CASE REPORT

First report of stereotactic body radiotherapy for large-volume spinal tumors

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Abstract Stereotactic body radiotherapy (SBRT) for spinal metastases is very effective for pain relief and local tumor control. However, high-level evidence is limited to lesions in a single vertebra or in 2 contiguous vertebrae. To clarify the toxicities, we report herein the results of treatment for 4 patients who received SBRT to large-volume spinal tumors. The lesions comprised bone metastasis from renal cancer, local recurrence of rectal cancer invading the spine, osteosarcoma, and giant cell tumor of bone in 1 case each. Tumor volumes ranged from 738 to 1,766 ml. Doses ranging from 24 Gy in 2 fraction to 35 Gy in 5 fractions were delivered. The median follow-up was 24 months (range 4–35 months). Pain reduction was achieved in all patients in 4 weeks after SBRT. The outcomes were partial response in 1 patient, stable disease in 2, and tumor progression in 1. One patient showed grade 3 acute radiation dermatitis 4 weeks after SBRT, and another patient showed grade 3 late radiation dermatitis.

Keywords Stereotactic body radiotherapy · Large-volume · Spinal tumor · Adverse events · Primary bone tumor

Introduction

Stereotactic body radiotherapy (SBRT) has emerged as a new treatment option for spinal metastases. Some phase II trials [1, 2] and numerous prospective and retrospective studies of these treatment methods have demonstrated that spine SBRT has a strong effect on pain and local control. SBRT can deliver high-dose radiation to the target volume, while sparing the adjacent organs at risk. This treatment modality is, therefore, considered to fit patients with oligo-metastases or re-irradiation cases, although it is based on experts' opinions only [3].

Only patients with lesions in 1 vertebra or 2 contiguous vertebrae have been treated with SBRT in clinical trials [1, 2]. It was reported that the median target volume in such cases was 38 ml (range 2–358 ml) [1]. However, among patients with oligo-metastases or who have already received radiotherapy, some have larger lesions in several contiguous vertebrae. For such cases, there are often no treatment choices available other than SBRT. However, none of those reports described SBRT for large-volume spinal tumors. We report here our treatment results for 4 patients who received SBRT for large (>500 ml) spinal tumors to clarify the toxicities.

Case reports

We have conducted spine SBRT for cases with oligo-metastases or re-irradiation. SBRT was conducted according to university of Toronto's treatment strategy in which the prescribed doses were 24 Gy in 2 fractions to the spine [4], 35 Gy in 5 fractions to sites other than the spine [5], and 30 Gy in 5 fractions to lesions at high risk of radiation injury. Taking into consideration previously

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delivered radiation doses based on the biological equivalent dose, we have set dose constraints to organs at risk (Table 1). Under the condition that the minimum isodose line was at least 95% of the planning target volume (PTV) receiving 70% of the prescribed dose, we set the delivered dose as high as the adjacent organs could tolerate. Two patients received SBRT using a Vero4DRT (Mitsubishi Heavy Industry, Tokyo, Japan), and the other 2 patients were treated using a TomoTherapy Hi-Art treatment system (Accuray, California). We evaluated tumor response by CT or MRI according to the Response Evaluation Criteria in Solid Tumors (version 1.1) [6], and adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

Patient #1: A 71-year-old man presented with oligometastases to the right iliac bone and 5th lumbar vertebra from left renal cancer (Table 2). He had pain without neurologic deficits. The primary lesion had been removed 2 months earlier. SBRT was chosen for the purpose of higher local control because of solitary bone metastasis. The PTV was 1,044 ml, and the prescribed dose was 35 Gy in 5 fractions (Fig. 1). The follow-up period was 35 months. Pain reduction was achieved 4 weeks after SBRT, with the numeric rating scale (NRS) improving from 4 to 0. The tumor response was judged as a partial response (Fig. 2), and the tumor shrinkage was maintained during follow-up. Seven months after SBRT, multiple bone metastases appeared in other sites, for which the patient received molecular-targeted drug therapy. Grade 1 nausea occurred in the acute period of SBRT. No late adverse events were observed.

Patient #2: A 79-year-old man presented with local recurrence of rectal cancer invading the sacrum, which had already been irradiated twice, at 60 Gy in 30 fractions

7 years earlier, and at 8 Gy in 1 fraction 6 months earlier. He experienced pain without neurological deficits. At the time of SBRT, the patient showed multiple lung and liver metastases, among others. The PTV was 1,766 ml, and the prescribed dose was 30 Gy in 5 fractions, delivered with palliative intent. Because this patient died due to the primary disease, the follow-up period was only 4 months. Pain reduction was achieved by 4 weeks after SBRT, with the NRS improving from 8 to 2, and the effect of pain control was maintained until 2 weeks before the death. The tumor response was progressive disease. No toxicity was observed during follow-up.

Patient #3: A 39-year-old man presented with local recurrence of osteosarcoma invading the 10th–12th thoracic vertebrae, which had been previously irradiated with a carbon ion beam to 70.4 GyE in 16 fractions. (GyE is defined as the physical doses multiplied by the relative biologic effectiveness of carbon ions [7]). At that time, the spinal cord was irradiated to 32 GyE. The patient had no pain, but neurologic deficits were present in the form of left leg palsy and grade 1 thermal hypoalgesia. The PTV was 739 ml and the prescribed dose was 24 Gy in 2 fractions. The follow-up period was 34 months. Although the tumor response was stable disease, tumor growth occurred 21 months after SBRT. Although there had been no deterioration or recovery of neurological functions during this time, paralysis of both lower legs developed with the tumor increase. Adverse events involved the development of grade 2 acute and grade 3 late radiation dermatitis (skin ulcer). The skin ulcer occurred 20 months after SBRT and continued thereafter.

Patient #4: A 49-year-old man presented with local recurrence of giant cell tumor of bone invading the 1st–3rd sacral vertebrae, which had been irradiated with 30 Gy in

Table 1 Summary of dose parameters for each case

	Case 1 35 Gy/5 fr	Case 2 30 Gy/5 fr	Case 3 24 Gy/2 fr	Case 4 30 Gy/5 fr
$D_{95} \%$ ($\geq 70\%$)	77.4%	57.7%	82.3%	73.3%
$D_{\max}$ ($\leq 140\%$)	112.9%	114.7%	122.0%	125.6%
Cord/cauda equine; $D_{\max}$	20.7 Gy (≤ 25.0)	16.7 Gy (≤ 17.0)	12.2 Gy (≤ 12.2)	15.7 Gy (≤ 18.0)
Lung; $V_{20 \text{ Gy}}$	–	–	0.9% (≤ 3.0)	–
Lung; $V_{10 \text{ Gy}}$	–	–	9.6% (≤ 10.0)	–
Lung; $V_5 \text{ Gy}$	–	–	29.0% (≤ 30.0)	–
Lung; D_{mean}	–	–	3.4 Gy (≤ 5.0)	–
Esophagus; $D_{1 \text{ cc}}$	–	–	17.5 Gy (≤ 20.0)	–
Heart; D_{mean}	–	–	6.1 Gy (≤ 4.0)	–
Stomach; $D_{\max}$	–	–	19.0 Gy (≤ 16.0)	–
Liver; $D_{1 \text{ cc}}$	–	–	18.2 Gy (≤ 20.0)	–
Small bowel; $D_{1 \text{ cc}}$	18.0 Gy (≤ 20.0)	14.7 Gy (≤ 20.0)	–	11.6 Gy (≤ 14.5)
Unilateral kidney; D_{mean}	–	4.1 Gy (≤ 5.0)	5.1 Gy (≤ 5.0)	–

(Dose constraints)

Table 2 Patient characteristics

Case	Tumor	Location	Volume (ml)	Reasons for SBRT	Prescribed dose
1	Bone metastasis from renal cancer	Rt. iliac and 5th lumbar bone	1,044	Oligo-metastasis	35 Gy/5 fr
2	Local recurrence of rectal cancer	5th lumbar—3rd sacral and both iliac bone	1,766	Re-irradiation	30 Gy/5 fr
3	Osteosarcoma	10th–12th thoracic bone	739	Re-irradiation	24 Gy/2 fr
4	Giant cell tumor of bone	1st–3rd sacral bone	1,385	Re-irradiation	30 Gy/5 fr

SBRT stereotactic body radiotherapy

Fig. 1 These images represent **a** axial CT and **b** dose distributions **Fig. 2** These images represent tumor response before and after SBRT. **a** Axial CT and MRI before treatment. **b** Axial CT and MRI after treatment. Tumor responses were partial response in Case 1, progressive disease in Case 2, and stable disease in Cases 3 and 4

15 fractions 9 years earlier. Neurological examination revealed palsy of the right lower leg and weakness in the right tibialis anterior muscle (manual muscle test [MMT] grade 1) and the right gastrocnemius and soleus muscles (MMT grade 3). The PTV was 1,385 ml, and the prescribed dose was 30 Gy in 5 fractions. Because this patient

died due to multiple metastases, the follow-up period was limited to 13 months. Pain reduction was achieved by 4 weeks after SBRT, with NRS improving from 10 to 4. Although the tumor response was stable disease, lung metastases occurred 8 months after SBRT. Grade 3 radiation dermatitis occurred 4 weeks after SBRT, which

improved at 12 weeks after SBRT. Neurological function showed neither deterioration nor recovery.

Discussion

We report 4 cases of large-volume spinal tumors treated using SBRT. Grade 3 acute and late radiation dermatitis occurred in 1 patient each. Grade 4 or greater toxicities were not observed during follow-up.

Some investigators have reported adverse events with spine SBRT. Sahgal et al. described a series of 9 cases of radiation-induced myelopathy (RM) and compared them with a cohort of 66 cases without RM [8]. They suggested that RM was caused by the small volume of the high-dose area in the thecal sac. Spine SBRT may increase the risk of vertebral compression fractures (VCF). Sahgal et al. reported that in a series of 252 patients with 410 spinal metastases treated using SBRT [9], 57 VCF (13.9%) were found. Multivariate analysis identified that higher risks of fracture were associated with doses ≥ 20 Gy per fraction, baseline fractures, lytic-type tumors, and misalignment. Esophageal toxicity with high-dose, single-fraction SBRT has also been reported. Brett et al. reported the rate of grade 3 or greater acute or late toxicity was 6.8% in 204 spinal metastases abutting the esophagus [10]. All organs adjacent to the target were considered to be at potential risk of serious adverse events.

We consider that SBRT for large-volume spinal tumors carries the following risks: (1) increase in the total number of monitor units delivered. (2) Correction of the intra-fraction error with image-guided radiation therapy is difficult. If the target involves part of the spine, correction of the error with distortion of the spine may be impossible, even with a six degree of freedom. (3) The area of contact between the target and the organ at risks is increased. As a result, there is a higher risk of serious adverse events if errors occur. (4) Large-volume spinal tumors treated with SBRT have a high risk of VCF. To evaluate this risk, the Spinal Instability Neoplastic Score (SINS) is used [11]. Large-volume spinal tumors tend to show high scores in 4 (pain; radiographic spinal alignment; spinal body collapse; and posterolateral involvement of spinal elements) of the 6 SINS components. In our study, the SINS was relatively high (12 in Case 1, 18 in Case 2, 16 in Case 3, and 18 in Case 4). Although we understood these potential risks, the patients did not have any treatment options other than SBRT except for Patient #1 with solitary bone metastasis, for whom SBRT was considered as an option for the purpose of higher local control. We conducted SBRT only after providing adequate explanation and obtaining informed consent from each patient.

As previously mentioned, SBRT is suitable for patients with oligo-metastases or for those who have previously undergone irradiation. Eligible cases in daily clinical practice are often found to have large-volume tumors, and it is important to determine the best treatment for such cases. Since the outcomes of SBRT for large-volume spinal tumors are unknown, evaluation of toxicities was the most important issue in the present study. Because SBRT for large-volume spinal tumor has the various risks as mentioned above, severe adverse events might occur. However, the adverse events in our study were considered acceptable. In addition, pain relief and local control were achieved for a certain period of time even for radio-resistant tumors. Despite of the preliminary experience of SBRT for 4 cases, this study made a role to suggest one of the treatment choices for such patients that local treatments other than SBRT were unavailable. Based on the results of this study, we are planning a multicenter trial to prove the efficacy and safety of SBRT for large-volume spinal tumors.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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