Advances in Radiation Oncology (2025) **10**, 101760

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Phase 2 Trial of Stereotactic Body Radiation Therapy with Dose Escalation Using Simultaneous Integrated Boost for Spinal Metastases

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Received 22 October 2024; accepted 3 March 2025

Purpose: Stereotactic body radiation therapy (SBRT) is an effective treatment approach for spinal metastases. However, local recurrence may occur. This prospective phase 2 trial evaluated whether SBRT with dose escalation in the gross tumor volume through simultaneous integrated boost (SIB−SBRT) can improve local control (LC) without increasing adverse events (AEs).

Methods and Materials: Eligible patients aged ≥ 20 years with spinal metastases and a life expectancy of > 1 year received SIB−SBRT in 5 fractions over 1 week. The prescribed dose was 30 Gy to the planning target volume for evaluation and an escalated dose of 40 to 45 Gy to the gross tumor volume through SIB. Neurologic examinations and magnetic resonance imaging were performed at 3-, 6-, and 12-month follow-up and every 6 months thereafter. The primary endpoint was the 1-year LC rate. The secondary endpoints included overall survival and AEs, such as vertebral compression fractures (VCFs).

Results: A total of 25 patients with 28 vertebral segments from September 2020 to March 2023 were enrolled in this study. The median follow-up was 26.2 months, and 24 segments in 21 patients were followed up for >1 year. The 1- and 2-year LC rates were 100.0% and 95.0%, respectively. Local recurrence developed in only 1 patient at 18 months. The 1- and 2-year overall survival rates were 92.0% and 72.8%, respectively. Six patients developed VCFs (3 cases each of grades 1 and 2), with 1- and 2-year cumulative incidence rates of 3.6% and 15.6%, respectively. No radiation myelopathy or other grade ≥ 2 AEs occurred, except for 1 case of grade 2 pain.

Conclusions: Dose-escalated SIB−SBRT for spinal metastases demonstrates excellent LC with acceptable toxicity, supporting the need for a larger comparative trial.

Sources of support: This work was supported by a Grant-in-Aid for Scientific Research (C) 19K17138 from the Japan Society for the Promotion of Science and by the Katakami Foundation for Clinical Research at Kobe City Medical Center General Hospital.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2025.101760

Introduction

In patients with advanced cancer, bone metastasis occurs most frequently in the spine.[1] Spinal metastases can sometimes cause pain and neurologic complications, including spinal cord compression.[2] Conventional palliative radiation therapy has been a standard treatment approach for relieving pain, preventing neurologic symptoms, and reducing pathologic fractures with minimal side effects.[3,4] However, local recurrence (LR) frequently occurs during long-term follow-up after conventional palliative radiation therapy. The use of new systemic therapies, including targeted therapies and immunotherapies, has considerably improved prognosis in patients with advanced cancers.[5,6] Therefore, achieving long-term local control (LC) after palliative radiation therapy is crucial.

Stereotactic body radiation therapy (SBRT) combined with intensity-modulated radiation therapy (IMRT) is a new treatment option for selected patients with spinal metastases and good prognosis.[7-11] SBRT can deliver higher biologically effective doses to spinal metastases than conventional palliative radiation therapy, resulting in long-term LC.[10-12] However, systematic reviews have reported that a subset of patients may experience LR after SBRT, with 1-year LC rates ranging from 80% to 90%.[7,8,11]

Several studies have demonstrated a correlation between the prescribed dose and LC, indicating that higher doses are associated with improved LC rates.[8,13,14] However, achieving uniform dose escalation in target volumes, such as the planning target volume (PTV) and clinical target volume (CTV), as recommended by consensus contouring guidelines for spinal SBRT,[15,16] is challenging because of the dose constraint of the spinal cord.[17] Meanwhile, some reports have suggested that the dose to the gross tumor volume (GTV) is a significant factor for LC.[18,19]

Based on these previous studies, we hypothesized that escalating the GTV dose rather than the PTV and CTV doses, within the limits of spinal cord dose constraints, can improve LC rates without increasing the risk of radiation myelopathy. Thus, we proposed a new SBRT method using IMRT with dose escalation in the GTV through simultaneous integrated boost (SIB−SBRT). A prospective phase 2 trial was conducted to evaluate the efficacy and safety of dose-escalated SIB −SBRT for spinal metastases in patients with intermediate or long overall survival (OS) expectancy. To the best of our knowledge, this is the first prospective evaluation of the clinical outcomes of SIB−SBRT for spinal metastases.

Methods and Materials

Study design and patient selection

This open-label, single-center, single-arm, prospective phase 2 trial evaluated the clinical outcomes of SIB −SBRT with dose escalation to the GTV in patients with spinal metastases. The study protocol was approved by our institutional ethical review board, and written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and was registered in a clinical trials registry.

Patients were included in the study based on the following criteria: (1) presence of spinal metastases; (2) expected life expectancy of at least 1 year; (3) aged ≥ 20 years; (4) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 to 2; and (5) signed informed consent. Exclusion criteria were as follows: (1) previous radiation therapy to the treatment area; (2) failure to meet dose constraints for nearby organs at risk; (3) emergency irradiation because of paralysis risk; (4) inability to assess precise dose distribution because of metal artifacts; (5) mental disorders affecting daily life and trial participation; and (6) deemed unsuitable by the patient's primary physician.

Evaluation of pretreatment

All patients underwent the following pretreatment evaluations: (1) systemic radiographic examinations, such as fluorodeoxyglucose-positron emission tomography, bone scintigraphy, or thoracoabdominal computed tomography (CT); (2) axial contrast-enhanced or non −contrast-enhanced high-resolution 3-dimensional T1- and T2-weighted magnetic resonance imaging (MRI) with a slice thickness of 1 mm covering at least 1 vertebral body above and below the target vertebra; (3) blood tests; (4) pain assessment; (5) neurologic symptom assessment; (6) assessment of spine stability in patients with metastatic spinal cord compression using the Spinal Instability Neoplastic Score[20]; (7) assessment of the degree of spinal cord compromise and compression caused by vertebral body metastasis using the Bilsky score[21]; and (8) ECOG-PS evaluation.

Treatment

All patients underwent treatment planning CT with a slice thickness of 1.25 mm while being immobilized using a thermoplastic head mask for lesions in the cervical or upper-thoracic spine or a vacuum cushion device for lesions in the midthoracic or lower spine. For radiation therapy planning, the CT and high-resolution MRI data sets were fused using Eclipse treatment planning software (version 16.1, Varian Medical Systems).

The GTV, representing the macroscopic metastasis, was delineated on the fused treatment planning CT with reference to MRI. The CTV was delineated according to the consensus contouring guidelines for spinal SBRT,[15,16] encompassing the GTV, surrounding vertebral body, and

all spinal structures deemed at risk for recurrence, including the pedicle, lamina, ala, and posterior elements. The PTV was created by expanding the CTV by 2 mm laterally and 5 mm superior-inferiorly. The PTV for evaluation (PTV_Eval) for the cervical, thoracic, and lumbar spines was created by excluding the spinal canal, whereas that for the sacrum was created by excluding the sacral canal and the bony foramen. The spinal cord and thecal sac were delineated based on T2-weighted MRI. The planning organ at risk volume for the spinal cord (SpinalCord_PRV02) was created with a 2-mm expansion. Below the L2 vertebral level, the thecal sac—including the cauda equina and the intrathecal and extrathecal nerve roots visible on T2-weighted MRI—was contoured without an additional margin. Other organs at risk were delineated using images acquired from the treatment planning CT. Figure 1 shows some examples of the treatment plan, including pretreatment axial T1-weighted MRI with the GTV (Fig. 1a), axial T2-weighted MRI with the spinal cord and SpinalCord_PRV02 (Fig. 1b), and axial CT images with the GTV, CTV, PTV_Eval, and all organs at risk (Fig. 1c).

Patients received a total dose of 30 Gy in 5 fractions over 1 week, with 90% coverage of the PTV_Eval by the prescribed dose. The GTV dose was escalated through SIB within dose constraints for the target volumes, SpinalCord_PRV02, and thecal sac, as shown in Table 1. Dose constraints for other organs at risk are described in Table E1. Volumetric modulated arc therapy was employed in all cases. Axial CT images with the dose distribution of SIB−SBRT are shown in Fig. 1d, and a dose−volume histogram is presented in Fig. E1. Treatments were delivered using a TrueBeam linear accelerator (Varian Medical Systems) equipped with a 2.5-mm multileaf collimator, kilovoltage cone-beam CT image guidance system, and robotic couch that allowed patient position corrections with 6 degrees of freedom.

Follow-up

Follow-up evaluations, including neurologic and pain assessments and MRI, were performed at 2 weeks (physical assessment only) and at 3, 6, and 12 months posttreatment, followed by assessments every 6 months thereafter. Systemic radiographic examinations, identical to those performed before treatment, were conducted annually posttreatment.

Endpoints

The primary endpoint was the 1-year LC rate for vertebral segments in patients who underwent the protocol treatment. We defined LC as the absence of progression within the treated area on serial imaging, assessed according to the SPIne response assessment in Neuro-Oncology (SPINO) criteria via follow-up MRI,[22] which was conducted every 6 months under the same conditions as pretreatment MRI. Additional imaging modalities were used as necessary. At least 1 radiologist and 1 radiation oncologist diagnosed the presence or absence of recurrence using MRI and other imaging examinations. The LC duration was defined as the period from SBRT initiation until the date of LR or until follow-up imaging confirmed no recurrence. The secondary endpoints included OS, pain improvement, and adverse events (AEs), including vertebral compression fractures (VCFs). VCF was defined as either a new fracture or collapse in a vertebral segment or the progression of an existing fracture in a segment with a baseline VCF, compared to pre-SBRT imaging. The OS duration was defined as the period from SBRT initiation to the date of death or last follow-up. AEs were graded according to the Common Terminology Criteria for Adverse Events version 5.0. VCF incidence was evaluated using MRI every 6 months.

Statistical analysis

All patients who received at least part of the protocol treatment were included in the analysis. LC and OS rates were estimated using the Kaplan−Meier method. VCF incidence was calculated via the cumulative incidence function, accounting for death without events as a competing risk. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) software.[23]

The study sample size was calculated using a 1-sided significance level of 10%, power of 80%, expected value of 95%, and threshold value of 80%, as reviewed in studies on spinal SBRT.[7,8] The calculated sample size was 26 vertebral segments. The sample size was increased to 28 to account for potential protocol deviations.

Results

A total of 25 patients with 28 vertebral segments between September 2020 and March 2023 were enrolled in this study. All patients met the inclusion criteria and underwent pretreatment evaluation. Patient and tumor characteristics are shown in Table 2. The GTV locations are shown in Table E2. Three patients underwent the protocol treatment for 2 unique vertebral segments each. Six patients experienced pain and 2 patients experienced neurologic symptoms before treatment.

All radiation therapy plans adhered to the protocol criteria with no major deviations. The median dose delivered to 50% of the GTV (GTV $D_{50\%}$) and 98% of the GTV (GTV $D_{98\%}$) were 43.2 (range, 41.3-45.7) Gy and 32.8 (range, 25.3-41.4) Gy, respectively. The dosimetric

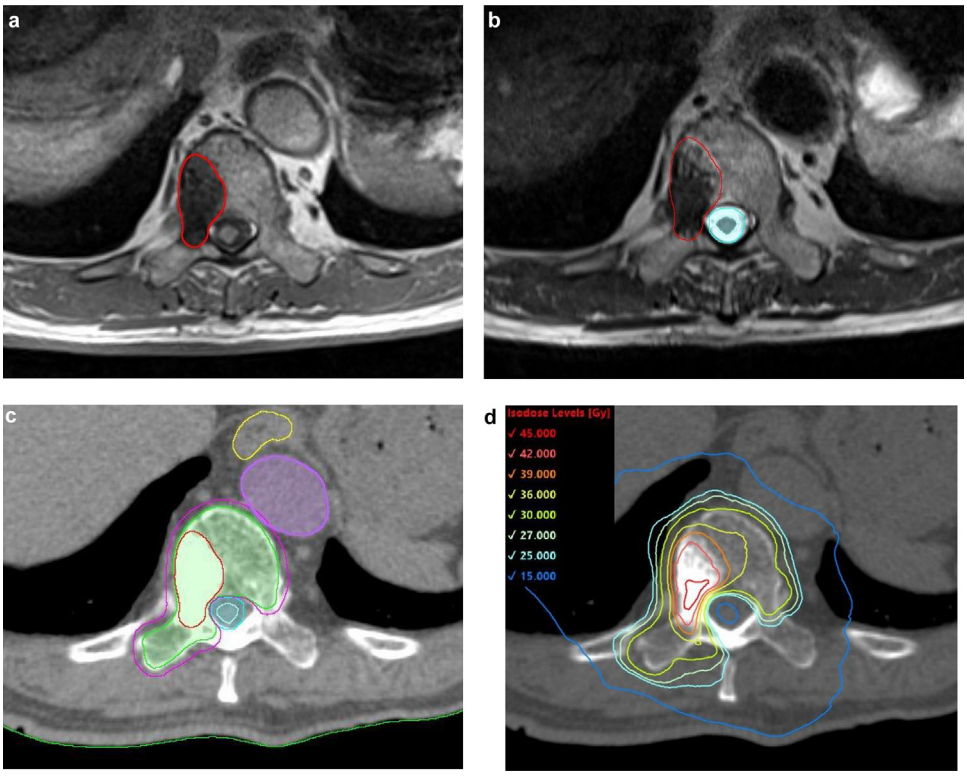

Figure 1 (a) Axial T1-weighted MRI with GTV (red). (b) Axial T2-weighted MRI with spinal cord and SpinalCord_PRV02 contours (light blue). (c) Axial CT images with CTV (yellow-green), PTV_Eval (pink), and organs at risk. (d) Axial CT images with dose distribution of SIB−SBRT.

Abbreviations: CT = computed tomography; CTV = clinical target volume; GTV = gross tumor volume; MRI = magnetic resonance imaging; PRV = planning organ at risk volume; PTV_Eval = planning target volume for evaluation; SBRT = stereotactic body radiation therapy; SIB = simultaneous integrated boost.

parameters for the GTV, PTV_Eval, SpinalCord_PRV02, spinal cord, and thecal sac are shown in Table E3. The field shapes are shown in Table E4. All patients received at least part of the protocol treatment and were included in the analysis. All but 1 patient completed the specified protocol treatment. One patient could not complete the protocol treatment because of excessive pain, which prevented hospital visits and treatment within the specified period.

The median follow-up time was 24.0 (range, 3.9-37.2) months per vertebral segment and 26.2 (range, 4.8-39.1) months per patient. Overall, 24 segments from 21 patients

Table 1 Upper and lower dose limits for target volume and organs at risk

Volume		Optimal	Mandatory
PTV_Eval	$D_{2\%}$	≥42 Gy and ≤48 Gy (≥140% and ≤160%)	≤51 Gy (170%)
	$D_{90\%}$	30 Gy (100%)	≥29.7 Gy and ≤30.3 Gy (≥99% and ≤101%)
	$D_{98\%}$	≥27 Gy (90%)	≥21 Gy (70%)
GTV	$D_{2\%}$	≥45 Gy and ≤48 Gy (≥150% and ≤160%)	≤51 Gy (170%)
	$D_{50\%}$	≥42 Gy (140%)	≥36 Gy (120%)
	$D_{90\%}$	≥36 Gy (120%)	≥27 Gy (90%)
	$D_{98\%}$	≥27 Gy (90%)	≥21 Gy (70%)
SpinalCord_PRV02	$D_{0.03cm^3}$		≤25 Gy
Thecal sac	$D_{0.03cm^3}$		≤30 Gy

Abbreviations: $D_{xx\%}$ = minimum dose delivered to xx% of the respective target volume; D_{yycm^3} = minimum dose delivered to yy cm^3 of the respective target volume; GTV = gross tumor volume; PRV = planning organ at risk volume; PTV_Eval = planning target volume for evaluation.

Table 2 Patient and vertebral segment characteristics

Patient characteristics (n = 25 patients)	Data
Median age (range), y	70 (43-86)
Sex	
Male	15
Female	10
ECOG performance status	
0	20
1	5
Tumor characteristics (n = 28 vertebral segments)	
Primary cancer	
Breast	9
Prostate	8
Lung	4
Renal	4
Other	3
Location of treated tumor	
Cervical	1
Thoracic	11
Lumbar	10
Sacrum	6
SINS classification	
Stable (score, 0-6)	22
Potentially unstable (score, 7-12)	6
Bone lesion characteristic	
Lytic	5
Mixed	16
Blastic	7
Baseline VCF	
Yes	1
No	27
Bilsky score (n = 22)	
0	7
1a	12
1b	0
1c	3
Median PTV_Eval, cm^3 (range)	70.2 (17.3-468.7)
Median GTV, cm^3 (range)	9.5 (1.1-183.4)

Abbreviations: GTV = gross tumor volume; ECOG = Eastern Cooperative Oncology Group; PTV_Eval = planning target volume for evaluation; SINS = Spinal Instability Neoplastic Score; VCF = vertebral compression fracture.

were followed up using MRI for >1 year. At the time of analysis, 18 patients were still alive, whereas 7 died from the primary disease. No cases were lost to follow-up. Figure 2 shows the LC and OS rates of the study cohort. The 1- and 2-year LC rates were 100% (95% CI, could not be calculated) and 95.0% (95% CI, 69.5%-99.3%), respectively (Fig. 2a). Only 1 patient developed LR, which occurred at 18 months; this patient had renal cell carcinoma with sacral metastasis and a GTV of 183 cm^3 in the sacrum, which was the largest GTV in the study. Details regarding this case are provided in the Supplementary Material, including the case description in Material E1, as well as Fig. E2 and Table E5. The 1- and 2-year OS rates were 92.0% (95% CI, 71.6%-97.9%) and 72.8% (95% CI, 48.7%-86.9%), respectively (Fig. 2b). Among the 25 patients, 6 experienced pain and 2 experienced neurologic symptoms, including numbness, at the time of SBRT. All 6 patients achieved pain relief after SBRT, with 5 of them showing complete relief. The 2 patients with neurologic symptoms showed improvement.

AEs occurred in 9 patients. Six vertebral segments developed VCFs, including grade 2 (symptomatic) and grade 1 (asymptomatic) AEs in 3 patients each. The median time to VCFs after treatment was 17.0 (range, 0.9-29.5) months. The segment and other characteristics of patients with VCFs are presented in Table E6. The 1-year and 2-year cumulative VCF incidence rates were 3.6% (95% CI, 0.2%-15.7%) and 15.6% (95% CI, 4.7%-32.4%), respectively (Fig. 3). All VCFs were managed conservatively within a few months after onset. Other radiation-induced AEs included grade 2 pain, grade 1 esophagitis, and grade 1 radiculitis in 1 patient each. No radiation myelopathy or neurologic AEs were observed; moreover, no other grade 2 or higher AEs were reported.

Discussion

This prospective phase 2 trial aimed to evaluate the efficacy and safety of SIB−SBRT with dose escalation to the GTV for spinal metastasis. The 1-year LC rate was 100%, achieving the predetermined primary endpoint. Systematic reviews have reported LC rates of 80% to 90% after spinal SBRT.[7,11] Most patients in the current study completed the 1-year posttreatment evaluations and underwent MRI every 6 months during the follow-up period. Therefore, the observed LC rates in the current study were considered reliable and favorable compared with those reported in previous studies,[7,11] indicating that the protocol treatment showed high effectiveness in dose delivery. No severe toxicity or radiation myelopathy occurred during the follow-up period, and the incidence of VCFs was within the acceptable range. Overall, our

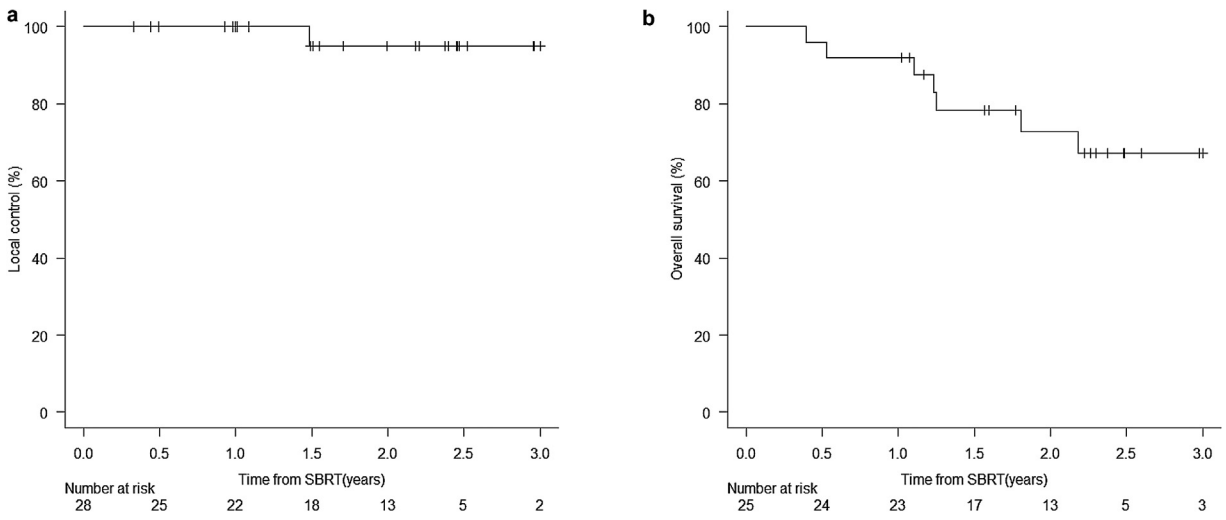

Figure 2 Kaplan−Meier curves showing (a) local control rate (n = 28 vertebral segments) and (b) overall survival rate after SIB −SBRT (n = 25 patients), including the number-at-risk at each time point for the survival curves and indicating when patients were censored.
Abbreviations: SBRT = stereotactic body radiation therapy; SIB = simultaneous integrated boost.

results demonstrated that the delivery of dose-escalated SIB−SBRT to the GTV is a highly effective method for treating spinal metastases with acceptable toxicities.

We also investigated whether the LC rate observed in our study was reasonable from the perspective of the biologic effective dose. A large retrospective study demonstrated that LC improves with higher prescribed doses.[14] Based on logistic dose−response models from the Hypofractionated Treatment Effects in the Clinic group encompassing 24 papers and 2619 spinal metastases, the α/β ratio for LC after spinal SBRT was estimated to be 6. To achieve a 2-year LC rate of 90% or higher, a dose of more than 40 Gy in 5 fractions was necessary.[13] In the present clinical trial protocol, the GTV $D_{50\%}$ dose was set at ≥42 Gy as an optimal goal and at least 36 Gy as a mandatory requirement. Although precise comparison with the doses from the logistic dose−response model from the Hypofractionated Treatment Effects in the Clinic group was difficult because the model was based on prescribed doses, all treatment plans in our study achieved a GTV $D_{50\%}$ of at least 40 Gy, indicating adequate dose delivery to the GTV. Other studies reported that a minimum dose of 14 Gy to the GTV in a single fraction is necessary to achieve durable LC, which is equivalent to a total dose of 25.3 Gy in

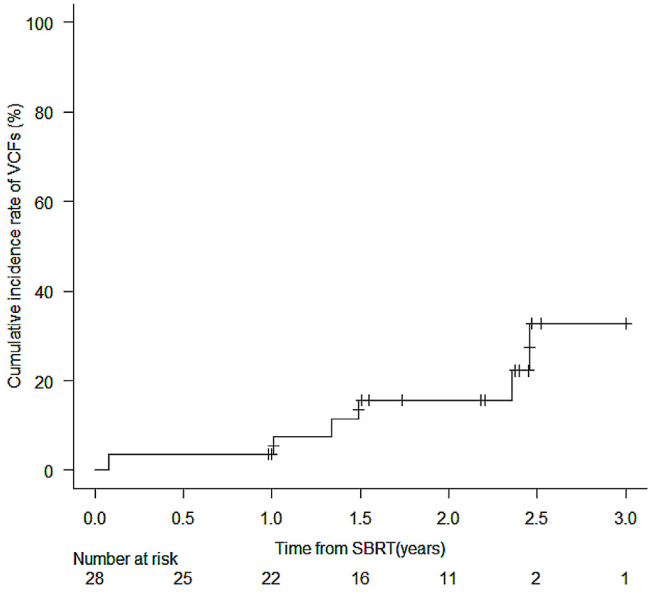

Figure 3 Cumulative incidence rate of vertebral compression fractures (VCFs).

5 fractions based on an α/β ratio of 6.[18,19] In our study, the minimum $D_{98\%}$ dose in all treatment plans was above the reported dose required to achieve durable LC. Therefore, the prescribed dose used in our study is theoretically sufficient in terms of dose calculation to achieve durable LC.

According to systematic reviews, VCF is one of the most common AEs that occur following SBRT for spinal metastases.[7,11,24] VCF occurs in 10% to 30% of patients and typically develops within 3 to 6 months after treatment.[25,26] A large retrospective cohort study that included 464 spinal metastases reported a VCF frequency of 18% and a median time to VCF development of 9 months after SBRT.[27] Despite the longer median follow-up period in our study compared with that in previous reports, the VCF rates were similar to those reported previously. Additionally, 50% of the VCF cases in our study were asymptomatic (grade 1) and were detected during routine follow-up imaging. Thus, the VCF frequency using our treatment protocol is within an acceptable range. Furthermore, no radiation myelopathy or neurologic AEs were observed. Hence, the overall incidence of AEs following the protocol treatment was acceptable.

Varying dose-fractionation schedules have been reported for spinal SBRT in systematic reviews,[9,11] although the volumes for which the prescribed doses are specified remain consistent. Most studies have specified the radiation dose only for the PTV, whereas a few retrospective studies have specified radiation doses for not only the PTV but also the GTV; moreover, the GTV doses in these studies were escalated using SIB.[28,29] Despite using conventional palliative radiation therapy, these studies reported favorable treatment outcomes. To the best of our knowledge, the method of specifying doses to both the PTV and GTV, with dose escalation to the GTV, has not been applied in spinal SBRT. Thus, this prospective clinical trial using this irradiation method in spinal SBRT and the comprehensive evaluation of both dosimetric parameters and clinical outcomes are novel.

This study had several limitations. First, the sample size was small and the study followed a single-arm design; thus, conclusive results could not be obtained. A larger randomized clinical trial is needed to confirm the efficacy and safety of dose-escalated SIB−SBRT for spinal treatments over a longer period. Second, although the 1-year LC rate appeared highly favorable, it is important to note that 4 out of the 28 segments did not undergo the 1-year MRI follow-up because of disease-related deaths, which may have contributed to the seemingly favorable results. Third, the evaluation of pain relief was limited because most patients (19 of 25 cases) did not experience pain at the beginning of the treatment. Thus, a larger study is necessary to assess the pain relief rate using this method. However, all 6 patients who experienced pain achieved pain relief, suggesting that our method can effectively control pain. Fourth, the study included only patients with an expected life expectancy of $\geq$ 1 year. Thus, the applicability of the proposed method in all patients, including those with shorter life expectancies, remains unclear. Traditional conventional palliative radiation therapy may be more appropriate in patients with shorter life expectancies, considering the risk of AEs.

Conclusions

This prospective phase 2 trial assessed the efficacy and safety of SIB−SBRT with dose escalation to the GTV for spinal metastases. The LC rate was excellent. The predetermined primary endpoint was achieved, demonstrating the effectiveness of the treatment. No severe toxicity or radiation myelopathy occurred, and the incidence of VCFs was within an acceptable range. Based on our results, this radiation therapy approach is an effective treatment method for spinal SBRT. Future studies should include large comparative trials to validate our findings and assess long-term clinical outcomes.

Disclosures

Takamasa Mitsuyoshi reports financial support, article publishing charges, and travel were provided by Japan Society for the Promotion of Science. Takamasa Mitsuyoshi reports a relationship with AstraZeneca Kabushiki Kaisha that includes: speaking and lecture fees. Masaki Kokubo reports a relationship with AstraZeneca Kabushiki Kaisha that includes: speaking and lecture fees. Masaki Kokubo reports a relationship with Varian Medical Systems that includes: speaking and lecture fees. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all involved colleagues from the Department of Radiation Oncology, Diagnostic Radiology, and Radiological Technology for their valuable support. Takamasa Mitsuyoshi was responsible for statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2025.101760.

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