164 patients, 81.2%). Five-year OS was 29%; in the 124 patients with lung-only metastasis, 5-year OS was 33%.

Long-term pulmonary function has been studied among patients who undergo recurrent pulmonary metastasectomy for osteogenic sarcoma during childhood.³¹ Denbo and colleagues³¹ examined 21 patients who had PFTs after pulmonary metastasectomy for osteosarcoma. Mean age at diagnosis of osteosarcoma was 13.2 years; mean age at PFTs was 34.9 years. Patients who underwent pulmonary metastasectomy for osteosarcoma as children often had abnormal PFTs on long-term follow-up but reductions in lung volumes and diffusing capacity for carbon monoxide were mild except in those who underwent multiple pulmonary metastasectomies.

Approach to recurrent metastases

Despite aggressive surgical management, recurrence rates are greater than 50% following pulmonary metastasectomy for STS.^{2,16,22,51} Some series have shown that repeated resection of recurrent metastasis can be associated with improved survival,^{3,11,12,25,35–38,52} although less invasive approaches may be associated with fewer morbidities and shorter hospital stay.^{2,3,25} Jaklitsch and colleagues³⁶ reported that 5-year OS remained greater than 33% for up to 4 procedures. With 5 or more procedures, the ability to maintain control of intrathoracic metastases became very low and median survival decreased to 8 months. The investigators concluded that repeating pulmonary metastasectomy may be indicated as long as removal of all clinically apparent disease is practical.³⁶ More recently, Kim and colleagues¹² reported that patients who underwent multiple pulmonary metastasectomies had longer 5-year OS compared with those who had undergone a single operation (69% vs 41%; $P = .017$). To be able to undergo repeated metastasectomy likely identifies a subset of patients with good physiologic condition and favorable tumor biology.^{16,48} Whether repeated pulmonary metastasectomy extends survival is unclear because it is unclear what the survival of these patients would have been without surgery.

Patients presenting with synchronous metastases

Approximately 10% of patients with STS have synchronous pulmonary metastases at initial presentation.^{16,53} It is known that patients with STS and synchronous metastases at presentation generally have poor prognosis. One study based on the American Joint Committee on Cancer staging system for sarcoma reported that patients who presented with metastatic disease (stage IV) had a 6% 5-year disease-specific survival.⁵³ Several groups have examined whether pulmonary metastasectomy for synchronous metastases offers any benefit.^{6,53}

In 2002, Kane and colleagues⁶ reported that, among 48 patients with synchronous metastases, 30 had pulmonary metastases. Thirteen patients underwent pulmonary metastasectomy with no difference in median OS between those who underwent

resection and those who did not (16 vs 14 months; $P = .3$). More recently, Ferguson and colleagues⁵³ examined 112 patients with bone sarcoma and STS who presented with synchronous metastases. Eighty-eight patients (79%) had pulmonary metastases at the time of presentation with STS. Of these, 18 patients underwent pulmonary metastasectomy. Median OS was 9 months for all patients with synchronous pulmonary metastases with no difference in OS between those who underwent pulmonary metastasectomy and those who did not.⁵³ Other investigators have reported pulmonary metastasis synchronous to the primary tumor to be a significant predictor of worse survival following pulmonary metastasectomy.^{39,40,42}

Thus, patients with pulmonary metastases at the time of STS diagnosis do not benefit from metastasectomy. Chemotherapy should be the initial treatment of those who have short DFI or a large number of metastatic lesions.⁵³ Subsequent surgery could be considered if the patient benefits from chemotherapy.

Hepatic Resection for Metastatic Sarcoma

Isolated liver metastases of STS are uncommon compared with pulmonary metastases. Patients with retroperitoneal and intra-abdominal/visceral STS are more likely to develop liver-only metastatic disease compared with patients with extra-abdominal primary STS.^{13,22} Although hepatic resection is increasingly being performed for colorectal and neuroendocrine liver metastases, surgical resection of hepatic metastases from STS remains controversial and hepatic metastases from STS are most often treated nonsurgically.¹³

There is currently no consensus on the role of resection for STS metastases to the liver and no prospective data available to guide surgical treatment.^{13,54,55} The available data regarding resection of hepatic STS metastases are limited to retrospective series reporting on resection of noncolorectal nonneuroendocrine liver metastases,^{20,56–59} case reports,⁶⁰ and case series reporting specifically on the treatment of STS liver metastases.^{7,26,50,61–64} In addition to limitations and biases inherent in retrospective studies, the available data also represent heterogeneous patient groups with mixed primary sarcoma histologies. Such studies often include patients with GIST, which is inappropriate because these tumors have significantly better outcomes and different management following the introduction of targeted TKI therapies.⁵⁴ In these studies, median OS ranged between 34 and 37 months and 5-year OS ranged between 20% and 39% for patients undergoing hepatic resection for sarcoma metastases.^{54,56,61,63,64} Survival outcomes are highly dependent on histologic subtypes, with leiomyosarcoma associated with worse outcomes and GIST associated with better outcomes in the postimatinib era, so hepatic resection may be considered with careful patient selection and may prolong survival in those with good performance status, longer DFI, oligometastasis, and when all gross hepatic disease is resectable.^{13,54}

As in sarcoma pulmonary metastasis, consistently reported prognostic factors in patients undergoing hepatic metastasectomy for liver metastases include ability to achieve a complete (R0) resection and longer DFI between resection of primary tumor and appearance of metastatic recurrence (**Table 2**).^{3,6,7,19,26,57,59,62}

Postoperative follow-up (described by Rehders and colleagues⁵⁰) includes physical examination and CT scan of the chest/abdomen/pelvis every 3 months for 2 years, then every 6 months until the end of the fifth postoperative year, then annually.

Outcomes following hepatic resection for metastatic soft tissue sarcoma

There are several large retrospective studies of patients undergoing liver resection for noncolorectal nonneuroendocrine metastases. In general, these patient cohorts are highly heterogeneous and the data difficult to apply.^{56,58} They do show the highly

Table 2
Results of sarcoma hepatic metastasectomy series

Reference	Institution	Patients Undergoing Metastasectomy (N)	Perioperative Mortality (%)	5-y OS (%)	Median OS (mo)	Factors Associated with Longer Survival
Leiomyosarcoma						
Chen et al, ²⁶ 1998	Johns Hopkins	11	0	NR	39	Complete resection
Ercolani et al, ⁵⁷ 2005	Bologna, Italy	10	NR	36	44	—
Lang et al, ⁶² 2000	Hannover, Germany	26	6	20	NR	None found
Yedibela et al, ⁵⁹ 2005	Erlangen, Germany	15	NR	NR	NR	Complete resection
Mixed Histologies						
Adam et al, ⁵⁶ 2006	Multi-institutional	125 (excluding GIST)	NR	31	32	—
DeMatteo et al, ⁶¹ 2001	Memorial Sloan-Kettering	56 (34 with GIST)	0	30	39	DFI >2 y, complete resection
Marudanayagam et al, ⁶³ 2011	Birmingham, UK	36 (5 with GIST)	0	31.8	24	Histologies other than leiomyosarcoma
Pawlik et al, ⁶⁴ 2006	MD Anderson	53 (of 66 patients, 36 with GIST)	0	27	47	No adjuvant therapy
Rehders et al, ⁵⁰ 2009	Dusseldorf, Germany	27 (of 45 patients, 6 with GIST)	7	49	44	DFI >2 y, no RFA treatment

Abbreviation: RFA, radiofrequency ablation.

variable survival outcomes between sarcoma histologies. In a study of 1452 patients who underwent hepatic resection for noncolorectal nonneuroendocrine liver metastases, Adam and colleagues⁵⁶ reported the highest 5-year OS among patients with GIST (70%, median survival not reached), whereas patients with all other sarcoma histologies had 5-year OS of 30% (median survival, 32 months; P value not reported).

DeMatteo and colleagues⁶¹ examined 331 patients with liver metastases from sarcoma admitted to Memorial Sloan-Kettering Cancer Center from 1982 to 2000. Fifty-six patients underwent resection of all gross hepatic disease. Of these, 34 (61%) had GIST or leiomyosarcoma. The sites of primary tumor in the resected patients were predominantly intra-abdominal (38 patients, 68%) or retroperitoneal (8 patients, 14%) and less commonly extremity/trunk (5, 9%) or head/neck (5, 9%). Five-year OS for patients who underwent R0 surgery was 30% compared with 4% among those who did not undergo complete resection ($P < .0001$). On multivariate analysis, only DFI from diagnosis of the primary tumor to the development of liver metastasis greater than 2 years was associated with longer OS after hepatic resection. Repeated liver resection for recurrent tumor was performed in 17 patients.

More recently, Rehders and colleagues⁵⁰ reported their series of 45 patients with liver metastases from sarcoma of whom 27 underwent surgery. Again, a significant proportion of these patients had leiomyosarcoma (30%) or GIST (22%). In this cohort, median OS was 44 months and 5-year OS was 49%. Longer DFI (>2 years) was associated with improved survival. Repeated liver resection for recurrent tumor was performed in 8 patients; median survival in this subset of patients was 76 months.

Both DeMatteo and colleagues⁶¹ and Rehders and colleagues⁵⁰ found that longer DFI (before development of liver metastatic disease) was associated with improved survival following hepatic resection for mSTS. However, the investigators of the former study emphasized that patients who underwent hepatectomy were highly selected and tended to have favorable characteristics, including longer DFI, fewer liver metastases (1–2), and smaller lesions (<10 cm). The observation that the DFI between resection of a primary cancer and subsequent tumor recurrence affects survival has been made across malignancies, including malignant melanoma, breast, and renal carcinoma, as well as in a large study of 2123 patients with completely resected primary STS.¹⁹ Thus, whether hepatic resection of sarcoma metastatic disease itself provides a survival benefit is unclear. It may be that patients selected for hepatic resection of metastatic disease tend to have longer DFI reflecting better/more indolent tumor biology, which may also result in these patients having metastatic disease that is more amenable to complete resection.

Outcomes following hepatic resection for metastatic leiomyosarcoma

Leiomyosarcoma is among the most commonly resected metastatic tumors to the liver, along with colorectal, neuroendocrine, and GIST hepatic metastases. Patients who undergo hepatic resection for leiomyosarcoma metastasis have worse survival outcomes compared with patients who undergo hepatic resection for GIST.^{26,57,59,62,63} Marudanayagam and colleagues⁶³ reported that, among their series of 36 patients who underwent hepatic resection for mSTS, factors associated with poor survival on univariate analysis included positive resection margin of liver metastasis, tumor grade, and primary leiomyosarcoma; only primary leiomyosarcoma remained prognostic as a risk factor for poor survival on multivariate analysis ($P = .01$).

Across studies, incomplete gross resection was associated with worse OS following liver resection for metastatic leiomyosarcoma. Median OS ranged between 20.5 and 44.4 months and 5-year OS ranged between 13% and 36% for those patients able

to undergo resection of leiomyosarcoma liver metastases, depending on whether R0 or R1/R2 resection was achieved.^{7,26,57,59,62}

Jaques and colleagues⁷ reported that, among 981 adult patients with STS admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and July 1987, 65 patients had hepatic metastases. The primary sarcoma in most patients was leiomyosarcoma ($n = 55$, 85%); the remainder were angiosarcomas, rhabdomyosarcomas, liposarcomas, and malignant fibrous histiocytomas. Thirteen patients (20%) had liver metastases on initial presentation. In the remaining patients, the median time from primary diagnosis to development of hepatic metastases was 12 months. Hepatic metastases were predominantly seen among patients with primary intra-abdominal (visceral or retroperitoneal) rather than extremity/trunk sarcomas. Hepatic resection was performed in 14 patients (22%) with median OS of 30 months in the resected group (vs 12 months in patients with unresectable disease; P value not significant). There were no 5-year survivors in this study.

In 1998, Chen and colleagues²⁶ examined outcomes of hepatic resection specifically for metastatic leiomyosarcoma. Of 11 patients in this series, 5 had retroperitoneal leiomyosarcoma and 6 had visceral primary leiomyosarcoma (3 gastric, 2 small bowel, 1 uterine/adnexal). Patients underwent hepatic lobectomies/extended lobectomies ($n = 4$), segmentectomies/wedge resections ($n = 5$), and complex liver resections ($n = 2$) with complete resection (R0) achieved in 6 patients. Average disease-free survival (DFS) was 16 months and median OS was 39 months. Only resection margin status was associated with OS ($P = .03$). The median survival time for the 6 patients who underwent R0 resection was not reached at 56-month follow-up; all 5 patients with incomplete (R1/R2) resection died by 39 months (median 25 months). In this small series, there was no association between OS and number or size of liver lesions, extent of hepatic resection, or tumor grade.

Lang and colleagues⁶² reported their series of 26 patients who underwent a total of 34 liver resections for leiomyosarcoma metastases. Of 23 first hepatic resections, R0 resection was achieved in 15 patients, R1 in 3 patients, and incomplete gross resection (R2) in 5 patients. Median OS after R0 resection was 32 months compared with 20.5 months after R1/R2 resection ($P = .31$). Five-year OS was 13% for all patients and 20% after R0 resection.

More recently, Ercolani and colleagues⁵⁷ and Yedibela and colleagues⁵⁹ studied the role of liver resection for noncolorectal metastases and reported outcomes for subsets of patients with metastatic leiomyosarcoma. Although the heterogeneity of these two patient cohorts makes interpretation of their data challenging, 5-year OS among patients who underwent liver resection for metastatic leiomyosarcoma were 36.4%⁵⁷ and 26%, respectively.⁵⁹ Yedibela and colleagues⁵⁹ reported that, among 9 patients who underwent hepatic resection for leiomyosarcoma metastases, those who underwent R0 resection experienced longer 5-year OS (42 vs 26 months) and median survival (41 vs 21 months; P value not reported). Ercolani and colleagues⁵⁷ reported a median survival of 44.4 months among 10 patients who underwent hepatic resection for metastatic leiomyosarcoma.

OTHER TREATMENT MODALITIES FOR METASTATIC SARCOMA

Chemotherapy

The first-line treatment of mSTS is chemotherapy.^{3,8,16} Doxorubicin and ifosfamide are the most active drugs and constitute the standard treatment of advanced STS. The recommended first-line treatment is doxorubicin at a dose of 75 mg/m². Ifosfamide is an alternative in patients with contraindication to doxorubicin or as second-line

treatment after doxorubicin failure. Ifosfamide in monotherapy is used at doses of 5 to 9 g/m². Doxorubicin and ifosfamide may be used in combination when obtaining an objective response to improve symptoms or before surgical resection.^{1,4,8}

Second-line therapy for unresectable mSTS is palliative. For most STS, there is no evidence that a particular drug sequence is superior to another. Some tumor types may be more sensitive to certain drugs and this may aid in selection of second-line therapy: high-dose ifosfamide for synovial sarcoma, trabectedin for myxoid liposarcoma and leiomyosarcoma, or gemcitabine with docetaxel or with dacarbazine (dimethyl triazeno imidazole carboxamide [DTIC]) in leiomyosarcoma. Symptomatic patients with good performance status are candidates for clinical trials. For symptomatic patients with poor performance status, radiation therapy or supportive care alone are appropriate options.

Gemcitabine and DTIC alone have limited activity in STS; however, the combination of gemcitabine (1800 mg/m² at 10 mg/m²/min) with DTIC (500 mg/m²) every 14 days seems to provide benefit, particularly in leiomyosarcoma. Gemcitabine in combination with docetaxel has also been reported in uterine leiomyosarcoma and undifferentiated pleomorphic sarcoma.⁸

Trabectedin has been explored in phase I to II trials with modest objective response rates and higher progression arrest rates in myxoid liposarcoma, synovial sarcoma, and leiomyosarcoma. In a phase III trial, trabectedin improved disease control compared with standard second-line DTIC in advanced metastatic liposarcoma and leiomyosarcoma.⁸ Trabectedin is now approved in Europe and the United States for patients with STS after failure on doxorubicin and ifosfamide or in patients unable to receive these first-line treatments.

Patients previously treated with ifosfamide may be treated with high-dose ifosfamide (>10 g/m²), which has shown activity in synovial sarcoma. Pazopanib, a multitargeted TKI, now constitutes a second-line option after first-line failure for nonadipocytic sarcoma.

Two recent retrospective analyses examined treatment patterns in patients with metastatic/relapsed STS. The earlier study, from 2012, was a multicenter, multicountry retrospective review,⁴ whereas the later study, from 2015, was performed in the United States.¹ In the former study, the most common first-line regimens were doxorubicin (34%) or anthracycline plus ifosfamide (30%) with median progression-free survival (PFS) and OS of 8.3 and 23.5 months from first favorable response to chemotherapy.⁴ In the latter study, the most common first-line regimens were anthracycline based (44%) or gemcitabine based (28%) with median PFS from initiation of second-line treatment of 5.4 months and median OS from first diagnosis of mSTS of 39 months.¹ Most patients receive multiple lines of chemotherapy with higher likelihood of favorable response to first-line therapy compared with second or later lines of therapy. Both studies highlight that PFS and OS in patients with metastatic STS with favorable response to chemotherapy are short and that there remains a significant unmet need in the treatment of patients with metastatic STS.^{1,4}

Radiation Therapy

For patients who are not candidates for surgical metastasectomy, radiation therapy can be used for control of limited metastatic disease.³ Stereotactic body radiation therapy (SBRT) delivers high doses of radiation with precise localization and limited exposure of adjacent tissue. Good local control rates have been noted in studies of SBRT for patients with liver and lung metastases from various primary tumors.^{65–67} In STS specifically, local control rates for patients with pulmonary metastases have

been reported to be as high as 80% to 88%.^{68,69} Further data on long-term toxicity and outcomes, particularly compared with metastasectomy, are needed.

Ablative Techniques

As thermoablative techniques continue to evolve, these techniques have been increasingly used as adjuncts in combination with surgical metastasectomy or as primary therapy in nonsurgical candidates for some disease processes.^{2,3,16} Thermal ablative methods include radiofrequency ablation (RFA) and microwave ablation. To date, there have been no studies to compare thermoablative techniques with surgical metastasectomy in patients with mSTS.³

Liver ablation

One retrospective study by Pawlik and colleagues⁶⁴ examined 66 patients who underwent hepatic resection, RFA, or both for mSTS liver lesions. Although most patients had GIST, patients with leiomyosarcoma and other sarcoma histologies were included. Compared with patients who underwent surgery alone, those who received RFA (either alone or combined with surgery) had shorter DFS ($P = .002$) with no difference in OS. RFA alone was used in patients who were deemed poor surgical candidates or who had lesions in unfavorable locations, whereas RFA plus surgery was used in those with large lesions not amenable to surgery alone.

Lung ablation

For patients with limited pulmonary metastatic disease but whose performance status or comorbidities prohibit surgery, minimally invasive procedures such as RFA may be of benefit. Palussiere and colleagues⁷⁰ published a series of 100 patients with mSTS of whom 47 had lung metastasis. Twenty-nine patients (with 47 lesions) were treated with RFA, and the remainder received chemotherapy. In 4 of 47 lesions ablated, there was progression on follow-up scans consistent with incomplete response. DFS was 7 months with 1-year and 3-year survival of 92.2% and 65.2%, similar to surgical series. Complications of ablation included pneumothorax (68.7% of cases). Similar results were reported by Nakamura and colleagues,⁷¹ with 1-year and 3-year survival of 88.9% and 59.2% and with pneumothorax occurring in 54% of procedures, with chest tube drainage required in 9%. In contrast, failure to eradicate all pulmonary metastases resulted in significantly worse 1-year and 3-year survival rates (29.6% and 0%).

SUMMARY

Half of all patients with sarcoma are diagnosed with or develop distant metastases during their disease course. The presence of distant metastatic disease significantly affects patient survival, reducing 5-year OS to less than 10% and median overall survival to 8 to 15 months. The most common sites of distant metastatic disease in STS are the lungs and liver. Those with limited metastatic disease may benefit from surgical metastasectomy or minimally invasive ablative approaches for disease control. In retrospective series, 5-year survival rates up to 30% to 50% have been reported. Given the absence of randomized controlled trials and other prospective data and the diversity of STS behavior, treatment decisions should be made in a specialty sarcoma center and with a multidisciplinary team of medical, radiation, and surgical oncologists who specialize in the care of such patients.

REFERENCES

1. Wagner MJ, Amodu LI, Duh MS, et al. A retrospective chart review of drug treatment patterns and clinical outcomes among patients with metastatic or recurrent soft tissue sarcoma refractory to one or more prior chemotherapy treatments. *BMC Cancer* 2015;15:175.
2. Hohenberger P, Kasper B, Ahrar K. Surgical management and minimally invasive approaches for the treatment of metastatic sarcoma. *Am Soc Clin Oncol Educ Book* 2013;457–64. http://dx.doi.org/10.1200/EdBook_AM.2013.33.457.
3. Cardona K, Williams R, Movva S. Multimodality therapy for advanced or metastatic sarcoma. *Curr Probl Cancer* 2013;37:74–86.
4. Leahy M, Garcia Del Muro X, Reichardt P, et al. Chemotherapy treatment patterns and clinical outcomes in patients with metastatic soft tissue sarcoma. The Sarcoma treatment and Burden of illness in North America and Europe (SABINE) study. *Ann Oncol* 2012;23:2763–70.
5. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10–29.
6. Kane JM, Finley JW, Driscoll D, et al. The treatment and outcome of patients with soft tissue sarcomas and synchronous metastases. *Sarcoma* 2002;6:69–73.
7. Jaques DP, Coit DG, Casper ES, et al. Hepatic metastases from soft-tissue sarcoma. *Ann Surg* 1995;221:392–7.
8. Garcia Del Muro X, de Alava E, Artigas V, et al. Clinical practice guidelines for the diagnosis and treatment of patients with soft tissue sarcoma by the Spanish Group for Research in Sarcomas (GEIS). *Cancer Chemother Pharmacol* 2016; 77(1):133–46.
9. Gossot D, Radu C, Girard P, et al. Resection of pulmonary metastases from sarcoma: can some patients benefit from a less invasive approach? *Ann Thorac Surg* 2009;87:238–43.
10. Predina JD, Puc MM, Bergey MR, et al. Improved survival after pulmonary metastasectomy for soft tissue sarcoma. *J Thorac Oncol* 2011;6:913–9.
11. Weiser MR, Downey RJ, Leung DH, et al. Repeat resection of pulmonary metastases in patients with soft-tissue sarcoma. *J Am Coll Surg* 2000;191(2):184–90 [discussion: 190–1].
12. Kim S, Ott HC, Wright CD, et al. Pulmonary resection of metastatic sarcoma: prognostic factors associated with improved outcomes. *Ann Thorac Surg* 2011; 92:1780–7.
13. Abdalla EK, Pisters PW. Metastasectomy for limited metastases from soft tissue sarcoma. *Curr Treat Options Oncol* 2002;3(6):497–505.
14. Rehders A, Hosch SB, Scheunemann P, et al. Benefit of surgical treatment of lung metastasis in soft tissue sarcoma. *Arch Surg* 2007;142:70–5.
15. Smith R, Pak Y, Kraybill W, et al. Factors associated with actual long-term survival following soft tissue sarcoma pulmonary metastasectomy. *Eur J Surg Oncol* 2009; 35(4):356–61.
16. Smith R, Demmy TL. Pulmonary metastasectomy for soft tissue sarcoma. *Surg Oncol Clin N Am* 2012;21:269–86.
17. García Franco CE, Algarra SM, Ezcurra AT, et al. Long-term results after resection for soft tissue sarcoma pulmonary metastases. *Interact Cardiovasc Thorac Surg* 2009;9:223–6.
18. Billingsley K, Burt ME, Jara EG, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. *Ann Surg* 1999;229:602–10 [discussion: 610–2].

19. Stojadinovic A, Leung DH, Allen P, et al. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. *J Clin Oncol* 2002;20:4344–52.
20. Groeschl RT, Nachmany I, Steel JL, et al. Hepatectomy for noncolorectal non-neuroendocrine metastatic cancer: a multi-institutional analysis. *J Am Coll Surg* 2012;214:769–77.
21. Ceppa DP. Results of pulmonary resection sarcoma and germ cell tumors pulmonary metastasis lung resection sarcoma germ cell tumor outcomes. *Thorac Surg Clin* 2016;26:49–54.
22. Gadd MA, Casper ES, Woodruff JM, et al. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. *Ann Surg* 1993;218:705–12.
23. Billingsley KG, Lewis JJ, Leung DH, et al. Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. *Cancer* 1999;85(2):389–95.
24. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37–49.
25. Casson AG, Putnam JB, Natarajan G, et al. Efficacy of pulmonary metastasectomy for recurrent soft tissue sarcoma. *J Surg Oncol* 1991;47:1–4.
26. Chen H, Pruitt A, Nicol TL, et al. Complete hepatic resection of metastases from leiomyosarcoma prolongs survival. *J Gastrointest Surg* 1998;2(2):151–5.
27. Paik ES, Yoon A, Lee YY, et al. Pulmonary metastasectomy in uterine malignancy: outcomes and prognostic factors. *J Gynecol Oncol* 2015;26(4):270–6.
28. Skinner KA, Eilber FR, Holmes EC, et al. Surgical treatment and chemotherapy for pulmonary metastases from osteosarcoma. *Arch Surg* 1992;127:1061–5.
29. Kager L, Zoubek A, Pötschger U, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2003;21:2011–8.
30. Canter RJ, Qin LX, Downey RJ, et al. Perioperative chemotherapy in patients undergoing pulmonary resection for metastatic soft-tissue sarcoma of the extremity: a retrospective analysis. *Cancer* 2007;110:2050–60.
31. Denbo JW, Zhu L, Srivastava D, et al. Long-term pulmonary function after metastasectomy for childhood osteosarcoma: a report from the St Jude Lifetime Cohort Study. *J Am Coll Surg* 2014;219:265–71.
32. Briccoli A, Rocca M, Salone M, et al. Resection of recurrent pulmonary metastases in patients with osteosarcoma. *Cancer* 2005;104:1721–5.
33. Briccoli A, Rocca M, Salone M, et al. High grade osteosarcoma of the extremities metastatic to the lung: long-term results in 323 patients treated combining surgery and chemotherapy, 1985-2005. *Surg Oncol* 2010;19:193–9.
34. Gelderblom H, Jinks RC, Sydes M, et al. Survival after recurrent osteosarcoma: data from 3 European Osteosarcoma Intergroup (EOI) randomized controlled trials. *Eur J Cancer* 2011;47:895–902.
35. Burt BM, Ocejio S, Mery CM, et al. Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extends survival. *Ann Thorac Surg* 2011;92:1202–7.
36. Jaklitsch MT, Mery CM, Lukanich JM, et al. Sequential thoracic metastasectomy prolongs survival by re-establishing local control within the chest. *J Thorac Cardiovasc Surg* 2001;121:657–67.
37. Kandioler D, Krömer E, Tüchler H, et al. Long-term results after repeated surgical removal of pulmonary metastases. *Ann Thorac Surg* 1998;65:909–12.

38. Pogrebniak HW, Roth JA, Steinberg SM, et al. Reoperative pulmonary resection in patients with metastatic soft tissue sarcoma. *Ann Thorac Surg* 1991;52:197–203.
39. Dossett LA, Toloza EM, Fontaine J, et al. Outcomes and clinical predictors of improved survival in a patients undergoing pulmonary metastasectomy for sarcoma. *J Surg Oncol* 2015;112:103–6.
40. Lin AY, Kotova S, Yanagawa J, et al. Risk stratification of patients undergoing pulmonary metastasectomy for soft tissue and bone sarcomas. *J Thorac Cardiovasc Surg* 2015;149:85–92.
41. Mizuno T, Taniguchi T, Ishikawa Y, et al. Pulmonary metastasectomy for osteogenic and soft tissue sarcoma: who really benefits from surgical treatment? *Eur J Cardiothorac Surg* 2013;43(4):795–9.
42. Reza J, Sammann A, Jin C, et al. Aggressive and minimally invasive surgery for pulmonary metastasis of sarcoma. *J Thorac Cardiovasc Surg* 2014;147:1193–200 [discussion: 1200–1].
43. Schur S, Hoetzenecker K, Lamm W, et al. Pulmonary metastasectomy for soft tissue sarcoma—report from a dual institution experience at the Medical University of Vienna. *Eur J Cancer* 2014;50:2289–97.
44. Stephens EH, Blackmon SH, Correa AM, et al. Progression after chemotherapy is a novel predictor of poor outcomes after pulmonary metastasectomy in sarcoma patients. *J Am Coll Surg* 2011;212:821–6.
45. Treasure T, Fiorentino F, Scarci M, et al. Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data. *BMJ Open* 2012;2:e001736.
46. van Geel AN, Pastorino U, Jauch KW, et al. Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. *Cancer* 1996;77:675–82.
47. Åberg T. Selection mechanisms as major determinants of survival after pulmonary metastasectomy. *Ann Thorac Surg* 1997;63(3):611–2.
48. Treasure T, Moller H, Fiorentino F, et al. Editorial comment: forty years on: pulmonary metastasectomy for sarcoma. *Eur J Cardiothorac Surg* 2013;43:799–800.
49. Treasure T, Milosevic M, Fiorentino F, et al. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? *Thorax* 2014;69(10):946–9.
50. Rehders A, Peiper M, Stoecklein NH, et al. Hepatic metastasectomy for soft-tissue sarcomas: is it justified? *World J Surg* 2009;33(1):111–7.
51. Sonett JR. Pulmonary metastases: biologic and historical justification for VATS. Video assisted thoracic surgery. *Eur J Cardiothorac Surg* 1999;16:13–5 [discussion: S15–6].
52. Blackmon SH, Shah N, Roth JA, et al. Resection of pulmonary and extrapulmonary sarcomatous metastases is associated with long-term survival. *Ann Thorac Surg* 2009;88:877–84 [discussion: 884–5].
53. Ferguson PC, Deheshi BM, Chung P, et al. Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. *Cancer* 2011;117:372–9.
54. Neri F, Ercolani G, Di Gioia P, et al. Liver metastases from non-gastrointestinal non-neuroendocrine tumours: review of the literature. *Updates Surg* 2015;67(3):223–33.
55. Page AJ, Weiss MJ, Pawlik TM. Surgical management of noncolorectal cancer liver metastases. *Cancer* 2014;120(20):3111–21.
56. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases. *Ann Surg* 2006;244:524–35.

57. Ercolani G, Grazi GL, Ravaioli M, et al. The role of liver resections for noncolorectal, nonneuroendocrine metastases: experience with 142 observed cases. *Ann Surg Oncol* 2005;12:459–66.
58. Lendoire J, Moro M, Andriani O, et al. Liver resection for non-colorectal, non-neuroendocrine metastases: analysis of a multicenter study from Argentina. *HPB (Oxford)* 2007;9:435–9.
59. Yedibela S, Gohl J, Graz V, et al. Changes in indication and results after resection of hepatic metastases from noncolorectal primary tumors: a single-institutional review. *Ann Surg Oncol* 2005;12:778–85.
60. Vij M, Perumalla R, Srivastava M, et al. Liver metastasis of extremity pleomorphic liposarcoma treated with hepatic resection. *J Gastrointest Cancer* 2014;45(Suppl 1):51–4.
61. Dematteo RP, Shah A, Fong Y, et al. Results of hepatic resection for sarcoma metastatic to liver. *Ann Surg* 2001;234(4):540–7 [discussion: 547–8].
62. Lang H, Nussbaum KT, Kaudel P, et al. Hepatic metastases from leiomyosarcoma a single-center experience with 34 liver resections during a 15-year period. *Ann Surg* 2000;231(4):500–5.
63. Marudanayagam R, Sandhu B, Perera MT, et al. Liver resection for metastatic soft tissue sarcoma: an analysis of prognostic factors. *Eur J Surg Oncol* 2011;37: 87–92.
64. Pawlik TM, Vauthey JN, Abdalla EK, et al. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg* 2006; 141(6):537–43 [discussion: 543–4].
65. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009;27: 1572–8.
66. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* 2009; 27(10):1579–84.
67. Fumagalli I, Bibault JE, Dewas S, et al. A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases. *Radiat Oncol* 2012;7:164.
68. Dhakal S, Corbin KS, Milano MT, et al. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. *Int J Radiat Oncol Biol Phys* 2012;82:940–5.
69. Stragliotto CL, Karlsson K, Lax I, et al. A retrospective study of SBRT of metastases in patients with primary sarcoma. *Med Oncol* 2012;29:3431–9.
70. Palussière J, Italiano A, Descat E, et al. Sarcoma lung metastases treated with percutaneous radiofrequency ablation: results from 29 patients. *Ann Surg Oncol* 2011;18:3771–7.
71. Nakamura T, Matsumine A, Yamakado K, et al. Lung radiofrequency ablation in patients with pulmonary metastases from musculoskeletal sarcomas [corrected]. *Cancer* 2009;115:3774–81.