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The role of stereotactic body radiotherapy in the management of oligometastatic soft tissue and bone sarcomas

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Sarcomas are a highly heterogeneous group of rare malignancies. Historically, metastatic disease was considered incurable and was an indication for a palliative approach. Modern local therapies have led to a paradigm shift, making long-term disease-free survival possible for selected groups of metastatic sarcoma patients. Oligometastatic and oligoprogressive disease constitute such indications. Although the administration of stereotactic radiation therapy (SBRT) for sarcoma metastases has been continuously rising over the past years, the evidence for such treatment is relatively scarce, lacking in larger prospective randomized clinical trials, and there is no consensus regarding strict indications, patient selection, and the time order of multimodal treatment. In this article, we discuss available clinical data regarding the efficacy and safety of SBRT in oligometastatic and oligoprogressive sarcoma, highlighting its indications in specific organ sites, as well as the possible limitations of this treatment modality.

Key words: stereotactic body radiotherapy, sarcoma, metastases, hypofractionation, radiotherapy

Introduction

Soft tissue and bone sarcomas (STBS) comprise a heterogeneous group of rare diseases that require treatment in specialized tertiary centers. The only curative method of treatment for localized spindle cell STBS is surgery, often combined with perioperative radiotherapy and chemotherapy whereas disseminated disease is an indication for systemic therapy [1–3].

Some patients with STBS present an intermediate state between localized and fully disseminated disease, so-called oligometastatic disease (OMD). The idea of OMD originates from the work by Hellmann et al. This classical definition covers up to three to five distant metastases amenable for medical imaging detection and involving one or two organ systems [4]. One of the modern definitions proposed by the European Society for Radiotherapy and Oncology (ESTRO), and the American Society of Radiation Oncology also use the numerical concept of one up to five metastatic lesions that can be safely controlled by local therapies [5]. Adopting this concept potentially rationalizes a curative treatment approach in patients with OMD, involving a definitive local treatment of single distant metastases, with the prerequisite of early and complete local control of the primary tumor. Furthermore, some macrometastases still present after systemic treatment might be successfully eliminated with the use of modern local ablative techniques.

Historically, the only potentially curative approach for distant sarcoma metastases that offered satisfactory local control was metastasectomy, applied only in selected patients eligible for surgery. The emergence of new local therapies, such as stereotactic body radiotherapy (SBRT), thermal, chemical, and radioablation has led to a paradigm shift in metastatic STBS

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treatment [6]. Initiating such a treatment pathway is possible only after a thorough consideration of multiple interacting factors, such as locoregional spread, tumor burden, involvement of organs, time setting (synchronous or metachronous metastases), and biological features, including tumor grade.

Moreover, even in the case of disseminated disease, modern systemic treatment frequently enables long-term disease control. In the past, any signs of disease progression caused treatment change or withdrawal. Nowadays local ablative therapies such as SBRT for progressive metastases may allow continuing the current effective line of systemic therapy after eliminating treatment-resistant clones. This concept is called oligoprogressive disease (OPD) [7]. The clinical benefit of such an approach was a matter of some retrospective studies and case reports [8–13]. The role of SBRT and other therapies in OPD is intensively investigated in various cancers, especially those susceptible to immunotherapy.

Concepts of OMD and OPD were summarized in consensus guidelines proposed jointly by ESTRO and the European Organisation for Research and Treatment of Cancer. This article contains a decision tree for OMD and OPD with relevant definitions [14].

Available clinical data, although relatively scarce, suggests highly promising advantages of SBRT in sarcoma patients with OMD:

- excellent local control rates and a potentially improved overall survival,
- good tolerability,
- a delay or even complete avoidance of systemic therapy,
- early prevention of tumor-related complications with avoidance of emergency/salvage surgery [15].

However, some of these features may reversely adversely influence clinical outcomes in many cases, raising some reasonable concern about overtreatment. The same advantages and risks are related to the SBRT for OPD with even less evidence.

Although the administration of SBRT for STBS OMD and OPD has been continuously rising over the past years, the evidence for such treatment is relatively scarce, lacking in larger prospective randomized clinical trials, and there is no consensus highlighting strict indications, patient selection, and the order of treatment in a multimodal setting.

In this article, we discuss available clinical data regarding the use of SBRT in STBS OMD and ODP and directions for further investigations.

Clinical data

Lung metastases

The lungs are the most common site of distant sarcoma metastases due to the hematogenous pattern of spread [16]. About 20% of patients with soft-tissue sarcoma and 40% of patients with bone sarcoma develop lung metastases during the course of the disease [17]. The first SBRT approaches for STBS lung metastases relied on the analogy to early-stage non-small cell lung cancer treated with SBRT with excellent clinical outcomes, comparable to the invasive surgical approach [18]. All the discussed studies were summarized in table I.

The first retrospective single institution SBRT study published by Dhakal et al. involved 52 patients with STBS pulmonary metastases [19]. Among them, 15 received SBRT for 72 lung lesions. The authors reported the most common fractionation regimen as 50 Gy in ten fractions. Three-year local control after SBRT was reached by 82% of patients who received SBRT, whereas the median overall survival in the SBRT group was significantly higher than survival in those who did not undergo SBRT (2.1 years *vs.* 0.6 years, $p = 0.002$). Moreover, no patients experienced severe toxicity of SBRT.

The abovementioned findings have been confirmed by several other trials over the following years [20, 21]. Bauman et al. published two manuscripts reporting the results of SBRT for STBS lung metastases using more aggressive fractionation regimens, namely 50 Gy in five and four fractions delivered by CyberKnife or conventional linear accelerators. In the first study, the authors analyzed a cohort of thirty consecutive STBS patients who received SBRT to 39 lung metastases [20]. Then the patients were monitored using CT or PET/CT scans every three months after SBRT. Local control at 12 and 24 months reached 94% and 86%, respectively. Overall survival (OS) at 12 and 24 months was 76% and 43%, respectively. The authors did not find an influence of SBRT technique, fractionation, target volume site, histopathology, and diameter on local control and survival. The treatment tolerance was good. The second study reported the results of a pooled analysis of 44 patients with 56 lung metastases who received SBRT and provided similar results to the previous one [21].

A small retrospective study on 16 patients with 25 lesions treated with SBRT also confirmed very good local control with a favorable toxicity profile of such irradiation, namely 94% at 43 months [22].

Excellent results of SBRT for lung metastases were found in another retrospective study performed by Navarria et al [23]. The authors analyzed a cohort of subsequent 28 patients with soft tissue sarcomas who underwent SBRT for 51 lung metastases not eligible for surgery. Various fractionation regimens were used, namely 30 Gy in one fraction, 60 Gy in three fractions, 60 Gy in eight fractions, and 48 Gy in four fractions. All patients were irradiated using volumetric modulated arc therapy in a conventional linac. The patients were followed-up every three months after SBRT. The median follow-up was 21 months. Five-year local control was 96%. Overall survival at two and five years was 96.2% and 60.5%, respectively. No grade 3 or higher toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) scale version 4.0 were observed.

Another retrospective study was conducted by Italian researchers that included STBS patients who were treated with SBRT for lung metastases [24]. The authors identified

Table I. The summary of studies on stereotactic body radiotherapy for sarcoma lung metastases

Study	Study design	Number of patients	Number of lesions	Median lesion size	The most common fractionation regimen	Local control rate	Overall survival	Toxicity
Dhakal et al., 2012 [19]	retrospective single center	52	74	nd	50 Gy in 10 fr.	3 y: 82%	median: 2.1 years *vs.* 0.6 years in control group (no SBRT)	no grade 3 or higher
Baumann et al., 2016 [20]	retrospective multicenter	30	39	2.4 cm	50 Gy in 4–5 fr.	1 y: 94% 2 y: 86%	1 y: 76% 2 y: 43%	no grade 3 or higher
Baumann et al., 2020 [21]	retrospective multicenter pooled analysis	44	56	2.0 cm	50 Gy in 4–5 fr.	1 y: 96% 2 y: 90%	1 y: 74% 2 y: 46%	no grade 3 or higher
Mehta et al., 2013 [22]	retrospective single center	16	25	nd	36–54 Gy in 3–4 fr.	43 m: 94%	4 y: 72%	no grade 2 or higher
Navarria et al., 2015 [23]	prospective observational	28	51	6.5 cm^3	30 Gy in 1 fr 60 Gy in 3 fr. 60 Gy in 8 fr. 48 Gy in 4 fr.	5 y: 96%	2 y: 96.2% 5 y: 60.5%	no grade 3 or higher
Frakulli et al., 2015 [24]	retrospective single center	24	68	nd	30-60 Gy in 3–8 fr.	1 y: 88.2% 2 y: 85.9%	1 y: 73.1% 2 y: 66.4%	no grade 3 or higher
Soyfer et al., 2017 [25]	retrospective single center	22	53	nd	24–60 Gy in 3–4 fr.	95 m: 96%	5 y: 50%	1 grade 3 no grade 4
Lindsay et al., 2018 [26]	retrospective single center	44	117	2.1 cm	36–50 Gy in 5–12 fr.	14 m: 95%	2 y: 82% 5 y: 50%	1 grade 3 no grade 4
Navarria et al., 2022 [27]	prospective phase 2 single arm clinical trial	44	71	2.0 cm	30 Gy in 1 fr. 60 Gy in 3 fr. 48 Gy in 4 fr.	1 y: 98.5% 5 y: 93.1%	1 y: 88.6% 5 y: 48.2%	no grade 3 or higher

fr. – fractions; m – month(s); SBRT – stereotactic body radiotherapy; y – year(s)

24 patients who underwent irradiation for 68 lung lesions not suitable for surgery. The patients received total doses between 30 and 60 Gy given in three up to eight fractions. Two-year local control was high and reached 86% whereas two-year overall survival was 66%. No significant toxicities of SBRT were reported.

Similarly designed studies were performed by Soyfer et al. and Lindsday et al. [25, 26]. The cohort from the first study comprised 22 patients with 53 STBS lung metastases who received SBRT [25]. After a long follow-up of 95 months, no progressive disease in all treated lesions was observed. Five-year overall survival was 50%. Treatment tolerance was described as very good. The second study analyzed a group of 44 patients with STBS lung metastases treated with SBRT [26]. Follow-up time was shorter than that presented in the first mentioned study – namely 14.2 months. The local control rate was 95%. Two- and 5-year overall survival was 82% and 50%, respectively. The most frequent side effects included radiation pneumonitis, cough, rib fracture, pain, dermatitis, and dyspnea.

The only prospective clinical trial on SBRT for STBS lung oligometastases was performed by Navarria et al. [27]. The authors enrolled adult patients with up to four inoperable STBS lung metastases. The allowed fractionation regimens included 30 Gy in one fraction for peripheral lesions ≤1 cm, 60 Gy in three fractions for peripheral lesions between 1.1 and 2 cm, 48 Gy in four fractions for peripheral lesions over 2 cm, and 60 Gy in eight fractions for central lesions. The proportion of progression-free treated lesions at 12 months was chosen as the primary endpoint of this study. Forty-four patients with 71 lung metastases met the inclusion criteria and received SBRT for metastatic lesions. Twelve-month local control was 98.5%. The median disease-free survival reached 12 months whereas the median overall survival was 49 months. Age, grade of STBS, the interval from diagnosis to disease dissemination, and the number of lung metastases were prognostic for survival. No significant pulmonary toxicity was reported.

Based on the described results, we may presume the high efficacy and favorable toxicity profile of SBRT for STBS lung metastases. However, the crucial issue is the identification of patients who are the best candidates for local therapy. Tanadini-Lang et al. calculated a nomogram predicting overall survival after SBRT for lung metastases from various cancers that could be helpful to choose the most appropriate candidates for lung SBRT [28]. The cohort consisted of 715 patients treated with SBRT for 964 pulmonary metastases, including 49 patients with STBS. Diagnosis of STBS moderately worsened the probability of two-year survival as compared with renal cell cancer and colorectal cancer but less affected survival than the diagnosis of breast

cancer, non-small cell lung cancer, esophageal cancer, melanoma, and other analyzed malignancies. Importantly, the authors concluded that long-term overall survival after SBRT for pulmonary metastases in this heterogeneous cohort was similar to survival achieved after metastasectomy. Thus, patients with STBS OMD seem to be excellent candidates for SBRT in the case of pulmonary metastases.

Various sites

Despite the lack of strong scientific evidence, SBRT seems to be also an effective local treatment for non-pulmonary metastases localized to various sites. An example of an SBRT plan in a patient with oligoprogressive myxoid liposarcoma during systemic treatment was presented in figure 1. This patient received 35 Gy in five fractions prescribed to covering 80% isodose. Irradiation was combined with hyperthermia.

The largest retrospective study on SBRT in STBS was published by a team from our institute [15]. We aimed to investigate the use and outcomes of SRT in this group of tumors, identify the patients who benefit the most, and check if there is any dose-response relationship. The cohort consisted of consecutive adult patients with primary, recurrent, or metastatic STBS treated with linac-based SBRT. SBRT was defined as highly conformal radiotherapy delivered in ten or fewer fractions using daily image guidance, and a biologically effective dose no lower than 50 Gy. We identified 141 patients who underwent 233 SBRT procedures. The median follow-up was 21 months. Local progression after SBRT occurred in 15 patients. We found that OMD, lung metastases, and soft tissue sarcomas get the highest benefit from SBRT.

In a relatively large retrospective study from Karolinska University Hospital, Stragliotto et al. reported the results of SBRT for 136 STBS metastases in 46 patients [29]. This cohort differed from the cohort published by our team in fractionation regimens allowing total doses closer to the palliative ones, for example, 20 Gy in five fractions or 10 Gy in one fraction. In both studies, local control was very high, namely 88% in the Swedish and 95% in the Polish cohort. Importantly, the authors

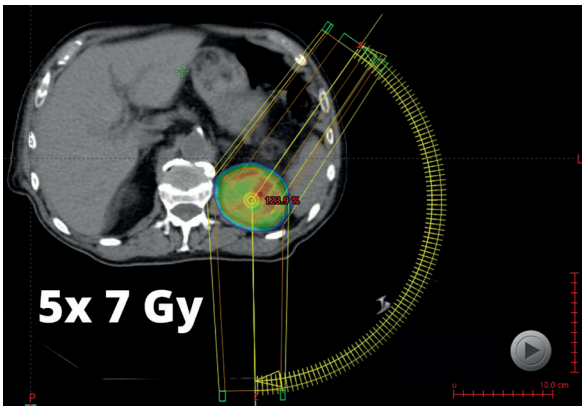

Figure 1. Stereotactic body radiotherapy for oligoprogressive myxoid liposarcoma

reported serious complications of SBRT, namely one colon perforation and contracture of the hip region. This study also highlighted the true benefit of SBRT, reporting 13 patients (31%) as long-term survivors who lived longer than three years after treatment.

Another retrospective study focused on patients with metastatic or recurrent osteosarcomas and Ewing sarcomas [30]. The authors analyzed a retrospective cohort of 14 patients with osteosarcomas and Ewing sarcomas who underwent SBRT for 27 lesions, mostly bone and lung metastases. The role of SBRT in this analysis was divided into definitive (n = 14) and palliative (n = 13). In those who were treated with definitive intent, the median follow-up reached two years with two-year estimated local control as high as 85%. Those who received palliative SBRT had significantly shorter 0.2 years of median follow-up. However, local control was also good despite lower doses used in this arm. Three clinically significant toxicities were observed in patients who were irradiated concomitantly with chemotherapy or underwent reirradiation.

Limitations

The main limitation of SBRT is the lack of convincing scientific evidence, namely results of prospective randomized clinical trials that confirm its non-inferiority to surgery. However, the only available single-arm prospective clinical trial showed excellent local control with minimal toxicity of SBRT. Furthermore, we may assume at least similar efficacy based on trials with early non-small cell lung cancer.

Another problem is the choice of an optimal fractionation regimen. The heterogeneous group of STBS covers a wide spectrum of radiosensitivity, from extremely radioresistant chondrosarcomas up to the highly radiosensitive Ewing sarcoma and myxoid liposarcoma [31–33]. Moreover, even within the same pathological subtype, the radiosensitivity may vary [34]. Moreover, data regarding stereotactic reirradiation in this group of patients are scarce. Thus, the choice of fractionation should be individualized, considering many factors, among others, predicted radiosensitivity, site, previous irradiation, concomitant systemic treatment, and performance status.

Finally, there is the fear of late complications, especially in patients who are believed to be long-term survivors. This issue may be answered by data collection in prospective registries of all STBS patients who are treated with SBRT.

Conclusions

Despite limited high-quality evidence, SBRT is a viable method of treatment for OMD and OPD STBS. Its excellent local efficacy, favorable toxicity profile, and wide availability make it a real alternative to more invasive surgical approaches. Data regarding the role of SBRT in rare diseases should be collected in prospective registries. The ongoing international project may answer the unsolved questions regarding the true benefit of SBRT in oligometastatic cancers [35]. Further investigations

should focus on the development of new predictive factors, models of patient selection for SBRT in STBS, biologically-guided treatment, and combined therapy.

Conflict of interest: none declared

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