Surgical Treatment of Metastatic Pulmonary Soft-Tissue Sarcoma

The lung is the most frequent site of metastasis from soft-tissue sarcomas. Due to the relative resistance of sarcoma to either chemotherapy or radiotherapy, compared to other solid tumors, surgical management of

Introduction

Soft-tissue sarcomas represent fewer than 1% of all new malignancies, and distant metastases are the most common cause of death from these mesenchymal tumors. The incidence of metastases is 5% in patients with low-grade tumors but is as high as 40% in patients with intermediate- or high-grade sarcomas of the extremity.

The most common site of distant spread of sarcomas is the lung. Thus, a new pulmonary nodule is likely to be metastatic if the primary malignancy was a sarcoma. Metastases may occur infrequently in the skin, soft tissues, liver, and, in 3% of cases, the lymph nodes. Although no prospective, randomized trials have evaluated the efficacy of surgical resection of pulmonary metastases from soft-tissue sarcomas, multiple retrospective studies support the use of metastasectomy in selected patients. Many single-institution series report 5-year actuarial survival rates of 15% to 35% after complete resection. However, survival data are usually presented without the true “denominator,” and patients with limited disease amenable to resection are likely to have favorable tumor biology.[1]

Recently, these single-institution results have been verified with the publication of two large multi-institutional international retrospective databases: the European Organization for Research and Treatment of Cancer (EORTC)–Soft Tissue and Bone Sarcoma Study Group[2] and the International Registry of Lung Metastases.[3]

History of Pulmonary Metastasectomy

In 1882, Weinlechener performed the first operation to remove two pulmonary metastases (en bloc chest wall resection) in a patient with sarcoma who subsequently died 1 day later.[4] Kronlein successfully resected a chest wall sarcoma and its pulmonary metastasis in 1883.[5] After 7 years, the patient died with recurrent disease.

Alexander and Haight published the first report on the feasibility of reoperation (8 months after the first operation) for secondary sarcomas to the lung in 1947.[6] In 1965, Thomford et al advocated the surgical treatment of pulmonary metastases in highly selected patients with a variety of primary malignancies.[7] In 1971, Martini et al[8] reported a 5-year survival rate of 32% and a 20-year survival rate of 18% after surgical extirpation of pulmonary metastases in patients with osteogenic sarcoma.
Prior to these reports, patients with sarcoma who developed pulmonary metastases died of pulmonary disease with no 5-year survivors. These results demonstrated the safety and survival benefits of pulmonary metastasectomy in patients with sarcoma and subsequently led to the expansion of the indications for resection in soft-tissue sarcomas, as well as tumors of epithelial origin.

**Characteristics of Secondary Pulmonary Sarcomas**

**TABLE 2**

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<th>Incidence and Correlation of High-Grade Lesions and Pulmonary Metastases</th>
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A prospective database from Memorial Sloan-Kettering Cancer Center[9] outlined disease patterns in patients with soft-tissue sarcomas and pulmonary metastases. The median overall follow-up was only 9.7 months, and most patients received optimal multimodality therapy. Important data on tumor location and histology were provided.

In 18% of all patients, the pulmonary metastases presented synchronously with the primary tumor, whereas in 38% of cases, the metastases developed metachronously. Soft-tissue sarcomas of the extremity and trunk accounted for 65% of all lung metastases (Table 1). This distribution is similar to data from the Roswell Park Cancer Institute.[10]

According to the Memorial Sloan-Kettering and EORTC databases, the frequency of histopathologic subtypes of soft-tissue sarcoma that metastasize to the lung is as follows: leiomyosarcoma (19% to 21%), malignant fibrous histiocytoma (18% to 24%), liposarcoma (12%), synovial cell sarcoma (14% to 23%), fibrosarcoma (10% to 12%), and undifferentiated sarcoma (9%).[2,9] The incidence of pulmonary metastasis correlates with the incidence of high-grade differentiation within each histologic group (Table 2). The majority (90%) of all lung metastases develop in patients whose primary tumor was high grade; 10% are of low-grade origin.

**Evaluation and Follow-up of Primary Tumor**

**FIGURE 1**

Diagnosis of Sarcoma Metastatic to the Lung

After surgical treatment of the primary soft-tissue sarcoma, patients should be followed with physical examinations and chest radiographs at 3-month intervals for the first 2 years (Figure 1). Changes in plain radiographs or physical findings warrant the performance of a chest computed tomographic (CT) scan. The frequency of follow-up assessments is predicated on the fact that approximately 80% of all recurrences occur within the first 2 years after primary resection. Moreover, there is a 10-fold likelihood that the new lung lesion is a metastatic deposit rather than a lung primary.

If there is no evidence of disease after 2 years, patients are then followed in a similar fashion every 6...
months. At 5 years, yearly examinations and chest radiographs are sufficient.

**Indications for Surgery**

When a suspicious pulmonary lesion is identified, a fine-needle biopsy may not be necessary to establish the diagnosis, especially in a high-risk patient (Figure 2). An excisional biopsy at surgical exploration is recommended. However, exploration may be negative in up to 16% of patients. Patients are eligible for metastasectomy if the following criteria are fulfilled: (1) disease at the primary site is controlled; (2) the patient has no other extrathoracic disease; (3) the patient has no significant comorbidities contraindicating a thoracotomy; (4) pulmonary function tests indicate that the patient can tolerate complete resection; (5) there is no extensive involvement of the mediastinum or chest wall; and (6) there is a reasonable likelihood that a curative resection can be performed.

At the Fox Chase Cancer Center, we further select for patients with favorable biological behavior. If the metachronous pulmonary lesion(s) has a short disease-free interval (ie, less than or equal to 6 months), a repeat CT scan 3 months later showing multiple new nodules would select out patients who would not have benefited from a resection. Patients with radiographically stable, resectable nodules on repeat scan or if the disease-free interval is greater than 6 months, indicating a tumor with a longer doubling time, are candidates for curative resection.

**Operative Approach**

Preoperative bronchoscopy is performed to evaluate endobronchial involvement. The surgical objective is to perform a complete resection and remove the minimal amount of functioning lung in anticipation of future resections. For most lesions, a wedge resection is appropriate with a margin of greater than 5 mm, if possible.

A posterolateral thoracotomy is the standard approach for unilateral lesions. A median sternotomy; staged, bilateral, posterolateral thoracotomies; or a clamshell thoracotomy (bilateral anterolateral thoracotomy) is used for bilateral lesions.

Some authors advocate bilateral exploration in every instance since CT scans may underdiagnose the extent of disease by 25% to 50%. The International Registry of Lung Metastases found a 25% incidence of underestimation and a 14% incidence of overestimation. Early detection and excision have not been shown to improve survival, and multiple reexcisions are an acceptable option.

With the advent of high-resolution spiral CT scans and newer biological imaging modalities, such as fluorodeoxyglucose–positron emission tomography (FDG-PET), the accuracy of diagnosis may be improved.

**New Radiographic Modalities for Diagnosis: PET**
PET technology utilizes special radiation-sensitive cameras, which detect radioactive isotopes that decay by positron emission. Fluorine has been commonly used in tumor localization. [18F]-2-Fluorodeoxyglucose (FDG) is a glucose analog that accumulates in cells and thus is a convenient measure of metabolism. FDG becomes phosphorylated to FDG-6-PO4, which is preferentially trapped in tumor cells. The imagery can be quantified by the actual number of positron emissions or by calculating a standardized uptake ratio, a value that is normalized for the patient’s body weight and injected dose. It is capable of detecting metastases by virtue of their metabolic differences from surrounding normal tissue. The utility of PET has been documented with solitary pulmonary masses; it is less well studied for multiple masses. False positives commonly occur with active inflammatory or infectious lesions; false negatives occur with tumors that have relatively low metabolic activity as well as small lesions (< 1 cm) due to limited resolution. At this time, PET is being used in conjunction with CT scan or MRI as a complementary diagnostic tool.

**Video-Assisted Thoracic Surgery**

The utility of video-assisted thoracic surgery (VATS) is limited for several reasons. First, many lesions that can be palpated intraoperatively may be overlooked at thoracoscopy. McCormack et al identified 10 of 18 patients with positive preoperative CT scans and initial thoracoscopy who had additional lesions at thoracotomy.[14] Second, resection of multiple secondaries may be difficult and incomplete with VATS, and the potential for port-site recurrence is a distressing complication.[15] Also, adhesive pleuritis encountered at reoperation may render VATS technically difficult or impossible.

Lin et al reviewed the experience with VATS metastasectomy at multiple institutions between 1991 and 1998, including only six patients with metastatic sarcoma.[16] All lesions were removed by VATS, and no thoracotomies were required. Hospitalization after VATS was reported to be 4.4 ± 2.1 days. Mean survival was 28 months for all histologic tumors combined. The incidence of locoregional recurrence was 31%, although no port-site recurrences were noted. Among the 18 patients who had a locoregional recurrence, technical failure was cited as the cause in 3 patients.

**Predictors of Survival**

Multiple studies have shown that the most important favorable predictor of survival is the ability to completely resect all disease.[2,3,9-11] The incidence of complete resection ranges from 57% to 88%.[2,10,17,18] Upon multivariate analysis, markers indicative of an unfavorable tumor biology, such as a rapid tumor doubling time, a short disease-free interval, the need for a radical excision, and the assignment of high-grade differentiation, appear to have a significant negative impact on survival (Table 3). Specific histologies, such as uterine sarcomas, seem to have a relatively favorable prognosis.[9,19] Only two studies have identified patient age > 40 years and age > 50 years old as poor prognostic indicators on multivariate analyses.[2,9] Although involvement of mediastinal or
hilar lymph nodes or endobronchial metastasis is rare (incidence of 4%), survival is less than 6 months if either is found.[18,20]
Data from the National Cancer Institute showed that, among patients presenting with synchronous lesions, 54% had unresectable pulmonary nodules.[18] However, survival in patients who underwent complete pulmonary metastasectomy was equal to that in those with completely resectable metachronous lesions.
Factors that have little impact on survival are gender, location of the primary tumor, number of metastases,[9,21] type of surgical access,[2] unilateral or bilateral disease,[20] and the use of chemotherapy either before or after resection.[20-22]

Survival Rates

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<td>Survival Following Pulmonary Metastasectomy for Soft-Tissue Sarcoma</td>
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Survival data quoted in the literature come from retrospective reviews and are conventionally calculated from the date of diagnosis of the pulmonary metastasis (Table 4). These data typically include a heterogeneous population of sarcomas, many of which have been treated with chemotherapy and/or radiation therapy. Some reviews include osteogenic sarcomas, a histologic subtype that responds well to adjuvant therapy, in contrast to adult soft-tissue sarcomas. Furthermore, most median follow-up durations are less than 5 years, and, therefore, the projected or actuarial 5-year survival rate is reported. Usually, this results in an underestimation of the actual 5-year survival rate.[10]
Finally, the favorable biological behavior of the tumors may underlie the favorable survival data. This possibility is supported by anecdotal reports suggesting that no resection[1] or later resection[12] do not have a negative impact on survival.
Although the data are inconclusive and depend on patient selection and the completeness of resection, the oft-quoted overall 5-year survival range of 30% to 40% is real. Until prospective, randomized trials are conducted, the resection of highly selected patients with metastatic soft-tissue sarcoma, applied empirically, may render a subset of patients cured.

Recurrence and Reoperation

The incidence of recurrent disease after complete resection of pulmonary metastases ranges from 53% to 61%.[3,19] Two-thirds of all recurrences are intrathoracic and one-third are extrathoracic.[3,19] Creagan et al noted that 10% of recurrences were situated near the original primary and 23% were distant metastases.[19] Verazin et al reported that local recurrence, whether identified before or after pulmonary resection, was a poor prognostic indicator.[10]
Nonetheless, patients with recurrent pulmonary metastases should be reevaluated for resection. Retrospective data reveal a median survival of 25 to 28 months among patients undergoing resection vs 7 to 10 months for unresected patients.[23]
Casson et al reviewed the results of repeat pulmonary metastasectomies in 34 patients with soft-tissue sarcoma. Resectability was the best predictor of survival. Patients with solitary nodules had a median survival of 65 months, as compared with 14 months in patients with two or more nodules (Table 5). In contrast, Rizzoni et al did not find a difference in actuarial survival after stratifying for the total number of operations.[24] Pogrebniak and Pass reported a median survival of 19.3 months after re-resection.[25] Rizzoni et al showed that patients with a longer second disease-free interval (³ 6 months) had a better outcome than those with shorter disease-free interval of < 6 months (median survival, 24 vs 7.5 months).

Alternative Treatments

Adjuvant and Neoadjuvant Chemotherapy

After pulmonary metastasectomy, relapse occurs most frequently in the pleura and lungs, suggesting the presence of micrometastatic disease that may not have been detected at the time of resection. However, unlike osteosarcomas, adjuvant chemotherapy[20,21] or neoadjuvant chemotherapy has not been shown to provide a survival benefit in patients with soft-tissue sarcomas.[21,22]

In a retrospective analysis of neoadjuvant chemotherapy using doxorubicin, cyclophosphamide (Cytoxan, Neosar), and dacarbazine (DTIC), Lanza et al reported on 24 patients who subsequently underwent thoracotomy for surgical extirpation of disease. Median survival was 18.5 ± 5.9 months, with an actuarial survival rate of 22%. Of the 24 patients, 5 (21%) had a complete clinical response (not verified by histology), and all developed recurrences in the lung within 4 to 57 months. A prospective, randomized, international trial is currently assessing the value of induction chemotherapy in the management of this disease. Targeted, biologically based therapy, as well as innovative approaches to counter genetic drug resistance, will hopefully enhance the success of future treatment of metastatic disease. Multimodality therapy may ultimately prove to be more successful than surgery alone.

Isolated Lung Perfusion

Isolated lung perfusion (ILP) is an alternative modality for the treatment of lung metastases for patients who are surgically unresectable, unresponsive to systemic chemotherapy, or dose-limited due to the systemic complication rate. This offers a selective delivery of effective drug concentrations to one or both lungs while keeping drug levels in other organs at a minimum. Various animal models and phase I studies using doxorubicin, tumor necrosis factor, and cisplatin have been described.

Isolated lung perfusion provides intense organ-only chemotherapeutic drug delivery in patients with isolated organ metastases. This approach is based on the premise that the majority of metastatic tumors derive most of their nutrient blood supply from the pulmonary artery. The anatomy of the pulmonary vasculature allows for the delivery of antitumor agents via isolated lung perfusion. Memorial Sloan-Kettering Cancer Center investigators have reported prolonged survival among rats with unilateral lung pulmonary metastases treated with isolated lung perfusion of doxorubicin.[26] In a phase I study, eight unresectable patients with a variety of sarcomatous histopathologies were treated with doxorubicin administered by isolated lung perfusion.[26] At a median follow-up of 11 months, only three of these patients were still alive.

Regional Lung Perfusion

Currently, isolated lung perfusion requires a thoracotomy. As a result, less invasive methods are being explored. Regional lung infusion involves the administration of drug distal to a balloon-tipped catheter in the pulmonary artery.[27] We await further data from both experimental and clinical phase I studies of this intervention. With newer and more innovative chemotherapeutic agents and with methods to increase the sensitivity of response in the target tissue, the future may hold more hope for this aggressive therapy.

Recent Data on Genetic Markers

In a study of 22 patients, Tarkkanen et al performed comparative genomic hybridization analyses on DNA samples derived from the primary tumors and their matching pulmonary metastases. All paired
samples revealed shared genetic alterations, as well as differences in DNA sequence copy numbers during the progression of disease.[28] Gaining an understanding of the genetic changes in the primary vs metastatic cells may help explain the tumors’ propensity for pulmonary parenchyma and also guide the development of genetic therapeutics.

**Conclusions**

Until more effective therapy becomes available, surgical resection of metastases is the standard of care in selected patients with soft-tissue sarcoma that metastasizes to the lung. Patients must be carefully selected for this approach, with no evidence of active disease outside the thorax, as well as adequate pulmonary reserve to survive a resection. In addition, the surgeon must ensure that a complete resection is possible. During the resection, care must be taken to prevent an involved margin and to prevent spillage of the tumor contents into the pleural space.

If a careful approach to patient selection and surgical technique is taken, a 5-year survival rate of 30% to 40% can be obtained after pulmonary metastasectomy for soft-tissue sarcomas. To date, no adjunctive therapy has been shown to affect ultimate survival.

**References:**


14. McCormack PM, Bains MS, Begg C, et al: The role of video-assisted thoracic surgery in the


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