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Stereotactic radiotherapy for bone oligometastases

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ABSTRACT

About 60–90% of cancer patients are estimated to develop bone metastases, particularly in the spine.

Bone scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) are currently used to assess metastatic bone disease; positron emission tomography/computed tomography (PET-CT) has become more widespread in clinical practice because of its high sensitivity and specificity with about 95% diagnostic accuracy. The most common and well-known radiotracer is 18F-fluorodeoxyglucose (^{18}FDG); several other PET-radiotracers are currently under investigation for different solid tumors, such as ^{11}C or ^{18}FDG-choline and prostate specific membrane antigen (PSMA)-PET/CT for prostate cancer. In treatment planning, standard and investigational imaging modalities should be registered with the planning CT so as to best define the bone target volume. For target volume delineation of spine metastases, the International Spine Radiosurgery Consortium (ISRC) of North American experts provided consensus guidelines. Single fraction stereotactic radiotherapy (SRT) doses ranged from 12 to 24 Gy; fractionated SRT administered 21–27 Gy in 3 fractions or 20–35 Gy in 5 fractions. After spine SRT, less than 5% of patients experienced grade ≥ 3 acute toxicity. Late toxicity included the extremely rare radiation-induced myelopathy and a 14% risk of de novo vertebral compression fractures.

Key words: stereotactic radiotherapy; radiosurgery; oligometastasis; bone metastases; spine metastases; hypofractionation; local control; toxicity

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Introduction

Solid tumors frequently spread to bones, most often the spine. About 60–90% of cancer patients are estimated to develop bone metastases [1, 2] which are associated with increased risk of complications such as pain, fractures and hypercalcemia. At the metastatic site, bone remodeling due to increased osteoblast and osteoclast activity seems to alter the microenvironment, promoting tumor growth and bone destruction. From the diagnostic point of view, this tissue remodeling is characterized by lytic and thickened areas within the bone [3].

In terms of survival, there is a huge heterogeneity between different histotypes with diverse molecu-

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lar phenotypes. For instance, prognosis is better in breast cancer patients with only bone involvement than in those with visceral metastases [4]. Moreover, patients with oligometastatic bone disease and few secondary localizations might be candidates for curative therapy [5, 6].

This overview provides a critical appraisal of the current evidence and future perspectives of bone oligometastatic disease.

Sources of information

By February 2021, Pubmed and the Cochrane library were searched for relevant literature.

Diagnostic imaging and target volume definition

Bone scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) are currently used to assess metastatic bone disease [7–9]. Bone scintigraphy has the advantage of detecting lesions with a low bone-matrix turnover, although false negatives may occur in lytic lesions without tissue remodeling [10, 11]. Over the past few years, the use of the positron emission tomography/computed tomography (PET/CT) has become more widespread in clinical practice because of its high sensitivity and specificity in detecting bone metastasis, even lytic lesions, and its diagnostic accuracy of about 95% [12–15]. The most common and well-studied radiotracer is 18F-fluorodeoxyglucose (^{18}FDG). With it, the PET/CT achieves the same sensitivity as, and greater specificity than, bone scintigraphy (96% *vs.* 66%) [14, 15]. Several other PET-radiotracers are currently under investigation for different solid tumors. For instance, ^{11}C or ^{18}FDG-choline and prostate specific membrane antigen (PSMA)-PET/CT are used for staging recurrent prostate cancer which might benefit from metastasis-directed therapy when an oligometastatic state is detected [16–18].

In radiation oncology, standard and investigational imaging modalities should be registered with the planning CT in order to define the bone target volume better. More specifically, MRI is the most sensitive in defining bone lesions and critical structures, such as the spinal cord, that need to be spared from irradiation. The International Spine Radiosurgery Consortium (ISRC) of North American experts in radiosurgery provided consensus guidelines for target volume delineation in spine SRT [19]. The gross tumour volume (GTV) has to be fully contoured whereas the clinical target volume (CTV) is defined according to the involved vertebral region: the vertebral body, pedicle, transverse process, lamina or spinous process. For example, when the lesion involves the spinous process the CTV encompasses the entire spinous process and bilateral laminae. When it is detected in any part of the vertebral body, the entire vertebral body must be included in the CTV. For extended metastases involving the vertebral body and bilateral pedicles, the CTV should encompass the entire vertebral body, bilateral pedicles, transverse processes and bilateral laminae. A circumferential CTV around the cord is not recommended when lesions involve the entire vertebral body, bilateral pedicles and spinous process as it should be used only in rare cases of massive vertebral involvement [19]. In spine stereotactic radiotherapy (SRT) the planning target volume (PTV) and planning organ at risk volume (PRV) margins should be determined on an institution-to-institution basis because these geometrical expansions depend on the immobilization system, treatment planning, image-guided technique and fractionation scheme.

Fractionation schedules and dose constraints to the organs at risk (OARs)

Although the safety and efficacy of spine SRT were reported in many retrospective series, consensus is still lacking on the optimal dose fractionation. Most treatments were delivered as single fractions, with doses ranging from 12 to 24 Gy [20, 21], or fractionated schedules with total doses of 21–27 Gy being administered in 3 fractions or 20–35 Gy in 5 fractions [22–24]. In a retrospective series of spinal metastases from different solid tumors, Heron et al. reported that no differences emerged in long-term pain control and toxicity after a 16.3 Gy spinal single dose or hypofractionated schedules (20–24 Gy in 3–5 fractions). SRT in single dose had a worse rate of 2-year local control (70% *vs.* 96%) and was associated with a higher re-treatment rate [25]. In patients with 1–3 spine metastases the phase II/III RTOG 0631 trial [26] demonstrated the safety of a single 16 Gy dose. In patients with spine metastases Wang et al. [23] prospectively analyzed outcomes after hy-

Table 1. Spine stereotactic radiotherapy (SRT) schedules and local control

Author (year)	No. of pts	Median total dose (range)/ Median no. of fractions (range)	Median follow–up [months] (range)	Local control (%)
Anand et al. (2015) [35]	52	24 Gy (24–27 Gy)/3 (1–3)	8.5 (3–40)	82.6
Guckenberger et al. (2014) [22]	301	24 Gy (10–60 Gy)/3 (1–20)	11.8 (0–105)	83.9
Ahmed et al. (2012) [27]	46	24 Gy (10–40 Gy)/3 (1–5)	Mean 8.2	91.2
Wang et al. (2012) [23]	149	27–30 Gy/3	15.9 (1–91.6)	72.4
Yamada et al. (2008) [32]	93	24 Gy (18–24 Gy)/1	15 (2–45)	90
Gerszten et al. (2007) [20]	156 (no. of lesions)	20 Gy (12.5–25 Gy)/1	21 (3–53)	90

pofractionated schemes (27–30 Gy in 3 fractions). No G4 toxicity was reported and local control, as assessed by MRI, was achieved in 72% of cases. Ahmed et al. [27], administered a total median dose of 24 Gy (range, 10–40 Gy) in 3 fractions (range, 1–5), achieving a 1-year local control of 91.2%. In oligometastatic patients, a phase III prospective randomized trial evidenced that a single high-dose of 24 Gy compared with hypofractionated SRT (3 × 9 Gy) was more effective in ablating bone metastases and led to a better time to distant metastatic progression [28]. Several studies showed that the primary tumor histology might influence the efficacy of ablative radiotherapy, as SRT seemed more effective in breast metastases than in melanoma or renal cell carcinoma metastases (100% *vs.* 75%) [29]. For instance, in a recent retrospective analysis of 605 patients treated with hypofractionated SRT (total dose 20–28 Gy in two daily fractions) for 1,406 spine metastases multivariate analysis showed that less radiosensitive histologies were associated with a worse outcome [29]. In radioresistant tumors, a single dose > 20 Gy might be considered to achieve high local control rates (95–100%) [28, 30–33].

Spine SRT was investigated in selected cases of cord compression [34, 35]. More specifically, total doses of 14–27 Gy in 1–3 fractions were delivered to the target volume encompassing the epidural mass and the vertebral body that was involved. A local control rate of 80% was reported [34, 35]. After surgical decompression, spine SRT might increase the local control rate. To date, few retrospective analyses and some phase I/II studies have reported local control rates ranging from 70% to 100% after single doses of 14–24 Gy or fractionated doses of 27–30 Gy in 3–5 fractions [36–40].

When treating spine metastases, sparing the spinal cord from high doses is crucial. The American Association of Physicists in Medicine (AAPM) Task Group 101 provided information about dose constraints to the OARs for SRT. If single fraction SRT is delivered < 1 cm^3 of cord tissue should receive < 7 Gy. Otherwise, the total dose to 1 cm^3 of cord tissue must be < 12.3 Gy and < 14.5 Gy when SRT is administered in 3 or 5 fractions, respectively. The maximum dose to the cord must be < 10 Gy for a single fraction, < 18 Gy for 3 fractions, and < 23 Gy for 5 fractions. In the RTOG 0631 trial, no more than 10% of spinal cord (defined as the cord corresponding to the metastatic vertebra plus 5 mm above and below the PTV) had to receive a total dose > 10 Gy [26]. The UK consensus on OAR dose constraints for SRT suggests a total maximum dose to the cord of 10 Gy, 18 Gy, 23 Gy and 25 Gy in 1, 3, 5 and 8 fractions, respectively [41].

Toxicity

Spine SRT was most commonly associated with the following acute toxicity: grade 1 or 2 fatigue and skin erythema. In 23–68% of patient transient pain flare occurred [42, 43], the incidence of which was significantly reduced by dexamethasone during SRT [44]. Acute gastro-intestinal symptoms, due to mucositis, were linked to the irradiation site (i.e., cervical, thoracic or lumbar spine). Under 5%

of patients experienced grade ≥ 3 acute toxicity [22, 23, 27, 38, 40].

Late toxicity included the extremely rare radiation-induced myelopathy and a 14% risk of de novo vertebral compression fractures (VCF) [45]. These severe complications can occur from 6 months to 3 years after radiotherapy. Spinal instability is assessed by the Spinal Instability Neoplastic Score (SINS) [46, 47] with scores ≥ 7 predicting increased risk of VCF after spine SRT [48].

Conclusions

A few data from the literature reported significant differences in the doses and fractionations used for SRT in bone oligometastatic disease, which were generally chosen on the basis of primary tumour histology and bio-pathological characterization, target volume size, location and its relationship with OARs. In most studies SRT was delivered to spinal bone metastases and only a few studies included other sites of disease. Furthermore, heterogeneity in study populations was observed. Although better results were achieved in oligometastases from radiosensitive than radioresistant primary disease, no firm indications emerged on patient selection [49, 50]. At present, the only limitation in delivering SRT is treatment safety, which can vary case-by-case. All these uncertainties suggest the need for clinical trials and consensus guidelines.

Conflicts of interest

The authors have no conflict of interest to declare.

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