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Management of Sarcoma Metastases to the Lung

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Synopsis

Pulmonary metastases are a common manifestation of sarcoma that requires special attention. For decades, surgical resection of pulmonary metastases has been performed, and despite limited randomized data, surgery is increasingly accepted as an integral part in the management of metastatic disease. Although sarcoma is heterogeneous, common prognostic factors have been identified to guide surgeons prior to pulmonary metastasectomy including long disease-free interval, ability to obtain a complete resection, and extra-pulmonary disease control. Patients with adequate pulmonary reserve may undergo resection via thoracotomy or in select cases video-assisted thoracoscopic surgery (VATS). Long-term results indicate resection is potentially curative with significantly improved survival following complete resection. Recurrence, however, is not uncommon with many patients undergoing repeat resection. With advancing surgical technique and adjuvant therapies, patients with high or recurrent tumor burden are increasingly afforded disease control and potential cure. In this review, the prognostic characteristics of pulmonary metastases from sarcoma, pre-operative evaluation, operative technique, long-term outcomes, and management of complex patients are highlighted.

Keywords

Sarcoma; pulmonary metastasectomy; thoracic surgery; prognostic factors; VATS; SBRT

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Introduction

Sarcoma comprises a heterogeneous group of histologic subtypes with a propensity to metastasize to the lungs. Isolated pulmonary metastases occur in as many as 20% of patients diagnosed with soft tissue sarcoma as many as 40% in those with a primary bone sarcoma [1, 2]. Although historically pulmonary metastasis represented advanced disease and the need for palliation, surgical resection for control of disease burden has become a mainstay of therapy and a potentially curative option for those with resectable pulmonary metastasis. The role for surgery continues to evolve with the introduction of adjunctive therapies including radiofrequency ablation, advanced radiation therapy such as stereotactic body radiation therapy (SBRT), and complex salvage operations. These advances have driven the need for complex multidisciplinary care, particularly with the inclusion of a thoracic surgeon [3]. Resection of metastatic pulmonary sarcoma has been reported since the late 1800's; however the first isolated resection of metastatic foci occurred in 1926 by Divis [4]. Despite this, there have been no published randomized controlled trials comparing surgery to systemic therapy or radiation for metastatic sarcoma, though significant research, particularly with the formation of the International Registry of Lung Metastases (IRLM), indicates that pulmonary metastasectomy (PM), when it can be performed, is associated with improved outcomes [4,5].

Many of the original reports of PM for sarcoma were small case series pointing toward improved overall survival with resection in eligible patients when compared to historical controls. For example, one center noted a high incidence of patients with osteosarcoma developing lung metastases follow extremity amputation. A system for iterative complete surgical resection of pulmonary metastases in these patients was developed with some patients requiring up to 9 thoracotomies. Five-year survival in this center's cohort significantly increased from 0 to 32% [4, 6].

The IRLM was formed in the 1990's as a consortium of high volume centers performing PM for a variety of malignancies, including sarcoma. In a long-term follow-up study from the IRLM, 5206 patients underwent metastasectomy with 42% having sarcoma as the primary tumor. A majority of patients underwent open thoracotomy or sternotomy and had an overall survival of 31% at 5 years and 26% at 10 years. Patients with sarcoma, however, were more likely to recur (64%) as opposed to those with epithelial (46%) or germ cell (26%) metastases. Favorable outcomes were reported in those with a longer disease-free interval (DFI), small number of nodules, and complete resection [5].

Guidelines for physicians and surgeons in the treatment of metastatic pulmonary sarcoma have been proposed dating back to Ehrenhaft in 1958; however the lack of randomized controlled trials has limited their overall utility [7]. Rusch et al. concluded that patients should meet the following criteria: 1) control of the primary tumor; 2) ability to resect metastatic disease completely; 3) ability of the patient to tolerate pulmonary resection; 4) absence of extrathoracic metastases; and 5) absence of better alternative systemic therapies [8]. The indications for resection of metastatic sarcoma to the lung continue to evolve as more studies examine the use of minimally invasive surgery, the utility of aggressive resections, and alternate therapies such as SBRT.

In this paper, we review the prognostic factors associated with improved survival following pulmonary metastasectomy for sarcoma, pre-operative evaluation, surgical techniques and management, long-term follow-up, and the complex management of large tumors and recurrent disease.

Prognostic Factors

Although the primary source of sarcoma may be highly variable and includes both indolent and aggressive subtypes, a number of characteristics have been identified to inform a patient's prognosis and treatment plan. It is again important to note that these characteristics have largely been identified based on single center, retrospective reviews that, although generally consistent, may be subject to bias from the pathologic heterogeneity of sarcomas, multiple adjuvant therapies involved, and careful case selection by surgeons [9]. In addition, while the characteristics may be useful in guiding the surgeon as well as the rest of the multidisciplinary team, they do not preclude a patient from undergoing PM, especially in those with limited disease. With this in mind, many of the prognostic factors characterized include the histology of the primary sarcoma, disease-free interval (DFI), number of lesions in the lung, a surgeon's ability to obtain a complete resection, the responsiveness to chemotherapy, and lymph node status. A summary of recent articles examining some of these factors can be found in Table 1.

Histology

Nearly 100 different histologic subtypes of sarcoma with varying grades of differentiation have been identified [10]. Sarcoma is generally divided into the broad categories of soft tissue and primary bone with undifferentiated pleomorphic sarcoma and primary bone being the most likely to metastasize to the lung [2, 11]. Among soft tissue sarcomas, undifferentiated pleomorphic sarcoma (formerly malignant fibrous histiocytoma) is the most common histology (25%), followed by leiomyosarcoma (18%), synovial sarcoma (10%), and liposarcoma (10%) [12]. Similar to osteosarcoma, soft tissue sarcomas arising on the extremities are more likely to metastasize to the lung than those arising from the viscera [13]. There is also an increase in frequency of metastasis associated with increasing histologic grade [14]. Survival varies widely in accordance with the many different histologic subtypes. Blackmon et al. demonstrated a median survival following resection for osteosarcoma, malignant fibrous histiocytoma, synovial sarcoma, and leiomyosarcoma as 28.9, 16.7, 30.2, and 41.8 months, respectively [15].

Disease-Free Interval (DFI)

Disease-free interval is defined as the time from the treatment of the primary lesion to the development of pulmonary metastases. DFI has been a clear prognostic indicator for many years and in nearly all studies. The IRLM showed that patients (including all primary sources of tumor) with a DFI of 0 to 11 months had a median survival of 29 months as opposed to patients with a DFI greater than 36 months where the median survival is 49 months [5]. In a recent retrospective review of 120 patients with pulmonary metastases specifically from sarcoma, Dosset et al. confirmed the results of the IRLM (Figure 1) [12].

Number of metastatic foci

Patients are at risk for developing multiple pulmonary lesions in the setting of metastatic sarcoma. Although several early studies demonstrated the number of metastatic lesions was inversely correlated with survival outcomes, larger studies including a single center study by Billingsley, did not show a significant difference in survival between patients with less than 4 lesions and those with greater than 4 lesions [1,12,16]. There is no universal consensus on what represents the maximum number of lesions, and likely the decision to proceed with surgery should be considered within the context of the patient and whether a complete resection is possible.

Completeness of resection

Complete (R0) resection of metastatic foci is associated with improved outcomes in most studies and is widely considered a requirement before proceeding with PM [1, 4, 16, 17]. Early reports suggested a true R0 resection may only be obtainable in as many as 30% of patients with soft tissue sarcoma metastases, however more advanced imaging and improved surveillance have likely resulted in resection of smaller lesions with fewer intra-operative surprises [1]. Although complete resection is the ultimate goal, treatment strategies are emerging that focus on complete control of disease. For instance, in a patient with multiple lesions some may be controlled with chemotherapy (no growth detected on serial imaging) whereas others may enlarge over time. In this case, the surgeon, in conjunction with a multidisciplinary team, may decide only to resect uncontrolled lesions, thus saving healthy lung parenchyma. Similarly, strategies combining surgery and SBRT are being used, highlighting the importance of individualizing care to achieve control of disease [18].

Response to chemotherapy

Although the need for neoadjuvant chemotherapy is controversial, response to chemotherapy is generally a positive prognostic factor when considering PM, while progression on chemotherapy is associated with worse outcomes. Stephens et al. examined patients who were started on chemotherapy after presentation with a synchronous metastasis, multiple pulmonary metastases, or short DFI. Patients with progression followed by PM (defined as an increase in size or number of nodules while on chemotherapy) had a 4-fold increased risk of death and none were alive at 5 years [19].

Pre-operative Evaluation

Pre-operative Imaging

A majority of patients with metastatic sarcoma initially present with an extrapulmonary primary tumor. Nearly a third of patients are discovered to have a synchronous pulmonary lesion at the time of presentation and the rest are found to have pulmonary metastasis at a later date. Thus surveillance chest imaging is routine for sarcoma patients [1]. Computed tomography (CT) is standard of care for staging of disease (for intermediate or high grade tumors) and for preoperative planning for metastatic sarcoma. High contrast between air in the lungs and soft tissue structures allows for detection of small pulmonary nodules. Metastatic foci typically appear as discrete soft tissue densities with smooth borders as

opposed to the classical spiculated appearance of primary non-small cell lung cancer [20]. Osteosarcoma metastases may appear as benign calcified pulmonary nodules, though as many as 40% of osteosarcoma lesions are not calcified [21]. CT is more sensitive than F18-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging for sarcomas with only 44% of metastatic sarcoma demonstrating FDG avidity [22]. There is some evidence, however, that FDG-PET may be useful in detecting recurrence [23].

Pre-operative Pulmonary Testing

Many patients with metastatic sarcoma will develop recurrent disease, and therefore careful consideration of a patient's preoperative pulmonary functional status must be undertaken. Among those enrolled in the IRLM, 20% of the 5,206 patients underwent repeat resection and 5% underwent three or more procedures [5]. Assessment of the percent-predicted FEV1 and DLCO in patients undergoing repeat resections for pulmonary metastases, demonstrated a 10.8% and 9.7% loss, respectively, three months following surgery. The need for post-resection chemotherapy or bilateral procedures was a predictor for worse lung function following metastasectomy [24].

Timing of Surgery

The timing of surgery has been debatable as some surgeons take an aggressive approach with resection soon after identification of pulmonary metastases and others allow for a diagnostic interval between identification and resection. Allowing an interval between detection and PM may provide the surgeon with clues to the tumor doubling time as well as to whether the patient will respond or progress while on chemotherapy [19]. For patients with few pulmonary lesions and a long DFI, the decision to proceed directly with PM is more clearly indicated, whereas patients with multiple new or rapidly growing metastases are less likely to gain benefit particularly if chemotherapy is not effective in preventing new lesions from appearing [25].

Surgical Technique and Management

Open Technique

Early on, surgical therapy for sarcoma metastases was based on gaining adequate access and visualization in order to perform a complete resection, including removal of any occult or residual disease. Standard posterolateral thoracotomy provided excellent visualization and allowed the surgeon to examine the entire pleural surface [26]. Bilateral lesions, however, are not uncommon with some surgeons performing either two-staged thoracotomies or median sternotomy for access to the bilateral chest cavities, although sternotomy can be particularly difficult for access to the lower lobes or posterior hilum. Some surgeons may also perform a clamshell incision or bilateral anterior thoracotomy. In children, bilateral anterior thoracotomies provided adequate access to the lower lobes with similar peri-operative outcomes to standard posterolateral thoracotomy [27, 28, 29]. Newer trends include limited skin incisions, particularly with video-assisted thoracoscopic surgery, and muscle sparing approaches when open thoracotomy is performed [26].

Video-assisted Thoracoscopic Surgery (VATS)

Video-assisted thoracoscopic surgery was introduced in the early 1990's as a minimally invasive alternative to open thoracotomy. VATS has become an increasingly popular method for pulmonary resection given many studies indicating shorter hospital stays and decreased postoperative lengths of stay while reducing perioperative morbidity and mortality [30, 31]. Given that the IRLM study reported a 16% increase in the number of metastatic nodules found at time of resection, there was a significant concern that even more occult metastases would be missed in the absence of bimanual palpation [5]. Ellis et al. demonstrated that when thoracotomy was performed, significantly more nodules were palpated and resected than were identified on preoperative CT (3.24 vs 2.12, $P=0.001$). Furthermore, significantly more of these nodules were confirmed as malignant on final pathology (2.40 vs 1.60, $P=0.01$). Some argue that missing these additional small nodules identified only by direct bimanual lung palpation may not be clinically relevant, and may not have a significant impact on overall survival and recurrence-free survival [32]. Gossot et al. questioned the need for traditional open thoracotomy and aggressive initial resection as many patients will relapse requiring re-operation, and a repeat thoracotomy is often technically more difficult. On retrospective analysis of patients eligible for wedge resection with less than 2 small lesions (<30 mm), no significant difference was shown among patients undergoing VATS versus open thoracotomy in either 5 year overall survival (52.5% vs. 34%, $P=0.2$) or 3 year disease-free survival (26.4% vs. 24.8%, $P=0.74$) [33]. It is important to note a majority of the 113 patients who received a thoracotomy were more likely to have larger lesions. This represents selection bias and highlights the careful selection of patients for thoracoscopy. With this in mind, several new studies (albeit with mixed tumor histologies) do support the increasing use of VATS in select patients for pulmonary metastasectomy [34, 35, 36]. The controversy of open vs. VATS resection for PM for sarcoma highlights the importance of careful patient selection and understanding disease behavior. The surgeon must balance the minimization of perioperative morbidity through the use of VATS with the risk of potentially inadequate access to often multiple and possibly deep nodules and thus failing to obtain a true R0 resection.

Extent of Resection

Although many studies have indicated better outcomes with complete resection and negative margins, there is little evidence that performing an anatomic resection (i.e. segmentectomy or lobectomy) provides additional benefit as long as an R0 resection is achieved [37]. This is in contrast to primary lung cancer where a larger anatomic resection results in improved staging and a lower risk of recurrence [38]. Given the tendency of metastatic sarcoma to recur and thus the need for additional pulmonary resections, parenchyma-sparing approaches to preserve pulmonary reserve are critically important. For lesions that are technically challenging to remove via wedge resection due to lesion location, segmentectomy may offer an advantage for achieving an R0 resection while sparing lung parenchyma and maintaining adequate lung function [37, 38, 39].

Lymph Node Sampling

Lymphadenectomy is not standard of care of patients with pulmonary metastases as the significance of nodal involvement is unclear, and lymph node involvement is rare in sarcoma [17, 40]. Lo Faso et al. found nodal involvement in only 20% of patients, and involvement was not significantly associated with an overall difference in survival [34]. In the only study in which a systematic mediastinal and hilar lymph node dissection was performed, Pfannschmidt et al. found thoracic lymph node involvement in 20.3% of patients with sarcoma, and an improved median survival for N0 patients (47 months for N0 and 18.3 months for N1, $p=0.036$) [41]. Lymphadenectomy has not been studied in a prospective, randomized study, and the additional dissection needed may increase the difficulty of subsequent resection.

Adjunctive therapies

Whole Lung Irradiation (WLI)

Whole lung irradiation is generally not performed in metastatic sarcoma with the exception of Ewing's sarcoma which is uniquely radiosensitive. WLI for Ewing's sarcoma demonstrates improved survival and little short- and long-term toxicity [42, 43].

Radiofrequency Ablation (RFA)

In one retrospective study, 29 patients with metastatic sarcoma to the lung underwent CT-guided radiofrequency ablation for treatment of a total of 47 pulmonary lesions. The 3-year survival rate was 65.2% (95% CI 0.42–0.81) with a median disease-free survival of 7 months. Although no major complications were reported, 68.7% of patients did develop a pneumothorax from the procedure with half requiring intervention [44].

Stereotactic Body Radiation Therapy (SBRT)

SBRT is a short period of external high-dose, focused radiation therapy, and is associated with minimal side effects [45]. Many sarcoma subtypes have traditionally been considered radioresistant; however the emergence of SBRT is changing this paradigm with some evidence pointing toward a different radiobiology associated with the high dose, hypofractionated SBRT [46]. In one center, SBRT was administered for the treatment of sarcoma metastases to the lung in cases of indolent or progressive disease, bilateral disease, multiple synchronous lesions, or in patients with contraindications to surgery. A significant response was recorded in 96% of patients, and no severe toxicity events were recorded [47]. Long-term results using SBRT for sarcoma metastases are lacking; however several studies have shown a 5-year overall survival ranging from 50% to 60.5% [47, 48].

Long-term follow-up

Long term survival for patients with soft tissue sarcoma following PM has been reported as low as 14%, though newer studies indicate that the 5-year overall survival for such patients is closer to 30–50% [2, 14, 49, 50]. Although survival rates are improving with new therapeutic modalities, recurrence remains as high 83% [12]. Thus, long-term and likely life-long follow-up and surveillance is a necessity, despite controversy as to the optimal follow-

up interval and imaging modality for surveillance [51]. If recurrence is discovered, patients with recurrent pulmonary metastases have undergone repeat resection with favorable outcomes [52]. With the potential for long-term survival, the cost-effectiveness of pulmonary metastasectomy is substantial particularly when compared to chemotherapy alone (\$14,357 per life-year gained for PM vs. \$104,210 for chemotherapy alone) [53].

Complex Management

With only small case series reported, the decision to perform an extended or large resection for pulmonary metastases is challenging. The IRLM reported a 3% pneumonectomy rate, with these patients having the highest perioperative mortality rate [5]. Casiraghi et al. studied the role of extended pulmonary metastasectomy in 29 patients (20.7% had metastatic sarcoma) in whom chest wall, diaphragm, extensive vascular resection and reconstruction, sleeve pulmonary resection or pneumonectomy were performed. Extended resections were found to have acceptable 30-day morbidity and mortality (38% vs 0%, respectively) [54]. Mody et al. reported on a large case series of extended resection for tumor invading the thoracic spine and requiring vertebrectomy. Sarcoma was present in 9 of the 32 cases with 82% achieving an R0 resection [55].

In a systemic review, Migliore et al. summarized the current studies done for extended resection of pulmonary metastasis, specifically pneumonectomy or completion pneumonectomy, confirming it is feasible and justified in select cases (large tumor yet amenable to complete resection, long DFI, etc). Furthermore, utilizing an aggressive approach to resect all metastases present (irrespective of the number of metastases and including repeat resections for all recurrences), resulted in a 5-year survival ranging from 19 to 52% [56]. Advanced tumors with invasion into the mediastinum affecting the heart and greater vessels have also been resected, and despite requiring cardiopulmonary bypass, favorable outcomes have been reported which are surprisingly superior to those obtained with extended resections for non-small cell lung cancer (Figure 2) [57].

Novel Therapy- Isolated Lung Perfusion

Den Hengst et al. recently reported the results of a Phase II clinical trial of pulmonary metastasectomy with isolated lung perfusion (ILuP) using melphalan, an alkylating chemotherapeutic agent. The authors studied 20 patients with sarcoma metastasis and showed an improved local pulmonary control without mortality and with comparable morbidity to historical PM [58]. Follow-up from the initial Phase I study using melphalan ILuP demonstrated an overall survival of 54.8% with no long term pulmonary toxicity [59].

Conclusion

Although sarcoma is a relatively rare disease, pulmonary metastases are a common occurrence among those with sarcoma. Treatment requires a multidisciplinary approach that typically involves the medical oncologist and thoracic surgeon. Despite an absence of randomized data, evidence exists in support of the surgical resection of metastatic sarcoma to the lung parenchyma, specifically in patients with favorable prognostic factors. Long term

results have demonstrated improved survival when compared to historical controls, though recurrence is common and life-long surveillance is required. With evolving indications for surgery and new adjunctive therapies, the overall treatment of pulmonary metastases from sarcoma continues to improve.

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Key points

- Sarcoma is a rare, heterogeneous disease with a common propensity to metastasize to the lungs
- With careful patient selection, pulmonary metastasectomy improves survival when compared to historical controls
- Many favorable prognostic factors have been identified including long disease-free interval and complete (R0) resection
- Video-assisted thoracoscopic surgery (VATS) is increasingly utilized in highly select patients with favorable prognostic characteristics
- Extensive resection for large or recurrent metastatic sarcomas can be safely performed in some patients

Figure 1. Kaplan Meier curve showing overall survival of patients PM from sarcoma stratified by DFI >12 months or ≤12 months. From Dossett LA, Toloza EM, Fontaine J, et al. Outcomes and clinical predictors of improved survival in a patient undergoing pulmonary metastasectomy for sarcoma. *J Surg Onc.* 2015;112(1):103–106, with permission.

Figure 2. Extended resections with support of cardiopulmonary bypass in patients with sarcoma. A. Contrast chest CT of patient with leiomyosarcoma invading pulmonary arteries. B. Survival following extensive resection of sarcoma vs non-small cell lung cancer on cardiopulmonary bypass. From Wiebe K, Baraki H, Macchiarini P, et al. Extended pulmonary resection of advanced thoracic malignancies with support of cardiopulmonary bypass. *Eur J Cardiothorac Surg.* 2006. 29(4):571–7, with permission.

Pulmonary Metastasectomy for sarcoma. A select review of recent series dedicated to pulmonary metastasectomy for sarcoma from 2009 to 2015.

Table 1

Study	Year	Sample Size	Histologic Subset ^a	Overall Survival (OS)	Disease-Free Interval (DFI)	Completeness of Resection ^b	Preoperative Chemotherapy	VATS (%)
Dossett LA et al. [11]	2015	120	• Undifferentiated pleomorphic (25%)	5-year survival: 44%	MOS ^d <12m: 43m MOS >12m: 93m (P=0.004)	R0 MOS: 29.6m R1/2 MOS: 6.3m (P=0.002)	22%	63
			• Osteosarcoma (18%)					
			• Leiomyosarcoma (18%)					
Blackmon et al. [15]	2009	234	• Osteosarcoma (19.5%)	5-year survival: 26%	N/A	N/A	100%	1.7
			• Leiomyosarcoma (17.5%)					
			• MFH ^c (14.1%)					
Smith et al. [17]	2009	94	• Leiomyosarcoma (22%)	5-year survival: 15%	MOS <25m: 13.5m MOS >25m: 32m (P=0.001)	R0 MOS: 22m R1 MOS: 11.5m (P<0.0001)	MOS Yes: 12m MOS No: 16m (P=0.2)	N/A
			• Synovial sarcoma (18%)					
			• MFH (16%)					
Gossot et al. [33]	2008	113	• Synovial sarcoma (21.7%)	5-year survival: 52.5%	N/A	N/A	N/A	27.4
			• MFH (20%)					
			• Osteosarcoma (15%)					
Reza et al. [60]	2013	145	• Leiomyosarcoma (24%)	5-year survival: 42%	Mean DFI 30.4 +/- 39.4m	5-yr OS R0: 42%	77.1%	25.5
			• Osteosarcoma (16%)					
			• Synovial Sarcoma (16%)					
Kim et al. [61]	2011	97	• Osteosarcoma (17.5%)	5-year survival: 50.1%	5-yr OS <12m: 21% 5-yr OS >12m: 65% (P<0.0001)	5-yr OS R0: 54% (P=0.004)	N/A	18.6
			• MFH (15.4%)					
			• Leiomyosarcoma (13.4%)					
Mizuno et al. [62]	2012	52	• Osteosarcoma (42%)	5-year survival: 50.9%	5-yr OS <12m: 17.2% 5-yr OS >12m: 38.3% (P=0.003)	5-yr OS R0: 54.2% (P<0.001)	N/A	59
			• MFH (14%)					
			• Liposarcoma (12%)					
García Franco et al. [2]	2009	52	• Osteosarcoma (59.6%) • Ewing's sarcoma (23.1%)	5-year survival: 31%	5-yr OS <20m: ~20% 5-yr OS >20m: ~42% (P=0.03)	N/A	N/A	19

Study	Year	Sample Size	Histologic Subset ^a	Overall Survival (OS)	Disease-Free Interval (DFI)	Completeness of Resection ^b	Preoperative Chemotherapy	VATS (%)
			•					
Raciborska A et al. [63]	2015	38	•	3-year survival: 60.7%	N/A	N/A	100%	0

^aThree most common histologic subtypes

^bR0 is equivalent to complete resection or negative margins

^cMFH: Malignant fibrous histiocytoma

^dMOS: median overall survival