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SARCOMAS (SR PATEL, SECTION EDITOR)

The Evolving Role of Radiation Therapy in Patients with Metastatic Soft Tissue Sarcoma

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Abstract

Purpose of Review The management of metastatic disease is evolving. As systemic therapies continue to improve, there is increasing recognition that local therapy to distant sites of disease impacts outcomes among many histologies, including sarcoma. Various local therapy strategies exist, but radiation therapy (RT) is particularly critical as it provides a non-invasive, yet locally ablative strategy for metastatic management.

Recent Findings Various delivery techniques including stereotactic body radiation therapy (SBRT) or hypofractionated RT can escalate the biologic dose while avoiding normal tissues in order to reduce tumor burden, provide durable local control, palliate symptoms, potentially prevent further seeding of metastatic lesions, and potentially prolong survival.

Summary This review summarizes the current state of the literature on the important role of RT for the treatment of metastatic sarcoma organized by the site of metastatic disease. Particularly for patients presenting with oligometastatic or oligoprogressive disease, consolidative RT is an important local therapy strategy to be considered in a multidisciplinary setting.

Keywords Sarcoma · Metastatic · Radiation · Stereotactic radiation · Stereotactic body radiation therapy · Palliative radiation

Introduction

Soft tissue sarcoma (STS) management is complex, both in the localized and the metastatic settings. For patients that present with localized disease, the mainstay of treatment is surgical resection in combination with either preoperative or post-operative radiation therapy (RT). Conservative limb-sparing surgery followed by RT produced equivalent survival to amputation in a landmark trial by Rosenberg et al. [1]. Subsequent trials conducted by Yang et al. and Pisters et al. confirmed the benefit of RT in improving local control (LC) compared with limb-sparing surgery alone [2, 3]. Using this combined modality treatment strategy, local recurrence rates for STS are estimated to be between 8 and 15%. Unfortunately, despite optimal management of the primary tumor, patients often have a relatively high competing risk of distant metastasis (DM). Approximately 25–40% of STS patients will develop DM with increased risk for those patients with larger tumors or with intermediate/high grade histologies [4–6]. Furthermore, even with advances in chemotherapy, overall survival rates for sarcoma have not budged over the past few decades [4].

The most common site of DM is the lungs (70–80%), followed by the bone, liver, and brain [7, 8]. To prevent hematogenous dissemination of the primary tumor, it was hypothesized that the addition of adjuvant chemotherapy would decrease rates of DM and improve survival. However, a large meta-analysis of early trials which tested the use of adjuvant chemotherapy in STS failed to demonstrate a significant overall survival (OS) advantage [9]. The EORTC recently tested the efficacy of post-operative doxorubicin + ifosfamide in higher grade STS, but there was no detectable survival benefit to the addition of chemotherapy [10].

Once patients develop metastatic disease, the median survival is estimated to be 12–19 months, but these statistics vary widely depending on histology and grade. Prognostic factors that predict for improved response to chemotherapy include

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good performance status, young age, and absence of liver metastases [11]. Anthracycline-based chemotherapy with doxorubicin ± ifosfamide continues to remain the standard first-line therapy in the majority of patients with metastatic STS; however, gemcitabine-based regimens are also considered in certain clinical scenarios [12, 13]. Chemotherapy for these patients is given with palliative intent, and yields an objective response rate of only ~ 33% with the majority of patients eventually progressing while on systemic therapy [14]. This general chemoresistant nature of STS continues to make the management of metastatic disease challenging.

Unlike most other epithelial solid tumor types, STS exhibit numerous copy-number alterations yet an overall low mutational burden with only a few genes (*TP53*, *ATRX*, *RB1*) found to be recurrently mutated [15]. Due to the lack of druggable molecular alterations, there are limited targeted therapy options of for STS management. Pazopanib, a multitargeted tyrosine kinase inhibitor, was recently approved to use as a second-line therapy in STS due to demonstrated progression-free survival (PFS) prolongation relative to placebo [16]. Similarly, trabectedin was recently approved as a second-line therapy for patients with metastatic leiomyosarcoma and liposarcoma due to PFS prolongation relative to dacarbazine [17]. However, an OS benefit was not observed in patients receiving pazopanib or trabectedin relative to the control arm in either of these trials.

The lack of durable responses to chemotherapy and limited targeted agents further highlights the importance of local therapy in the management of metastatic STS. Indeed, among selected patients who develop sarcoma metastases, performance of surgical metastasectomy is associated with better survival [18]. Therefore, local management of metastatic disease is an important option for consideration in patients with metastatic STS.

Historically, RT has been delivered with palliative intent in the metastatic setting for symptom management, but recently a trend has emerged of using ablative radiotherapy dosing in select cases. Possible justification for more aggressive radiation regimens includes circumstances where there may be a possibility of cure, a prolonged disease course that benefits from more durable local control, an isolated site of disease progression, or an opportunity to use locally directed therapy to provide a patient a break from systemic therapy. With the advent of conformal RT techniques including intensity-modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT), safe biological dose escalation with ablative RT doses is now possible. There is significant interest in evaluating the use of these advanced techniques in the setting of metastatic STS, especially in those patients for whom surgical resection is not an option.

Stereotactic body radiation therapy is a technique where a large dose of radiation is given in a single or few large dose fractions. Radioresistant tumors, such as STS, are estimated to have α/β ratios (derived from linear-quadratic equation of cell kill following radiation) of 3–5 or less, suggesting a greater DNA repair capacity [19–22]. It has been proposed that these radioresistant tumors are more sensitive to increasing dose-per-fraction as is done with SBRT and other hypofractionated regimens [23]. Technological advances in the delivery of radiation and image guidance have allowed for the widespread adoption of SBRT and it is currently standard of care for early stage NSCLC patients who are not candidates for surgical resection [24].

Treating patients aggressively at diagnosis in the advanced setting may be especially beneficial for patients presenting with oligometastatic disease at diagnosis with an overall low tumor burden and few metastatic sites [25, 26]. In non-small cell lung cancer, patients with oligometastatic disease treated with comprehensive local therapy, consisting of either RT or surgery, plus maintenance systemic therapy saw an improvement in both PFS and OS when compared with systemic therapy alone [27–29]. Similar data are emerging for other tumor types, including sarcomas. The French Sarcoma Group recently published retrospective outcomes of 281 patients with oligometastatic STS treated with or without ablative therapy for their metastatic lesions. They found that patients undergoing local ablative therapy, consisting of surgery, RT, or radiofrequency ablation had significantly decreased risk of death [30•]. Although the subgroup of patients undergoing RT was small in this study, the importance of LC in the metastatic STS setting was clearly established.

The aim of this review is to summarize the available literature regarding the evolving role of RT in the treatment of metastatic sarcoma. Given radiation treatment techniques vary widely by body site, we have organized by the site of metastatic disease involvement.

Lung Metastases

The lungs are the most common site of metastasis for STS, and isolated pulmonary lesions are seen in approximately 20% of patients with STS and 40% of patients with primary bone sarcomas [31, 32]. In a single-institution series of STS patients with pulmonary metastases, the median survival was 33 months for those with complete resection of pulmonary metastases versus 11 months for those who underwent non-operative treatment only [31]. In this study, only one-third of patients presenting with isolated pulmonary disease were eligible for a complete pulmonary metastasectomy. Factors that may limit a surgical approach include patients with an uncontrolled primary tumor, extrathoracic disease, pleural effusions, or medical comorbidities that increase perioperative risk. In select patients, RT may offer an equivalent alternative to surgery with favorable LC outcomes that could translate into prolonged survival.

Several studies have reported outcomes for patients who received SBRT for oligometastatic sarcoma in the lung (Table 1) [33–35,36•,37]. Navarria and colleagues analyzed outcomes for 28 patients with good performance status who received treatment to 51 lesions with SBRT for unresectable pulmonary STS metastases [36•]. Administered SBRT doses were dependent on tumor size: 30 Gy in 1 fraction for peripheral lesions ≤ 10 mm, 60 Gy in 3 fractions for peripheral lesions 10–20 mm, 48 Gy in 4 fractions for peripheral lesions > 20 mm, and 60 Gy in 8 fractions for lesions located centrally in the thorax. With a median follow-up of 21 months from completion of SBRT, actuarial 5-year LC of treated lesions was excellent at 96%. Two- and 5-year OS was 96% and 60%, respectively. Importantly, no patient experienced grade 3/4 pulmonary toxicity.

Similarly, Frakulli and colleagues reported their experience using SBRT to treat 68 lung metastases in 24 patients with metastatic bone or soft-tissue sarcoma [34]. They delivered 30–60 Gy in 3–8 fractions. With a median follow-up of 17 months, 2-year LC for treated lesions was 86%, and 2-year OS was 66%. As expected, a larger tumor volume (5 cm^3) was associated with worse LC. Soyfer et al. also noted a similar trend where SBRT was able to control 100% of metastatic pulmonary STS lesions measuring < 1 cm but 72% of lesions > 1 cm in size, and a more recent study by Lindsay and colleagues reported LC to be 95% at 5 years for 117 metastatic STS lung nodules treated with SBRT in 44 patients [35, 37]. Ultimately, these studies reveal favorable local control with low toxicity for pulmonary metastases treated with SBRT, supporting SBRT as a possible alternative strategy to surgical resection.

At our institution, lung SBRT for metastatic STS is often recommended for patients with oligometastatic or oligoprogressive disease. Additional meaningful endpoints in the use of local therapy is delaying initiation of systemic therapy or delaying a switch in systemic therapy if all but one to several lesions are controlled on a current regimen. Stereotactic doses are selected based on the location of the tumor and the proximity to normal structures/tissues [38]. As the lesion(s) can move with each breath, four-dimensional imaging at the time of CT simulation takes into account movement of the tumor through all phases of the breath cycle. This facilitates detailed target acquisition for more accurate treatment delivery.

Taken together, the literature reveals favorable outcomes for patients with metastatic STS who receive SBRT for lung metastases. As advances in radiation delivery continue, these data continue to show promising results and will hopefully stimulate further investigation through prospective clinical trials investigating SBRT as a valuable therapeutic strategy specifically for patients with STS.

Bone Metastases

The second most common site for metastasis of STS are to the bones of the axial skeleton, including the spine. Bone metastases can be painful and are a significant cause of morbidity if untreated, including pathological fractures, hypercalcemia, and neurologic compromise for which urgent surgery and RT is required to prevent irreversible damage [39, 40]. When surgery is not required, spinal metastases have traditionally been treated with palliative intent using conventionally fractionated 3D-conformal irradiation (3DCRT), commonly to a total dose of 30 Gy in 10 fractions or a single 8 Gy treatment [41–43]. However, 3DCRT does not attempt to spare the spinal cord, which limits the total RT dose that can be safely delivered to metastatic disease in the vertebral column. Thus, although palliation of symptoms is achieved in the vast majority of patients who receive 3DCRT, the low biologically

Table 1 Recent series outlining outcomes after SBRT for sarcoma lung metastases

Series	No. of patients	No. of lesions	Radiation dose	Median size of lesion (cm^3)	Median F/U (months)	2-year OS (%)	2-year LC (%)
Navarria et al., Milan	28	51	30 Gy in 1 fx 60 Gy in 4 fx 48 Gy in 4 fx 60 Gy in 8 fx	6.5	21	56	96
*Frakulli et al., Bologna	24	68	30–60 Gy in 3–8 fx	5.0	17	66	86
Lindsay et al., Connecticut	44	117	50 Gy in 10 fx (71%)	2.1	14.2	82	95
Soyfer et al., Israel	22	53	24–40 Gy in 3–4 fx	N/A	95	50	98
*Baumann et al., Pennsylvania	30	39	50 Gy in 4–5 fx	12.6	23	43	86

*These studies included patients with both soft tissue and bone sarcomas

effective dose (BED) results in limited disease control, especially for STS histologies that are relatively radioresistant.

An alternative delivery technique to 3DCRT is spine stereotactic radiosurgery (SSRS), which is a highly conformal method of delivering an ablative dose of radiotherapy for metastatic spinal disease [44]. The use of SSRS allows for delivery of treatment plans with steep dose gradients that spare the spinal cord and allow for biological dose escalation akin to SBRT for lung lesions. Among all histologies, SSRS provides greater than 85% LC at 1 year with less than 1% incidence of severe neurologic toxicities following treatment [45–50]. The use of SSRS has been shown to be especially beneficial in radioresistant histologies where there is an increased rate of post-treatment progression with conventionally fractionated 3DCRT [51–53].

Folkert and colleagues reported excellent outcomes following SSRS for 88 patients with 120 discrete metastatic sarcoma lesions to the spine [54•]. LC and OS following treatment was 88% and 61%, respectively, at 12 months. Patients in this study received a median 24 Gy (range, 18–24 Gy) in one fraction, and acute and chronic grade 3 toxicities were low at 1% and 5%, respectively. Similarly, Bishop and colleagues reported outcomes for 48 patients with metastatic sarcoma treated to 66 spinal lesions [55]. Actuarial 1-year LC and OS was 81% and 67%, respectively. These data support SSRS as an important treatment option that provides durable tumor control in patients with metastatic sarcoma to the spine (Fig. 1, example).

Given the highly ablative, conformal nature of SSRS, the fidelity of treatment setup is crucial. When larger treatment volumes are required, particularly volumes spanning more than three vertebral body levels, there is increased opportunity for variation in alignment and rotation that can make it difficult to achieve stringent dose constraints, primarily to the spinal cord [56]. In such scenarios, radiation treatment options can include traditional palliative 3DCRT, or, in select instances, where a higher BED and durable control is warranted (for example, in the oligometastatic setting), a spinal simultaneous integrated boost technique (SSIB) can be utilized [57]. With SSIB, dose escalation over that of standard palliative RT is achievable. Although this strategy does not deliver similarly ablative dosing as SSRS, SSIB still allows for dose escalation over that of standard palliative RT and, thus, can increase chances of durable local control when treating radioresistant histologies such as STS. However, for the acutely symptomatic patient for which palliation is the priority, standard conventional RT is the recommended approach to provide a rapid relief of symptoms. Salvage SSRS can be considered at a later date to prevent local progression and has been demonstrated to be a safe and tolerable approach [58].

Liver Metastases

Similar to published data regarding lung metastases, isolated hepatic STS metastases may also be amenable to curative resection, and this may offer patients increased chance of survival [59–61]. Unfortunately, there are currently no published data addressing whether SBRT improves outcomes for oligometastatic sarcoma to the liver. In a recently published abstract, a single institution reported their outcomes on 30 patients with local treatment to 44 sarcoma liver metastases [62]. Of these, 25 lesions were resected and 19 received SBRT with two patients receiving both. None of the patients who received SBRT progressed locally. The authors concluded that SBRT provided excellent LC for sarcoma liver metastases when surgery was not an option. The median dose delivered was 50 Gy (range, 32–60 Gy) given in 5 fractions. These outcomes are consistent with the literature on liver SBRT for other histologies that reveal favorable LC rates ranging between 92 and 95% based on the size of the lesion [63]. Thus, liver-directed SBRT is a feasible and favorable non-invasive treatment option for select patients, particularly when surgical resection is not recommended.

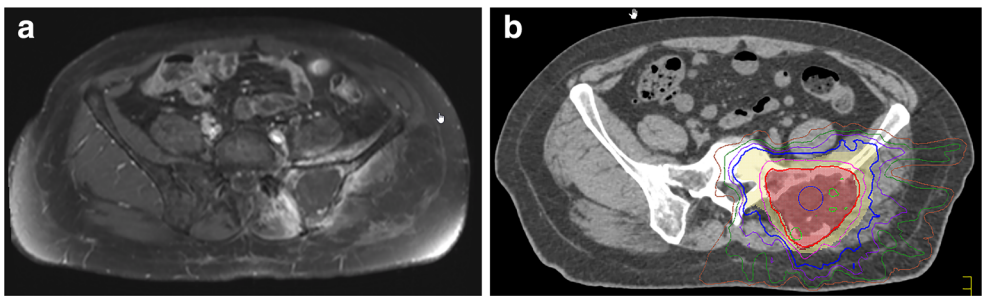

Fig. 1 This illustrates a classic oligometastatic STS case—a 47-year-old female with a 6-year disease free interval from uterine leiomyosarcoma presented with a single site of bony involvement. Recommendation following systemic therapy was for aggressive consolidative local therapy with SBRT. **a** A representative T1+c MRI image of the left iliac bone metastasis. **b** The SBRT plan dosed to 24 Gy in a single fraction to the tumor. Her oligometastasis appears treated and remains stable 14 months following treatment

Similar to SBRT to other anatomic sites, RT dose/fractionation selection is primarily driven by the location and the proximity to critical structures. When feasible, SBRT in 4–5 fractions is commonly employed with motion management (i.e. breath-hold technique) to minimize intrafractional movement of the tumor. For larger lesions or tumors that are centrally located, the short-course ablative nature of SBRT may have increased risk; therefore, in those situations, hypofractionated RT, similar to the previously discussed SSIB technique, allows higher doses to be delivered to the tumor with the aim for durable control while keeping the normal tissues at biologically safer doses. Data extrapolated from the treatment of unresectable intrahepatic cholangiocarcinomas is applicable to the sarcoma patient population with tumors in this location; for example, one study recently published revealed improved local control for patients receiving hypofractionated liver-directed ablative RT. The 3-year OS rate for patients receiving a BED greater than 80.5 Gy was 73% versus 38% for those receiving lower doses ($P = .017$). Similarly, local control rate was significantly higher (78%) after a BED greater than 80.5 Gy than after lower doses (45%, $P = .04$) [64]. These data indicate that for radioresistant histologies, a higher delivered BED improves outcomes. This strategy is a good option for patients with metastatic sarcoma who have a limited disease burden in the liver and a location that is not abutting critical structures.

Brain Metastases

The incidence of brain metastases among patients with sarcomas is rare, yet particular histologies have an increased risk and include angiosarcoma or alveolar soft parts sarcoma. Management of sarcoma brain metastases does not differ from strategies used to treat other tumors. Importantly, the treatment of brain metastases has evolved considerably over the past few decades with increased utilization of stereotactic radiosurgery (SRS) and advanced surgical techniques. In keeping with the radiobiologic principle that hypofractionated RT may be beneficial in radioresistant histologies, two key studies have established that control of brain metastases treated with stereotactic radiosurgery (SRS) was similar among patients with metastatic sarcoma to that observed for typically "non-radioresistant" tumors, both in an intact and post-operative setting where the tumor cavity is irradiated [65, 66]. Although local control of the treated lesions following SRS is expected to be > 90%, intracranial control (i.e. outside of the radiation field) is around ~ 50% based on randomized data at 12 months. If SRS is combined with whole brain radiation therapy (WBRT), intracranial control at 12 months improves to 85%; however, this results in increased neurocognitive deficits including problems with memory, recall, and verbal fluency and thus is not commonly combined with SRS [67, 68]. Therefore, we favor SRS for patients with a limited number of brain metastases and reserve WBRT for patients with more diffuse intracranial disease as it treats both macroscopic and microscopic intracranial disease.

Future Directions and Conclusions

While chemotherapy is an important component for the treatment of metastatic STS, it has been difficult to establish it as part of the standard up front management for patients with localized STS. A rapidly growing field of newly developed systemic therapies such as tyrosine kinase inhibitors and immune checkpoint-inhibitors are being tested in metastatic STS. Many newer agents such as trabectedin, eribulin, pazopanib, and regorafenib are showing improved outcomes in the metastatic setting relative to historical traditional chemotherapeutic agents such as dacarbazine, and patients will potentially live longer with problematic disease burden that could benefit from local therapy [16, 69–71]. Additionally, the rationale of combining RT with immunotherapy is already showing great potential for improving outcomes in various cancer histologies, including potentially sarcoma [72–75]. As the role of systemic therapy continues to expand, the role of RT to metastatic STS lesions will also continue to evolve in the coming years with likely increased utility for patients with oligometastatic and oligoprogressive disease. Trials assessing the efficacy of RT in combination with these newer agents will also inform future treatment strategies.

In conclusion, the decision to use ablative RT in patients with STS metastases requires multidisciplinary collaboration, preferably at an experienced sarcoma center with high sarcoma patient volume. This is especially important in settings of oligometastatic disease where the balance for goals of therapy between palliation and cure require collaborative decision making between the various medical teams and patients themselves.

The use of ablative, hypofractionated radiation techniques, such as SBRT, SSRS, and SRS, should be reserved for patients with reasonable performance status and life expectancy, as these treatments are time and resource intensive with significantly higher cost. As discussed, if a patient has widely metastatic or rapidly progressing disease, 3DCRT as a form of palliation and symptom control is a more appropriate treatment strategy. Conversely, for selected patients with oligometastatic or oligoprogressive disease, ablative radiation techniques can provide more durable tumor control while perhaps delaying the need to change or initiate systemic therapy and may potentially improve survival outcomes. While palliative radiation therapy currently has a critical role in the treatment of symptomatic sarcoma metastases, ablative radiation approaches will likely become a more integral component of multidisciplinary care as systemic therapies evolve and the

quality of life and life expectancy of patients with metastatic STS continue to improve.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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- •• Of major importance

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