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A prospective multicentre feasibility study of stereotactic body radiotherapy in Japanese patients with spinal metastases

Kei Ito[1,*], Tomohisa Furuya[1], Naoto Shikama[2], Keiji Nihei[1], Hiroshi Tanaka[3], Yu Kumazaki[4], Hideki Nishimura[5], and Katsuyuki Karasawa[1]

[1]Division of Radiation Oncology, Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan [2]Department of Radiology, Juntendo University, Tokyo, Japan [3]Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, Japan [4]Department of Radiation Oncology, Saitama Medical University International Medical Center, Hidaka, Japan [5]Shion Daini Clinic, Osaka, Japan

*For reprints and all correspondence: Kei Ito, MD, PhD, Division of Radiation Oncology, Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. E-mail: keiito@cick.jp

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Abstract

Objective: Stereotactic body radiotherapy has emerged as an attractive alternative to conventional radiotherapy for spinal metastases. However, it has limitations, including the need for advanced techniques and specific adverse effects. The present trial aimed to validate the feasibility and safety of stereotactic body radiotherapy in Japanese patients with spinal metastases.

Methods: Patients with one or two spinal metastases received stereotactic body radiotherapy of 24 Gy in two fractions. The primary endpoint was the proportion of severe adverse effects ($\geq$ grade 3) in patients within 6 months after spine stereotactic body radiotherapy. Adverse effects were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4. The treatment protocol was considered feasible and tolerable if the proportion of severe adverse effects was 10% or less.

Results: Overall, 20 spinal segments in 20 patients who registered between March 2014 and October 2015 were included. Minor and major deviations were observed in the planning of 2 and 0 cases, respectively. The treatment completion rate was 100%. The median follow-up after registration was 24.5 (range: 1–61) months. Although four patients experienced acute grade 2 adverse effects, no grade 3 or higher adverse effects were observed within 6 months after spine stereotactic body radiotherapy. Vertebral compression fractures were observed in two patients (14 and 16 months after stereotactic body radiotherapy). The local control and pain response rates at 6 months were 100 and 83%, respectively.

Conclusion: This study demonstrated the feasibility and safety of spine stereotactic body radiotherapy in Japanese patients with spinal metastases.

Key words: spine SBRT, prospective clinical trial, feasibility study

Introduction

Spinal metastases may cause pain, spinal cord compression, hypercalcemia and pathologic fracture (1). Conventional external beam radiotherapy (EBRT) has been a standard-of-care management option and provides successful palliation of painful bone metastases with very few side effects (2).

However, this treatment has some limitations. First, the long-term local and pain control rates are low. One study using radiographic findings reported that local progression occurred in ~70% patients 1 year after conventional EBRT (3). Conventional EBRT has been found to result in progressively higher rates of pain failure with longer follow-up (4). Second, in cases having a history of high-dose radiotherapy, a second course of radiation is difficult to administer owing to the risk of radiation myelopathy (5). Since innovations in systemic therapy have extended the life expectancy in patients with metastatic disease, the need for long-term tumour and pain control and safe re-irradiation for spinal metastases is growing.

Stereotactic body radiotherapy (SBRT) with intensity-modulated radiotherapy in conjunction with an image-guidance technique has emerged as a new treatment option for spinal metastases (1). SBRT can deliver high doses of radiation to the target volume, while sparing adjacent organs at risk (OAR). Spine SBRT could therefore overcome the limitations of conventional EBRT. However, SBRT has certain limitations, including the need for advanced techniques (6,7) and unique adverse effects (AEs) (8–10). To the best of our knowledge, prospective clinical trials of spine SBRT from Japanese institutions have not been published. Hence, the present feasibility study was initiated to assess the feasibility and tolerability of SBRT in Japanese patients with spinal metastases.

Materials and methods

Patients

The eligibility criteria for patients were as follows: (i) aged 20–75 years, (ii) an Eastern Cooperative Oncology Group performance status of 0–1, (iii) group 1 or 2 on recursive partitioning analysis (RPA) (11), (iv) pathologically proven primary malignancy, (v) localized spinal metastasis (a solitary spinal metastasis or two contiguous spinal levels) diagnosed by magnetic resonance imaging (MRI), (vi) spinal lesions with no history of radiation, (vii) target spines classified as 'stable' according to the Spinal Instability Neoplastic Score (SINS) (12) and (viii) no spinal cord compression by the lesion, defined as Bilsky grade 0–1 (13). The following patients were excluded: (i) those who received systemic therapy, including cytotoxic chemotherapy, molecular target drugs and immune checkpoint inhibitors within 7 days prior to SBRT and (ii) those with advanced deformities in spinal alignment owing to vertebral compression fractures (VCF).

Study design

This was an open-label prospective feasibility study, conducted across three centres (Komagome Hospital, Saitama Medical University International Medical Center and Kobe Minimally Invasive Cancer Center) in Japan. The primary endpoint was the proportion of grade 3 or higher AEs within 6 months after spine SBRT. The treatment protocol was considered feasible and safe if the proportion of severe AEs was 10% or less. The secondary endpoints were the proportion of major deviations in SBRT planning and local control and pain response rates at 6 months after SBRT.

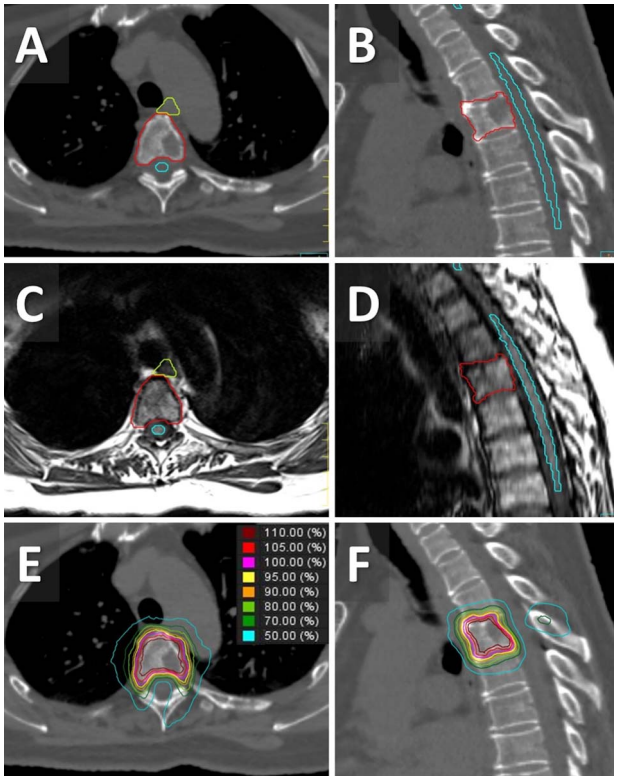

Figure 1. Images obtained from a 61-year-old woman with metastasis to the fourth thoracic vertebra from lung cancer. (A, B) Axial and sagittal computed tomography (CT) images with contouring for planning stereotactic body radiotherapy (SBRT). (C, D) Axial and sagittal T1-weighted magnetic resonance (MR) images with contouring for planning SBRT. (E, F) Axial and sagittal CT images with dose distributions of SBRT.

The study protocol was approved by all participating institutional ethical review boards (number: 1359 in the research representative institution), and written informed consent was obtained from all patients. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000013428).

SBRT

Planning computed tomography (CT) simulation was performed with a slice thickness of 1 mm, and all patients underwent MRI for delineation of the tumour and spinal canal. The clinical target volume (CTV) included the gross tumour, and immediately adjacent bony anatomic compartments at risk of microscopic disease extension, as described by the contouring guidelines for spine SBRT (14). The spinal cord and cauda equina were contoured based on T1- or T2-weighted MRI. Other OARs were contoured based on simulation CT images. A 1.5- to 2-mm margin was added to the CTV to create the planning target volume (PTV). A 1.5- to 2-mm margin was added to the spinal cord and defined as the planning OAR volume of the cord (PRV_{cord}). For the cauda equina, the thecal sac was contoured with no additional margin. The prescribed dose (PD) was 24 Gy in two fractions. All planning goals were to maximize PTV irradiated to 100% of the PD, on the condition that 95% of PTV be irradiated to 70% of the PD even if it is in proximity to the OARs ($70\% \times PD \leq D_{95\%}$). In addition, we set two constraints for the PTV: dose to 50% of the volume to be between 95 and 105% of PD ($95\% \times PD \leq D_{50\%} \leq 105\% \times PD$) and maximum dose to be limited

Table 1. Dose constraints

Organs	Dose constraints
Larynx	$D_{1\ cc} < 20$ Gy
Bronchus	
Oesophagus	
Rib	
Stomach	
Duodenum	
Bowel bag	
Rectum	
Lung	As low as possible
Liver	$D_{5\ cc} < 20$ Gy
Kidney	Unilateral: $D_{mean} < 5$ Gy
	Bilateral: $D_{mean} < 9$ Gy
Skin	$D_{1\ cc} < 26$ Gy

$D_{X\ cc}$ = dose irradiated to the X cc of the planning target volume.

to 140% of PD ($D_{max} \leq 140\% \times$ PD) (Fig. 1). Dose constraints were set for the PRV_{cord} and cauda equina so that the maximum point dose (the point indicated as 0.035 cc [15]) was <17 Gy based on the report by Sahgal et al. (16). Dose constraints of other OARs are summarized in Table 1.

Evaluation and statistical analysis

All patients were followed up 2 weeks; 1, 3 and 6 months after SBRT and every 3 months thereafter. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (17). Acute AEs are those arising within 90 days, and late AEs are those arising after 90 days of completion of protocol treatment. Tumour response was evaluated as elimination, shrinkage, stable disease and tumour progression on MRI or CT, and local control was defined as elimination, shrinkage or stable disease of the tumour. In cases showing pain at SBRT, pain response was evaluated as complete response or partial response based on the International Consensus Pain Response Endpoints guideline (18), using the numerical rating pain score and the amount of analgesic consumption as indicators.

Local control was calculated in months from the date of registration to the date of tumour progression for the treated spinal segment or the last follow-up imaging study if local control was maintained; death was not included as an event in terms of local control. Overall survival (OS) was defined as the interval between registration and the most recent follow-up or death from any cause. Local control and OS were estimated using the Kaplan–Meier method. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) software (19).

Results

A total of 20 spinal segments in 20 patients registered between March 2014 and October 2015 were included. All patients satisfied the eligibility criteria. Patients' characteristics are summarized in Table 2. The numbers of patients treated in the cervical, thoracic, lumbar and sacral spine were 2, 7, 10 and 1, respectively. Two patients had metastases in two adjacent spines. Lesions with VCF before SBRT were not confirmed.

Minor deviations were observed in the planning of two patients (10%); $D_{1\ cc}$ of skin was higher (27.2 Gy) than constraints (26 Gy), and $D_{50\%}$ of PTV was higher (27.4 Gy) than the protocol dose (25.2 Gy). There were no major deviations. All patients completed the treatment protocol without interruption. Median follow-up was 24.5 (range: 1–61) months. Eight patients died owing to disease progression. The OS rate at 6 months was 80% and median survival time was 51 months (Fig. 2). Overall, three patients experienced grade 2 acute nausea and one patient experienced vomiting. Additionally, pain flare was confirmed in three patients. Grade 3 or higher acute toxicities were not observed. Regarding late AEs, no grade 2 or higher treatment-related toxicities were observed during follow-up. However, *de novo* VCF was observed in two patients (14 and 16 months after SBRT). The local control rates at 6 and 12 months were 100 and 85%, respectively (Fig. 2). In terms of pain control, seven (100%) of the seven patients experiencing pain at SBRT achieved pain response following SBRT, and five (71%) patients achieved complete response. The pain response rate (complete + partial response) at 6 months was 83% (5/6 patients).

Table 2. Patient and tumour characteristics

Characteristic	20 segments in 20 patients
Sex	
Male/female	12/8
Mean age (years)	61 (range, 35–75)
RPA	
Group 1/2	12/8
Lesion histopathology	
Lung	4
Breast	4
Thyroid	3
Colorectal	3
Other	6
Levels treated	
Cervical/thoracic/lumbar/sacral	2/7/10/1
Number of spinal levels	
1/2	18/2
Bilsky grade	
0/1a/1b/1c	12/2/4/2

RPA, recursive partitioning analysis.

Discussion

In the current trial, major deviations in planning were not observed, and all patients completed the treatment protocol without interruption. Moreover, no serious AEs were observed during follow-up.

SBRT is associated with additional risks compared to conventional EBRT, including the potential for VCF, pain flare or radiculopathy (8–10). In particular, the incidence of VCF has been reported to be 5.7–39% (8). The rate of VCF observed in our trial was relatively low, at 10% (2/20 patients). The reasons were considered to be as follows: (i) only patients with good performance status were included, (ii) the lesions with advanced VCF at SBRT were excluded, (iii) the PD per fraction was not extremely high and (iv) the central dose was not increased. The present trial confirmed that the methodology of spine SBRT was feasible and safe.

There are considerable variations in dose fraction schedules among reports, and the optimal dose is unknown (20). Currently, several large-scale randomized control trials using pain response as primary endpoints are ongoing (21–24). The results may aid in defining standard dose fraction schedules (16 or 18 Gy in a single

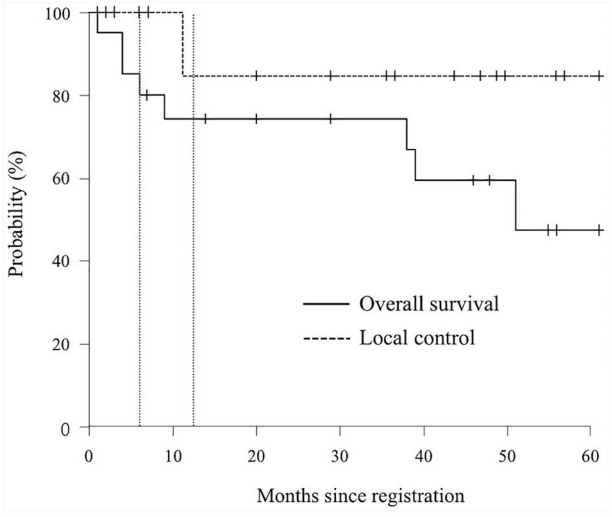

Figure 2. Kaplan–Meier estimates of overall survival and local control after spine SBRT.

fraction, 20 Gy in a single fraction or 24 Gy in 2 fractions). The dose of 24 Gy in two fractions used in this study was adopted from Canadian methodology. Additionally, there is no consensus on planning methods with regard to the optimal PD for the target. Furuya et al. reported that a simplified set of target dose constraints (e.g., only $D_{95\%}$ PD delivery) causes substantial target dose variations (25) and concluded that the target dose should be defined by multiple dose-volume objectives to minimize such a dose variability in spine SBRT (26). Based on this suggestion, we prescribed the target dose using three dose objectives ($D_{95\%}$, $D_{50\%}$ and D_{max}). However, regarding clinical data, some studies have reported positive correlations between $D_{95\%}$ of the gross tumour volume and tumour control rates (27–29). These studies have suggested that the dose inside the target should be increased rather than be limited.

The current study had several limitations. First, the sample size was small; hence, this study confirmed that spine SBRT has a minimum safety margin. Second, this trial could not establish whether the set-up margin of 1.5–2 mm was feasible, particularly in patients with painful metastases. Although the set-up accuracy of spine SBRT depends on the pain intensity during treatment, most patients did not suffer from pain at SBRT (13 and 3 patients without and with mild pain, respectively). Third, since the purpose of the present study was to determine the feasibility and safety, it was difficult to evaluate the efficacy. The treatment purpose of spine SBRT is complete control of oligometastasis, pain relief, local control of epidural spinal cord compression or safe re-irradiation. It is necessary to confirm each benefits; we are conducting phase II clinical trials using the methodology of the current trial (UMIN000030056, UMIN000033132 and UMIN000036849).

In conclusion, this is the first prospective study to investigate the feasibility and safety of spine SBRT in Japanese patients with spinal metastases. The results and treatment techniques described will be of particular benefit to Japanese radiation oncologists to perform spine SBRT.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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