

Review

Localized Management of Soft Tissue Sarcoma Metastasis: A Review of a Multidisciplinary Approach

Meena Bedi^{1*}, David M. King², Hina Saeed¹, Sean Tutton³, John A. Charlson⁴, Donald A. Hackbarth², John C. Neilson²

Departments of Radiation Oncology¹, Orthopaedic Surgery², Interventional Radiology³, and Medical Oncology⁴ at the Medical College of Wisconsin.

ABSTRACT

The rate of distant metastasis from soft tissue sarcoma (STS) primaries ranges from 25-30%. The most common site of distant spread is hematogenously to the lung, however other sites of metastasis may occur, particularly in the liver and bone. Although systemic therapy has long been the foundation of treatment in patients, particularly with widespread disease, localized treatments of metastatic deposits have been increasingly used and shown to be safe and effective in the control of disease. Moreover, a combination of local and systemic therapy has been shown to improve survival. As the technical advancements in local therapy evolve, it is imperative that patients with metastatic STS are presented in a multidisciplinary setting to ensure that all disease aspects are evaluated and determination of the most effective therapies may be presented to each individual.

Keywords: Soft tissue Sarcoma, Metastasis, Multimodality treatment, Metastatic survival

INTRODUCTION

Soft tissue sarcomas (STS) are a rare malignancy that has unpredictable clinical and pathologic behaviors. In 2014, there were approximately 12,000 new cases of STS in the United States, with an estimated 4000 deaths. Despite excellent rates of local control with surgery, radiation and chemotherapy, metastasis develops in approximately 25-30% of patients (1-5). STS metastasis most commonly spreads to the lungs, however, other areas of distant disease, such as soft tissue, bone, and visceral organs have also been identified (6). The metastatic potential for primary STS may be a result of various factors, and identifying these factors that influence metastatic survival is crucial if

sarcoma specialists are to be able to discuss treatment options and prognosis with their patients.

The mainstay of therapy for disseminated metastatic STS is chemotherapy. However, in patients with limited disease burden, improved survival has been demonstrated in patients that are amenable to multimodality therapy (7). As such, there has been an evolution in this patient population toward the utilization of less invasive treatment modalities such as radiation and percutaneous ablative techniques to treat metastatic lesions (8-12).

The purpose of this review article is to highlight localized therapies including novel techniques in the management of STS metastasis, as well as to review the

***Corresponding author:** Meena Bedi, MD, Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53045, United States; Tel: (414) 805-4496; Fax: (414) 805-4405; Email: mbedi@mcw.edu

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importance of multimodality therapy in patients with this disease.

METHODS

A search of the published literature was conducted for patients with metastasis from STS. The literature search was conducted by using the national library of medicine search engine, PubMed and MEDLINE. For each of the STS, the search terms “metastasis”, “liver”, “lung”, “bone” and “lymph node” were combined with the “soft tissue sarcoma”, “malignant fibrous tumor”, “undifferentiated pleomorphic sarcoma”, “fibrosarcoma,” “liposarcoma”, “leiomyosarcoma”, “rhabdomyosarcoma” and “malignant peripheral nerve sheath tumor”. Pertinent articles describing case reports including multiple cases or clinical studies were selected and references from these articles were also inspected for other relevant articles. Each of the chosen articles were examined and reported in this review. Only publications in English, peer-reviewed journals were included.

Following a thorough investigation, 1,461 manuscripts were identified by the above methods. After excluding duplicate articles, case reports with one subject, and treatment modalities that only investigated systemic therapy, a total of 166 articles that assessed localized therapies for metastatic STS were reviewed meticulously prior to determining which studies would be appropriate for this review. There were a limited number of publications in which specific localized therapies for various subtypes of STS were evaluated. The pertinence of these studies for this manuscript was assessed upon comprehensive review.

RESULTS

Metastectomy

Systemic therapy may not always be efficacious or well tolerated, thus surgery, particularly in the setting of oligometastatic disease, plays a large role in management of selected patients. Prolonged survival has been demonstrated in patients that are amenable to resection (13-17). Several studies have shown that those that undergo complete resection of their pulmonary metastases can have 3 year survival rates of up to 30 to 46% (5, 13, 18-21).

Historically, patients who have had lung-only metastatic disease have had metastatic survival rates between 11 to 38 months (5, 7, 13, 20-27) (**Table 1**). Canter et. al, showed that the median post-metastasis disease-specific survival rates in patients with pulmonary-only metastases were lower for those that were administered chemotherapy compared to those that were treated with surgery alone, 24 vs 33 months (25). Moreover, studies have demonstrated that patients with limited burden pulmonary disease (≤ 5 pulmonary metastases) have higher median metastatic survival of up to 55 months (7).

Perhaps the largest series on metastectomy for STS was from the EORTC where 255 patients with bone or STS pulmonary metastasis underwent resection of their disease. The 2 and 3-year post-metastectomy survival rates were 54% and 45%, respectively. Improved outcomes were associated with disease-free intervals of ≥ 2.5 years, R0 resection, age < 40 and low or intermediate grade disease (14). Other factors that predict for improved overall survival vary between studies. Small tumor size, low grade tumors, increased disease-free interval, and age have all been shown to improve metastatic survival (5, 14, 19, 22, 28).

In contrast to the abundant data on metastectomy for pulmonary metastasis in STS, resection for non-pulmonary metastasis is sparse. Hepatic metastasis often times is a result of intra-abdominal or retroperitoneal STS. Resection of hepatic metastasis from STS primaries has also been shown to be feasible and effective (Table 1) (29-32). DeMatteo, et al. evaluated 331 patients with STS metastasis to the liver, of which 56 underwent complete resection of their hepatic disease. The survival of patients who underwent complete resection was significantly improved compared to those that did not. The 3 and 5-year survival for patients who underwent metastectomy was 50% and 30%, respectively, compared to 13% and 4%, respectively in the 275 patients that did not undergo surgery ($p=0.001$). The median survival in the hepatic resection group was 39 months versus 12 months in the non-resected cohort. Patients who had gross residual disease, however, still had a poor outcome with a median survival of only 8 months (29).

Although regional nodal involvement is considered stage III disease, the presence of nodal disease is a poor prognostic indicator and warrants aggressive management. Lymphadenectomy yields improved outcomes in patients with localized disease (33-35).

Fong *et al.* identified 46 patients with nodal metastasis from STS. Thirty-one patients had lymphadenectomies with curative intent, whereas the 15 had less curative interventions (i.e biopsy) for their nodal disease. Patients who underwent curative lymph node dissection had an improved median survival of 16.3 months versus 4.3 months in those that do not undergo resection ($p=0.003$) (34).

The European Society for Medical Oncology/European Sarcoma Network Working Group has established parameters for management of patients who present with advanced disease. Surgery, with or without the consideration for chemotherapy (based on patient and disease factors) should be recommended in patients with metachronous lung-only lesions, with a disease-free interval of ≥ 1 year. In patients with synchronous lung-only metastasis, chemotherapy is recommended, with surgery reserved in select cases (8).

Certainly, selection of patients who are offered resection is integral in the overall treatment goals, as patients who have large volume or rapidly progressive disease are not typically referred for this localized therapy. Thus, as outlined in other studies, candidates for metastectomy and lymphadenectomy should have resectable disease, be medically fit for operation, have control of their primary disease, and have low burden disease outside the intended resection site (8, 18, (35).

Radiation Therapy

Often times, patients are not amenable to surgical resection due to co-morbidities or preference, and thus radiation therapy is often provided as a treatment choice in this setting. Conventional radiation therapy to the lung for metastatic disease has been shown to produce inferior rates of local control compared to surgery.

Stereotactic body radiation therapy (SBRT) is a form of treatment that delivers conformal and high dose radiation over a relatively few number of fractions, for the treatment of limited sized, (typically ≤ 5 cm), extracranial tumors. This is accomplished through the use of multiple beams, such that a small fraction of the total dose is administered through each beam, thereby effectively minimizing toxicity through the trajectory of the beam (8, 36-38).

Hypofractionated SBRT is an emerging method of treatment for metastatic disease in the lungs. Several studies have evaluated outcomes and toxicity in patients who have undergone SBRT for pulmonary

oligometastasis from various tumor primaries, including STS (8, 39-41). Lesions were usually central or peripherally located with crude local control rates between 67-100% and 2-year survival ranging between 32-87% (36, 39-43).

Dhakal, *et al.* retrospectively reviewed 52 patients with pulmonary sarcoma metastases. Fifteen patients were treated to 74 lesions using SBRT and compared to their non-SBRT cohort. The preferred treatment regimen was delivered over 2 weeks to 50 Gy in 5 fractions using SBRT. The 3-year local control in patients managed with SBRT was 82%, and the median overall survival in patients treated with SBRT was 2.1 years versus 0.6 years in those who did not receive SBRT (41).

SBRT has also been shown to be feasible and effective in sarcoma metastasis to the spine. Levine *et al.*, prospectively reviewed 10 patients with 16 spinal sarcoma metastasis. A median of 30 Gy was delivered to the 80% isodose line, with a dose range of 20 to 30 Gy. Median survival was 11.1 months and there were no major complications in this group of patients (44).

SBRT has also been utilized in the treatment of liver metastasis for various primaries; however, there has been a paucity of data in solely STS metastasis (45, 46).

Radiofrequency Ablation

Malignant cells are susceptible to extreme temperatures, which allows for the use of different techniques to treat metastatic disease. Radiofrequency ablation (RFA) employs temperatures as low as 41°C to cause tumor death and has been historically used in the treatment of unresectable tumors of the lung, liver and kidney (47, 48). This technique has also been shown to provide excellent rates of local control and survival in patients with STS metastasis (9, 12, 49).

Nakamura *et al.* retrospectively reviewed 20 patients with 89 pulmonary metastases from sarcomas, all of which were < 4 cm in size. The median follow-up was 18 months, and the median survival was 12.9 months and the 3-year survival rate was 29%. The only prognostic indicator on univariate and multivariate analyses in this study was the ability to ablate all lung tumors. Patients with complete ablation of all tumors had a 1- and 3-year survival rate of 88.9% and 59.2%, respectively. Pneumothorax was the most common complication, which occurred in 38% of patients. Thus, the authors concluded that RFA for pulmonary

metastases was a safe and beneficial therapeutic option for appropriate candidates (12).

Due to the lack of efficacious systemic therapy for liver metastasis, RFA has also been utilized in patients with hepatic disease from STS primaries (50). Although this experience is limited, RFA does appear to be well tolerated and feasible, although local control of hepatic metastasis is one drawback of RFA in this setting (51).

MD Anderson retrospectively reviewed a cohort of 66 patients who received resection with or without RFA in metastatic STS with hepatic disease. Resection with RFA was performed in 18 patients and RFA alone was done in 13 patients. Patients who underwent RFA or RFA with resection were more likely to develop local recurrence compared to those that underwent resection alone (84.6%, 88.9%, and 57.1%, respectively), although patterns of recurrence did not differ between treatment modality. While local control may be a problem, the ability to repeat the ablative procedures is one unique advantage of RFA (51).

Cryoablation

Cryoablation is an alternative interventional technique that exploits the temperature sensitivity of tumors in STS metastasis. Cryoablation involves the insertion of dual chamber probe(s) into the target tissue and exposes tumors to freezing temperatures of approximately -100°C. Cell death is known to occur when temperatures are below -20°C. Multiple probes can be used to allow for the creation of larger balls of ice and thus, the treatment of larger lesions (52).

Cell death from cryoablation is due to ice formation within the cell through immediate freezing of tissue adjacent to the probe. Gradual cooling away from the probe causes osmotic variation between the cell and membrane, leading to cell dehydration and eventual death (52).

Cryoablation is an approach in the treatment of several malignancies as well as in the treatment of primary STS, however there is minimal data in the setting of STS metastasis. Cryotherapy has been used as an adjunct with hepatic metastasis in the setting of STS. Chua *et al.* assessed 15 patients with STS metastasis to the liver who underwent resection with or without cryoablation. Median survival in this population was 103 months and the median disease-free survival was 14 months. The 5 and 10 year survival was 51% and 37%, respectively (53).

Other Localized Therapies

Chemoembolization

Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure performed to restrict a vascular supply to a tumor through the administration of embolic particles coated with chemotherapeutic agents. These particles are selectively placed into a feeding artery to the tumor and leads to a high drug concentration and tumor ischemia (54-58). Chemoembolization of primary and metastatic liver tumors has shown to be effective and yield a long-lasting effect for therapeutic management (55). Although there has been abundant experience in the setting of hepatocellular carcinomas and metastatic colorectal malignancies, the data on unresectable metastatic STS to the liver is limited.

Rajan *et al.* evaluated tumor response and survival outcomes in 16 patients with STS metastasis to the liver who were treated with chemoembolization with cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol. Chemoembolization was performed 1 to 5 times with a mean interval of 2.8 months followed by imaging 1 month and then every 3 months after completion of this procedure. Median survival was 20 months and from the time of chemoembolization was 13 months. The 2 and 3-year survival from the time of diagnosis was 54% and 50%, respectively. The 2 and 3-year survival from the date of chemoembolization was 50% and 40%, respectively. Thirteen patients responded to chemoembolization and of these, 3 became resectable (55).

Isolated Lung Perfusion

Isolated lung perfusion (ILP) is a method for delivering high dose chemotherapy directly to the pulmonary system without the systemic adverse events. This modality of treatment is typically reserved for patients who are not amenable to surgical resection due to location, number of metastasis, or multiple comorbidities (59, 60). One of both lungs may be targeted with this regimen and has been studied in the setting of phase I trials using doxorubicin, tumor necrosis factor, and cisplatin. The delivery of chemotherapeutic agents is by way of the pulmonary vasculature as this system is where metastatic disease receives their blood supply and nutrients for continued growth. ILP has been investigated in both rat models and patients and been shown to be feasible in terms of drug delivery and minimizing side effects (59, 60).

Multimodality Localized Therapy

The integration of aggressive management in patients with STS may be challenging and various patient factors including performance status, co-morbidities, patient preference and tolerance of therapies must be taken into consideration. Although the implementation of this approach is made on a case-by-case basis, evidence exists that aggressive treatment plays an integral role in improvement of survival (7, 61, 62). Burt *et al.* revealed that patients with metastatic leiomyosarcomas benefited from repeated metastasectomy with a median survival of 70 months compared to their non-leiomyosarcoma counterparts who underwent the same intervention (62).

Bedi *et al.* retrospectively reviewed patients who developed metastatic disease in STS primaries. Patients who underwent multimodality treatment with a regimen consisting of some combination of chemotherapy, surgery, radiation, cryotherapy or RFA had an improved median metastatic survival of 40 months versus 22 months in those patients that underwent single modality treatment, independent of performance status. Additionally, when comparing unimodality, bimodality versus multi-modality (≥ 3) therapies, patients who received therapy with three or more treatment regimens had increased survival (55 months) compared to those that received unimodality (22 months) and bimodality (26 months) therapies (7). Thus, aggressive intervention may be appropriate in certain patient populations with metastatic disease (7, 35, 62).

SUMMARY

There has been an evolution in the management of metastatic STS. Although traditionally systemic therapy is administered in this setting, localized therapies, particularly in patients with limited disease burden, have been increasingly used and may improve patient outcomes.

Patients who present or develop with metastasis should have an extensive staging workup, including imaging of the chest, abdomen, and pelvis and well as imaging of the primary tumor. Moreover, all patients should be presented in a multidisciplinary tumor board in which input from surgical, medical, and radiation oncologists, as well as radiologists and interventional radiologists have been elicited to provide a comprehensive treatment plan. These recommendations may not only be based on disease burden, but also patient

performance status, including comorbidities, tolerance to therapies, social factors and patient wishes.

Patients with limited metastatic disease may be amenable to one or more localized therapies. Typically, metastectomy is recommended, especially in low burden, lung only disease. Patients with poor pulmonary functioning or other issues that may preclude them from surgery may be offered SBRT or ablation. Patients with hepatic metastasis may benefit from chemoembolization or resection depending on the location and extent of disease.

Establishment of the exact modality of treatment is based on extensive discussion in a multidisciplinary setting and these recommendations should be communicated with each patient to ensure they have a complete understanding of current and future treatment options.

Patients with extensive disease may also benefit from localized therapy, particularly in settings where patients manifest symptoms and may need palliation through the use of radiation, ablation or chemoembolization. In the future, emerging localized techniques that target more diffuse disease, such as ILP, may be beneficial in selected patients as well.

CONCLUSION

Although chemotherapy is commonly used in the setting of metastatic STS, there has been increasing evidence for the use of localized therapies to treat these patients. Multimodality management with the addition of localized treatment may prolong survival and control of metastatic disease in appropriately selected patients.

Ongoing research and innovative localized procedures will continue to be developed and allow patients who cannot or prefer not to undergo systemic treatment options for disease control. Given the diversity of the clinical behavior of STS, it is important treatment decisions are made in a multidisciplinary setting with surgical, medical, and radiation oncologists, pathologists and radiologists who specialize in the care of such patients.

Abbreviations

STS, soft tissue sarcomas; SBRT, stereotactic body radiation therapy; Gy, Gray; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; ILP, isolated lung perfusion; NR, not reported; Yr, year.

Table 1: Historical Data: Metastatic Survival-Lung and Hepatic Metastasis

Author	Year	Institution	Total No. of Patients	Total No. of Metastatic Patients	Metastatic Site	Management	Metastatic Survival (%)	Median Metastatic Survival (months)
Billingsley, et al. ⁵	1999	MSKCC	3149	719	Pulmonary	Multimodality	3-yr: 25	15
Bedi, et al. ⁷	2014	MCW	182	55	Pulmonary	Multimodality	3-yr: 45	38
Jablons, et al. ¹³	1989	NIH	NR	74	Pulmonary	Resection	NR	20.3
Garcia Franco et al. ²⁰	2009	Clinica Universidad Navarra (Spain)	NR	22	Pulmonary	Resection	3-yr: 47.6 5-yr: 23.1	19
Smith, et al. ²¹	2009	Roswell Park Cancer Institute	NR	94	Pulmonary	Resection	5-yr: 15	16
Canter, et al. ²⁵	2007	MSKCC	1897	508	Pulmonary	Resection	NR	30
Gadd, et al. ²⁶	1993	MSKCC	716	135	Pulmonary	Multimodality	3-yr: 7	12
Kim, et al. ²⁷	2011	Harvard	NR	97	Pulmonary	Resection	5-yr: 18.9	10.9
De Matteo, et al. ²⁹	2001	MSKCC	331	56	Hepatic	Resection	1-yr: 88 3-yr: 50 5-yr: 30	39
Marudanayagam, et al. ³⁰	2011	Queen Elizabeth Hospital (England)	NR	36	Hepatic	Resection	1-yr: 90.3 3-yr: 48 5-yr: 31.8	24
Jaques, et al. ³¹	1995	MSKCC	981	65	Hepatic	Multimodality	NR	30
Nunobe, et al. ³²	2005	National Cancer Center (Japan)	NR	18	Hepatic	Resection	3-yr: 63.7 5-yr: 34	36

NR: Not Reported

References:

1. Brennan MF, Casper ES, Harrison LB, Shiu MH, Gaynor J, Hajdu SI. The role of multimodality therapy in soft-tissue sarcoma. *Ann Surg.* 1991 Sep;214(3):328-36; discussion 36-8.
2. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol.* 1996 Mar;14(3):859-68.
3. Nijhuis PH, Schaapveld M, Otter R, Molenaar WM, van der Graaf WT, Hoekstra HJ. Epidemiological aspects of soft tissue sarcomas (STS)--consequences for the design of clinical STS trials. *Eur J Cancer.* 1999 Nov;35(12):1705-10.
4. Brennan MF. Management of extremity soft-tissue sarcoma. *Am J Surg.* 1989 Jul;158(1):71-8.
5. Billingsley KG, Burt ME, Jara E, Ginsberg RJ, Woodruff JM, Leung DH, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. *Ann Surg.* 1999 May;229(5):602-10; discussion 10-2.
6. King DM, Hackbarth DA, Kilian CM, Carrera GF. Soft-tissue sarcoma metastases identified on abdomen and pelvis CT imaging. *Clin Orthop Relat Res.* 2009 Nov;467(11):2838-44. DOI: 10.1007/s11999-009-0989-1.
7. Bedi M, King DM, Charlson J, Whitfield R, Hackbarth DA, Zambrano EV, et al. Multimodality management of metastatic patients with soft tissue sarcomas may prolong survival. *Am J Clin Oncol.* 2014 Jun;37(3):272-7. DOI: 10.1097/COC.0b013e318277d7e5.
8. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol.* 2010 Jul;5(7):1091-9. DOI: 10.1097/JTO.0b013e3181de7143.
9. Palussiere J, Italiano A, Descat E, Ferron S, Cornelis F, Avril A, et al. Sarcoma lung metastases treated with percutaneous radiofrequency ablation: results from 29 patients. *Ann Surg Oncol.* 2011 Dec;18(13):3771-7. DOI: 10.1245/s10434-011-1806-0.
10. Yan TD, King J, Sjarif A, Glenn D, Steinke K, Morris DL. Percutaneous radiofrequency ablation of pulmonary metastases from colorectal carcinoma: prognostic determinants for survival. *Ann Surg Oncol.* 2006 Nov;13(11):1529-37. DOI: 10.1245/s10434-006-9101-1.
11. de Baere T, Palussiere J, Auperin A, Hakime A, Abdel-Rehim M, Kind M, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. *Radiology.* 2006 Aug;240(2):587-96. DOI: 10.1148/radiol.2402050807.
12. Nakamura T, Matsumine A, Yamakado K, Matsubara T, Takaki H, Nakatsuka A, et al. Lung radiofrequency ablation in patients with pulmonary metastases from musculoskeletal sarcomas [corrected]. *Cancer.* 2009 Aug 15;115(16):3774-81. DOI: 10.1002/cncr.24420.
13. Jablons D, Steinberg SM, Roth J, Pittaluga S, Rosenberg SA, Pass HI. Metastasectomy for soft tissue sarcoma. Further evidence for efficacy and prognostic indicators. *J Thorac Cardiovasc Surg.* 1989 May;97(5):695-705.
14. van Geel AN, Pastorino U, Jauch KW, Judson IR, van Coevorden F, Buesa JM, 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 Feb 15;77(4):675-82.
15. Creagan ET, Fleming TR, Edmonson JH, Pairolero PC. Pulmonary resection for metastatic nonosteogenic sarcoma. *Cancer.* 1979 Nov;44(5):1908-12.
16. Kang S, Kim HS, Kim S, Kim W, Han I. Post-metastasis survival in extremity soft tissue sarcoma: a recursive partitioning analysis of prognostic factors. *Eur J Cancer.* 2014 Jun;50(9):1649-56. DOI: 10.1016/j.ejca.2014.03.003.
17. Abdalla EK, Pisters PW. Metastasectomy for limited metastases from soft tissue sarcoma. *Curr Treat Options Oncol.* 2002 Dec;3(6):497-505.
18. Casson AG, Putnam JB, Natarajan G, Johnston DA, Mountain C, McMurtrey M, et al. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. *Cancer.* 1992 Feb 1;69(3):662-8.
19. Putnam JB, Jr., Roth JA, Wesley MN, Johnston MR, Rosenberg SA. Analysis of prognostic factors in

- patients undergoing resection of pulmonary metastases from soft tissue sarcomas. *J Thorac Cardiovasc Surg.* 1984 Feb;87(2):260-8.
20. Garcia Franco CE, Algarra SM, Ezcurra AT, Guillen-Grima F, San-Julian M, Mindan JP, et al. Long-term results after resection for soft tissue sarcoma pulmonary metastases. *Interact Cardiovasc Thorac Surg.* 2009 Aug;9(2):223-6. DOI: 10.1510/icvts.2009.204818.
 21. Smith R, Pak Y, Kraybill W, Kane JM, 3rd. Factors associated with actual long-term survival following soft tissue sarcoma pulmonary metastasectomy. *Eur J Surg Oncol.* 2009 Apr;35(4):356-61. DOI: 10.1016/j.ejso.2008.01.004.
 22. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol.* 1996 May;14(5):1679-89.
 23. Gronchi A, Miceli R, Colombo C, Collini P, Stacchiotti S, Olmi P, et al. Primary extremity soft tissue sarcomas: outcome improvement over time at a single institution. *Ann Oncol.* 2011 Jul;22(7):1675-81. DOI: 10.1093/annonc/mdq643.
 24. Stefanovski PD, Bidoli E, De Paoli A, Buonadonna A, Boz G, Libra M, et al. Prognostic factors in soft tissue sarcomas: a study of 395 patients. *Eur J Surg Oncol.* 2002 Mar;28(2):153-64. DOI: 10.1053/ejso.2001.1242.
 25. Canter RJ, Qin LX, Downey RJ, Brennan MF, Singer S, Maki RG. Perioperative chemotherapy in patients undergoing pulmonary resection for metastatic soft-tissue sarcoma of the extremity : a retrospective analysis. *Cancer.* 2007 Nov 1;110(9):2050-60. DOI: 10.1002/cncr.23023.
 26. Gadd MA, Casper ES, Woodruff JM, McCormack PM, Brennan MF. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. *Ann Surg.* 1993 Dec;218(6):705-12.
 27. Kim S, Ott HC, Wright CD, Wain JC, Morse C, Gaissert HA, et al. Pulmonary resection of metastatic sarcoma: prognostic factors associated with improved outcomes. *Ann Thorac Surg.* 2011 Nov;92(5):1780-6; discussion 6-7. DOI: 10.1016/j.athoracsur.2011.05.081.
 28. Choong PF, Pritchard DJ, Rock MG, Sim FH, Frassica FJ. Survival after pulmonary metastasectomy in soft tissue sarcoma. Prognostic factors in 214 patients. *Acta Orthop Scand.* 1995 Dec;66(6):561-8.
 29. DeMatteo RP, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF. Results of hepatic resection for sarcoma metastatic to liver. *Ann Surg.* 2001 Oct;234(4):540-7; discussion 7-8.
 30. Marudanayagam R, Sandhu B, Perera MT, Bramhall SR, Mayer D, Buckels JA, et al. Liver resection for metastatic soft tissue sarcoma: an analysis of prognostic factors. *Eur J Surg Oncol.* 2011 Jan;37(1):87-92. DOI: 10.1016/j.ejso.2010.11.006.
 31. Jaques DP, Coit DG, Casper ES, Brennan MF. Hepatic metastases from soft-tissue sarcoma. *Ann Surg.* 1995 Apr;221(4):392-7.
 32. Nunobe S, Sano T, Shimada K, Sakamoto Y, Kosuge T. Surgery including liver resection for metastatic gastrointestinal stromal tumors or gastrointestinal leiomyosarcomas. *Jpn J Clin Oncol.* 2005 Jun;35(6):338-41. DOI: 10.1093/jjco/hyi091.
 33. Al-Refaie WB, Andtbacka RH, Ensor J, Pisters PW, Ellis TL, ShROUT A, et al. Lymphadenectomy for isolated lymph node metastasis from extremity soft-tissue sarcomas. *Cancer.* 2008 Apr 15;112(8):1821-6. DOI: 10.1002/cncr.23363.
 34. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. *Ann Surg.* 1993 Jan;217(1):72-7.
 35. Cardona K, Williams R, Movva S. Multimodality therapy for advanced or metastatic sarcoma. *Curr Probl Cancer.* 2013 Mar-Apr;37(2):74-86. DOI: 10.1016/j.currprobcancer.2013.03.003.
 36. Le QT, Loo BW, Ho A, Cotrutz C, Koong AC, Wakelee H, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. *J Thorac Oncol.* 2006 Oct;1(8):802-9.
 37. Leksell L. The stereotactic method and radiosurgery of the brain. *Acta Chir Scand.* 1951 Dec 13;102(4):316-9.
 38. Lax I, Blomgren H, Naslund I, Svanstrom R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol.* 1994;33(6):677-83.
 39. Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, et al. Multi-institutional

- phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol*. 2009 Apr 1;27(10):1579-84. DOI: 10.1200/JCO.2008.19.6386.
40. Mehta N, Selch M, Wang PC, Federman N, Lee JM, Eilber FC, et al. Safety and efficacy of stereotactic body radiation therapy in the treatment of pulmonary metastases from high grade sarcoma. *Sarcoma*. 2013;2013:360214. DOI: 10.1155/2013/360214.
41. Dhakal S, Corbin KS, Milano MT, Philip A, Sahasrabudhe D, Jones C, 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 Feb 1;82(2):940-5. DOI: 10.1016/j.ijrobp.2010.11.052.
42. Wulf J, Baier K, Mueller G, Flentje MP. Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol*. 2005 Oct;77(1):83-7. DOI: 10.1016/j.radonc.2005.09.003.
43. Ricardi U, Filippi AR, Guarneri A, Ragona R, Mantovani C, Giglioli F, et al. Stereotactic body radiation therapy for lung metastases. *Lung Cancer*. 2012 Jan;75(1):77-81. DOI: 10.1016/j.lungcan.2011.04.021.
44. Levine AM, Coleman C, Horasek S. Stereotactic radiosurgery for the treatment of primary sarcomas and sarcoma metastases of the spine. *Neurosurgery*. 2009 Feb;64(2 Suppl):A54-9. DOI: 10.1227/01.NEU.0000339131.28485.4A.
45. Rusthoven KE, Kavanagh BD, Cardenas H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol*. 2009 Apr 1;27(10):1572-8. DOI: 10.1200/JCO.2008.19.6329.
46. Fumagalli I, Bibault JE, Dewas S, Kramar A, Mirabel X, Prevost B, et al. A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases. *Radiat Oncol*. 2012;7:164. DOI: 10.1186/1748-717X-7-164.
47. Simon CJ, Dupuy DE. Percutaneous minimally invasive therapies in the treatment of bone tumors: thermal ablation. *Semin Musculoskelet Radiol*. 2006 Jun;10(2):137-44. DOI: 10.1055/s-2006-939031.
48. Dupuy DE, Mayo-Smith WW, Abbott GF, DiPetrillo T. Clinical applications of radio-frequency tumor ablation in the thorax. *Radiographics*. 2002 Oct;22 Spec No:S259-69. DOI: 10.1148/radiographics.22.suppl_1.g02oc03s259.
49. Ding JH, Chua TC, Glenn D, Morris DL. Feasibility of ablation as an alternative to surgical metastasectomy in patients with unresectable sarcoma pulmonary metastases. *Interact Cardiovasc Thorac Surg*. 2009 Dec;9(6):1051-3. DOI: 10.1510/icvts.2009.218743.
50. Jones RL, McCall J, Adam A, O'Donnell D, Ashley S, Al-Muderis O, et al. Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. *Eur J Surg Oncol*. 2010 May;36(5):477-82. DOI: 10.1016/j.ejso.2009.12.005.
51. Pawlik TM, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg*. 2006 Jun;141(6):537-43; discussion 43-4. DOI: 10.1001/archsurg.141.6.537.
52. Biermann JS, Holt GE, Lewis VO, Schwartz HS, Yaszemski MJ. Metastatic bone disease: diagnosis, evaluation, and treatment. *J Bone Joint Surg Am*. 2009 Jun;91(6):1518-30. DOI: 91/6/1518 [pii].
53. Chua TC, Chu F, Morris DL. Outcomes of single-centre experience of hepatic resection and cryoablation of sarcoma liver metastases. *Am J Clin Oncol*. 2011 Jun;34(3):317-20. DOI: 10.1097/COC.0b013e3181e1d078.
54. Hansch A, Neumann R, Gajda M, Marintchev I, Pfeil A, Mayer TE. Transarterial catheter embolization of a sarcoma for preoperative conditioning. *Vasa*. 2010 May;39(2):185-8. DOI: 10.1024/0301-1526/a000026.
55. Rajan DK, Soulen MC, Clark TW, Baum RA, Haskal ZJ, Shlansky-Goldberg RD, et al. Sarcomas metastatic to the liver: response and survival after cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol chemoembolization. *J Vasc Interv Radiol*. 2001 Feb;12(2):187-93.
56. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised

- controlled trial. *Lancet*. 2002 May 18;359(9319):1734-9. DOI: 10.1016/S0140-6736(02)08649-X.
57. Hunt TM, Flowerdew AD, Birch SJ, Williams JD, Mullee MA, Taylor I. Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases. *Br J Surg*. 1990 Jul;77(7):779-82.
58. Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC, et al. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. *Cancer J*. 2003 Jul-Aug;9(4):261-7.
59. Ratto GB, Toma S, Civalleri D, Passerone GC, Esposito M, Zaccheo D, et al. Isolated lung perfusion with platinum in the treatment of pulmonary metastases from soft tissue sarcomas. *J Thorac Cardiovasc Surg*. 1996 Sep;112(3):614-22.
60. Burt ME, Liu D, Abolhoda A, Ross HM, Kaneda Y, Jara E, et al. Isolated lung perfusion for patients with unresectable metastases from sarcoma: a phase I trial. *Ann Thorac Surg*. 2000 May;69(5):1542-9. DOI: 10.1016/S0003-4975(00)01131-0
61. Weiser MR, Downey RJ, Leung DH, Brennan MF. Repeat resection of pulmonary metastases in patients with soft-tissue sarcoma. *J Am Coll Surg*. 2000 Aug;191(2):184-90; discussion 190-1. DOI: 10.1016/S1072-7515(00)00306-9.
62. Burt BM, Ocejio S, Mery CM, Dasilva M, Bueno R, Sugarbaker DJ, et al. Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extends survival. *Ann Thorac Surg*. 2011 Oct;92(4):1202-7. DOI: 10.1016/j.athoracsur.2011.05.052.