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Review

Appropriate endpoints for stereotactic body radiotherapy for bone metastasis: Classification into five treatment groups

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ABSTRACT

Treatment of bone metastasis using stereotactic body radiotherapy (SBRT) is being widely used in clinical practice. The reported clinical advantages of SBRT include high pain and local control rates, high response rates against bone metastasis from radio-resistant tumors, and safe re-irradiations. Although most reports in the literature use local control as the primary treatment endpoint, this endpoint is not appropriate because local control does not relate directly to patient benefit. Herein, we proposed five pathophysiology-based patient groups, as well as appropriate endpoints for each group.

1. Background

Conventional external-beam radiotherapy (cEBRT) has been the standard-of-care for painful bone metastasis and metastatic epidural spinal cord compression (MESCC).[1] However, cEBRT has limitations, including poor long-term tumor control rates[2] and difficulties in re-irradiations due to adverse events.[3] With increasing life expectancies owing to innovations in systemic therapy for metastasis patients, there is a need for solutions to overcome these limitations.

Stereotactic body radiotherapy (SBRT) is a new treatment option for bone metastasis and can deliver high-dose radiation to the target volume, sparing adjacent at-risk organs; therefore, it is a promising approach for overcoming the limitations of cEBRT. Studies on spine SBRT report clinical advantages like high pain and local control rates,[4] high response rates against bone metastases from radio-resistant tumors,[5] and safe re-irradiation treatments.[6]

2. What are the appropriate endpoints?

While local control (LC) has commonly been used as the primary endpoint for bone metastasis treatment, this is not appropriate because it is not directly related to patient benefit. However, SBRT for bone metastasis has various utilities as described above. These can be roughly classified as either of curative or palliative intent. When SBRT is conducted with curative intent for bone oligometastases, the purpose is to prolong overall survival (OS), which should be evaluated as a primary endpoint. Incidentally, progression-free survival (PFS) is, theoretically, applicable as a surrogate endpoint for OS (although PFS has only been accepted as a surrogate endpoint for OS in colorectal cancer),[7,8] with LC comprising just one component of PFS. When bone SBRT is used with palliative intent, the purpose is to improve the quality of life (QOL); clinical symptoms like pain, neurologic function, and adverse events should be evaluated as primary endpoints. Although LC may correlate with improvement in pain and neurologic function, it can only indirectly evaluate the improvement of QOL. Therefore, even if SBRT is conducted for both curative and palliative intent, LC cannot be a direct evaluation method for therapeutic purposes. As data on SBRT for bone metastases was insufficient, evaluation of the biological effects of SBRT according to the LC rate might be beneficial. However, evaluation of clinically meaningful data using appropriate endpoints is necessary in the future.

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Table 1
Classification of bone SBRT according to treatment purpose.

	Oligo-metastases	Pain	MESCC*
De novo	Group **A-1/B-1**	Group **A-2/B-2**	Group **A-4**
Re-irradiation		Group **A-3/B-3**	Group **A-5**

A, spine metastases; B, non-spine bone metastases.
*MESCC, metastatic epidural spinal cord compression.

3. The five groups and endpoint of each group

We propose a new classification according to pathophysiology; SBRT for bone metastasis is categorized into five groups (Table 1). The treatment purpose for bone SBRT corresponds to a complete control of oligometastasis, pain relief, or LC of MESCC. Additionally, standard treatment and dose constraints differ depending on patient radiation history; hence, grouping is achieved by multiplying these values (three of the treatment purposes by two of radiation history). In SBRT treatment, the irradiation method differs depending on the presence or absence of the spinal cord; this necessitates the classification of patients into different categories. Appropriate endpoints are selected for the five groups, none of which includes LC.

3.1. Group A-1: spine SBRT for oligometastases

SBRT is used with curative intent in this group. The purpose of SBRT treatment for these patients is to prolong OS, with OS being used as the primary endpoint.

One optimal inclusion criterion for spine SBRT treatment is oligometastatic disease (≤5 extracranial metastases).[9] However, standard treatment for this group is systemic therapy; therefore, a randomized controlled trial (RCT) to evaluate the added effect of local treatments, including SBRT, on systemic treatment is required. Although several large-scale RCTs regarding this are ongoing,[10–14] they have limitations: metastatic lesions of various organs, in addition to the bone, are included in these trials; local treatment is not prescribed in protocols; and it is necessary to conduct trials for each type of primary cancer.

Recently, an RCT clarified the added effect of SBRT on systemic therapy in terms of median OS and PFS in patients with up to five metastatic lesions.[15] Thirty-five percent of cases allocated to the SBRT arm of the trial involved bone metastases; these results can be the foundation for guiding SBRT in patients classified into this group.

As SBRT is used as a curative treatment in this group, adverse events are less valid than survival for use as endpoints, meaning that mild toxicities are allowed in curative treatment and severe toxicities should be reflected in OS. Accordingly, we did not distinguish between cases with or without radiation history for group A-1.

3.2. Group A-2: de novo treatment involving spine SBRT for pain

SBRT is used with palliative intent in this group. The therapeutic purpose is the improvement of QOL, with clinical symptoms, such as pain and adverse events, being evaluated as primary endpoints.

Standard treatment is cEBRT. Several RCTs and subsequent meta-analyses[1] have shown no significant differences in pain relief rates between single and multi-fraction palliative radiotherapy for bone metastasis. In a recent randomized phase II trial in which SBRT was used for group A-2,[16] although significant differences were not observed in the primary endpoint of pain response rate at 3 months between the studied groups, a significant difference was observed after 6 months. Currently, several large-scale RCTs using initial pain response or pain response at 3 months as primary endpoints are ongoing.[17–20] Even with no significant difference in the primary endpoints, subclass analyses of radio-resistant spinal metastases or long-term observation may show superiority of SBRT.

Additionally, adverse events also are important contributors to QOL. Spine SBRT carries additional risks compared to cEBRT, including potential for pain flare,[21,22] vertebral compression fractures (VCF),[23] and radiculopathy.[24] Yamada et al. reported that spine SBRT using high-dose radiation (24 Gy in a single fraction) achieved good LC[5] with high VCF incidence.[25] Since SBRT for group A-2 has palliative intent, there is room for discussion regarding balance between efficacy and toxicity.

3.3. Group A-3: spine SBRT with re-irradiation for pain

SBRT is used with palliative intent in this group. The purpose is to improve QOL, with clinical symptoms, such as pain and adverse events, being evaluated as primary endpoints.

Adverse events significantly reduce QOL, especially in patients who have received previous high-dose radiotherapy. Nieder et al. reported the risk of radiation myelopathy induced by conventional re-irradiation.[26] Demonstrating SBRT safety with respect to avoiding radiation myelopathy is important, because this group includes cases in which conventional re-irradiations are difficult due to dose constraints of the spinal cord. While clinical trial data and retrospective data from large-scale long-term observations are valuable, retrospective data regarding patient background (i.e., previous irradiation dose) and SBRT methodology used (i.e., prescribed dose, dose constraints) needs to be similar.

An RCT on repeated cEBRT for lesions with an initial irradiated dose of ≤20 Gy reported a pain response rate of 28–32% on intention-to-treat analysis and of 45–51% in per-protocol population.[27] Contrastingly, a systematic review of re-irradiation SBRT that mainly involved retrospective studies showed a pain response rate of 65–81%.[6] Thus, superiority of SBRT seems apparent, even with differences in patient background. Although a phase I/II trial on re-irradiation SBRT for group A-3 has been reported, it was limited in terms of endpoints because no primary endpoint was included, in addition to no evaluation of analgesic consumption[28]; the study quality was judged as "low".[6] Since a part of this group cannot receive conventional re-irradiation, an RCT comparing SBRT and cEBRT is not necessarily required; however, high quality data regarding SBRT is required.

3.4. Group A-4: de novo treatment involving spine SBRT for MESCC

SBRT is used with palliative intent in this group. The purpose is to improve QOL; neurologic symptoms, mainly with ambulatory function, should be evaluated as primary endpoints.

Surgical intervention along with cEBRT plays a central role in the management of patients with MESCC, particularly in patients with neurologic deficits and high-grade compression.[29] In a previous RCT, surgical decompression followed by cEBRT of 30 Gy in 10 fractions was used as first-line therapy in patients with symptomatic single-level MESCC.[30] They reported post-treatment ambulatory rates in surgical decompression followed by cEBRT arm were superior to cEBRT arm alone. However, one study using radiographic findings reported that local progression occurred in 69.3% patients one year after conventional postoperative radiotherapy of 30 Gy in 10 fractions.[2] cEBRT of 30 Gy in 10 fractions was suggested to be insufficient for LC.

A practice guideline states that spine SBRT for MESCC alone is contraindicated in patients with high-grade epidural disease.[9] SBRT-based decompression is a slow process and, therefore, a long time is required to start SBRT[31]; it is difficult to deliver a sufficient dose to a tumor adjacent to the spinal cord. A retrospective study showed that decompression surgery before SBRT improves the LC rate, especially for MESCC of Bilsky grades 2 or 3,[32] and therefore, as with cEBRT, decompression, surgery is required before SBRT. The decision framework used at the Memorial Sloan-Kettering Cancer Center, called the neurologic, oncologic, mechanical, and systemic (NOMS) framework, recommends decompression surgery followed by SBRT as first-line treatment for high-grade MESCC.[33] However, based on the clinical evidence, the standard treatment for MESCC is decompression surgery followed by cEBRT of 30 Gy in 10 fractions. In the future, an RCT comparing cEBRT and SBRT after decompression surgery should be conducted.

3.5. Group A-5: spine SBRT with re-irradiation for MESCC

SBRT is used with palliative intent in this group. The purpose of treatment is to improve QOL and primarily neurologic symptoms with ambulatory function should be evaluated as the primary endpoint.

Although decompression surgery should be used before radiation in patients with surgical indications, standard radiation dose of 30 Gy in 10 fractions cannot be applied; 30 Gy in 10 fractions as second-course RT has not been proven to be safe in prospective clinical trials. Therefore, even if the safety of re-irradiation SBRT can be demonstrated, SBRT is accepted as a standard treatment for this group. To date, only a small-scale retrospective study limited to patients with both elements of re-irradiation SBRT and SBRT after surgical decompression has been reported[34]; the safety of re-irradiation SBRT has not been demonstrated.

3.6. Group B-1: non-spine bone SBRT for oligometastases

SBRT is used with curative intent in this group. The purpose is to prolong OS, with OS being used as the primary endpoint.

It is highly likely that patients in group B-1 will be included in clinical trials of populations similar to that of group A-1 (spine/oligo-metastases). Hence, evidence for group B-1 can be established by RCTs involving group A-1 patients. However, we classified group B-1 as independent because the irradiation methods of non-spine bone SBRT and spine SBRT are different. In bones with large volumes, like the sacral bone, intramedullary dissemination has been suggested,[35] indicating that a precise clinical target volume should be selected for SBRT with curative intent.

3.7. Group B-2: de novo treatment involving non-spine SBRT for pain

SBRT is used with palliative intent in this group. The purpose of treatment is to improve QOL, with clinical symptoms, such as pain, being used as primary endpoints.

The standard treatment for group B-2 patients is cEBRT, which is the same as that for group A-2 (spine/pain/de novo).[1] In a recent randomized phase II trial for painful non-spinal bone metastases, SBRT was found to be superior to cEBRT in terms of pain control at 2 weeks, 3 months, and 9 months with per protocol analysis.[36] Based on the study, large scale randomized trials comparing SBRT and cEBRT in group B-2 patients are warranted. However, the optimal dose fraction schedule is controversial because of a lack of data.

3.8. Group B-3: non-spine bone SBRT with re-irradiation for pain

SBRT is used with palliative intent in this group. The purpose of treatment is to improve QOL, with clinical symptoms, such as pain and adverse events, being evaluated as primary endpoints.

Standard treatment in this scenario is cEBRT, which is the same as that in group A-3 (spine/pain/re-irradiation), based on an RCT reported by Chow et al.[27] This trial included patients treated with an initial dose of up to 30 Gy in 10 fractions for non-spine bone metastases, with a standard second course of radiation using 20 Gy in multiple fractions or 8 Gy in a single fraction. Although RCTs that compare cEBRT and SBRT, with pain relief as a primary endpoint, are ultimately desired for group B-3, previous studies on SBRT in this situation, including retrospective studies, have not been reported.

In a daily clinical practice, a certain number of patients require re-irradiation after definitive radiotherapy, such as in cases of coxal bone metastases from prostate or cervical cancer and sternal metastases from breast cancer. There is no standard treatment for these cases due to initial radiation treatment of more than 30 Gy. If safety of re-irradiated SBRT can be demonstrated, SBRT may be accepted as standard treatment for such cases with risks of severe radiation toxicity.

4. Conclusions

We advocate the use of five groups for classification of SBRT treatment for bone metastases, according to pathophysiology. Evidence needs to be collected for each group, and prospective clinical trials using the appropriate endpoints should be conducted. We believe that the present report directs future clinical trials and helps in identifying appropriate treatment endpoints for each clinical scenario.

Author declaration

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We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Conflict of interest

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