

Treating metastatic sarcomas locally: A paradoxe, a rationale, an evidence?

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Abstract

Purpose: The mainstay of first line treatment in metastatic sarcomas is chemotherapy with response rates of $\approx 25\%$ but the optimal management of further events is debated. We assessed the benefit of local metastatic treatment in metastatic sarcomas.

Results: Local control of local treatment strategies ($\approx 85\%$) is excellent but highly institution-dependent and subject to selection biases. Formal evidence of an improvement of survival with local ablative treatments has been limited to retrospective studies. On the other hand, some chemotherapy trials are inconclusive because about 20% of patients receive local metastatic ablation as it is considered unethical to omit

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local treatment in these patients. Further, technology has made surgery, stereotactic irradiation and radiofrequency ablation highly effective on local control with limited morbidity.

Conclusion: The benefit on survival of metastatic ablation deserves prospective studies integrating quality of life, cost effectiveness and patient-reported outcomes assessment.

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1. Introduction

Sarcomas represent a rare (1% of cancers) and heterogeneous group of about 100 subtypes of soft-tissue and bone tumors of mesenchymal origin [1,2]. When surgically removed at an early stage, sarcomas can be cured [1]. However, up to 50% of patients develop metastases during the course of their disease [3]. Median survival measured from the diagnosis of metastases has improved from 12 to over 18 months in the last decades [4]. Such improvement is multifactorial, including advances in imaging, lines of systemic treatment, better supportive care and metastatic ablation. Chemotherapy remains the standard of care of metastatic sarcomas but hardly cures any patient and rather prolongs survival by a few weeks or months. Performed alone, it results in 5-year overall survival rates of less than 10% with exceptional long survivors [5,6]. Further, most series include both oligometastatic (defined as 1–3 or 6 synchronous metastases) and polymetastatic patients. These might overestimate the benefit of chemotherapy in polymetastatic patients. The management of metastatic sarcomas raises several other controversial issues. It is uncertain whether local metastatic ablation truly improves outcomes or rather represents a selected population with slowly progressive limited tumor bulk of spontaneously better prognosis regardless of treatment. Additionally, recent evidence suggests that numerous metastatic patients indeed receive metastatic resection in addition to systemic treatment [7]. Local metastatic treatments are associated with chemotherapy delivered sequentially or perioperatively, or may be used as exclusive therapy. Lung metastasectomy has been performed in many cancers for more than 20 years [8]. In sarcomas, lung metastases are the predominating site of metastases and the exclusive site in over 50% of patients at first metastatic event [9–11]. Lung metastases are rarely symptomatic and often discovered during follow-up Computed Tomography scan (CT). Extra-pulmonary and atypical metastatic sites become more likely with prolonged disease course [12,13]. While surgery has the largest ground of evidence, other local ablative techniques like radiofrequency ablation (RFA), and focused high-dose whole-body stereotactic radiation therapy (SBRT) also show promising local control rates and excellent tolerance for pulmonary and extra-pulmonary metastases.

In the present review, we addressed the current level of evidence for local ablative treatments in metastatic sarcomas.

2. History of local treatments in sarcomas

Pulmonary metastasectomy was first reported by Weinlecher in 1882 and by Divis in 1927 as a planned procedure [8]. Following publication of a first case series, Thomford described the principles of lung metastasectomy in 1965 [8]. Both cytotoxic chemotherapy and metastasectomy emerged in the 1970s as major advances in sarcomas (and in colorectal cancers). Moreover, sarcomas occur in young patients and are often relatively chemoresistant. Both reasons provided a strong rationale for aggressive local management of metastases from sarcomas. Among 184 osteosarcoma patients treated at the Memorial Sloan Kettering Cancer Center by limb amputation, 75% presented lung metastases within 18 months of their primary and there were no 5-year survivors [14]. In contrast, a pilot study by Martini et al., in 1971, reported a 3-year survival of 40% in 22 patients after lung metastasectomy [15]. Eligibility criteria for surgery were controlled primary tumor, planned complete resection, adequate cardio-pulmonary function and absence of progressive extra-thoracic metastases. Since then, lung metastasectomy has been performed on a case-by-case basis, with yet limited overall evidence. In the same period, doxorubicin and ifosfamid-based chemotherapy also considerably changed the management of metastatic sarcomas. However, first-line chemotherapy yields limited overall response rates in the order of 10–25% and aims at improving three-month progression-free survival (PFS), suggesting that sustained response is rarely achievable [5]. Second-line (and over) systemic therapies are even less supported despite being routinely performed in practice [5]. Moreover, such sarcoma subtypes as alveolar and clear cell sarcomas have been very poorly sensitive to chemotherapy (although this may change with new histology-driven targeted therapies) (Fig. 1).

3. Strategy adapted on metastatic burden

The justification of treating metastases aggressively includes [16]:

- (1) *Anecdotal experience* suggests that selected patients benefit from metastatic ablation, irrespective of systemic therapy.
- (2) *Consolidative local therapy* yields good outcomes in partial responders to systemic therapy.

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