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ORIGINAL ARTICLE

Dose-intensified stereotactic body radiotherapy for painful vertebral metastases: A randomized phase 3 trial

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Abstract

Background: The purpose of this randomised study was to determine whether dose-intensified stereotactic body radiotherapy (SBRT) for painful vertebral metastases results in increased rates of pain improvement compared with conventional external beam radiotherapy (cEBRT) (control) 6 months after treatment.

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Methods: This randomized, controlled phase 3 trial was conducted between November 2016 and January 2023, when it was stopped early. Patients were eligible if they were aged 18 years or older; had one or two painful, stable, or potentially unstable vertebral metastases; and had a life expectancy of 1 year or longer according to the investigator's estimates. Patients received 48.5 grays (Gy) in 10 fractions (with epidural involvement) or 40 Gy in five fractions (without epidural involvement) in the SBRT group and 30 Gy in 10 fractions or 20 Gy in five fractions in the cEBRT group, respectively. The primary end point was an improvement in the pain score at the treated site by at least 2 points (on a visual analog scale from 0 to 10 points) at 6-month follow-up. Data were analyzed on an intention-to-treat and per-protocol basis.

Results: Of 214 patients who were screened for eligibility, 63 were randomized 1:1 between SBRT (33 patients with 36 metastases) and cEBRT (30 patients with 31 metastases). The median age of all patients was 66 years, and 40 patients were men (63.5%). In the intention-to-treat analysis, the 6-month proportion of patients who had metastases with pain reduction by 2 or more points was significantly higher in the SBRT group versus the control group (69.4% vs. 41.9%, respectively; two-sided $p = .02$). Changes in opioid medication intake relative to baseline were nonsignificant between the groups. No differences were observed in vertebral compression fracture or adverse event rates between the groups.

Conclusions: Dose-intensified SBRT improved pain score more effectively than cEBRT at 6 months.

KEYWORDS
bone metastases, conventional external beam radiotherapy, pain, stereotactic body radiotherapy (SBRT), vertebral metastases

INTRODUCTION

Approximately one third of all patients with cancer develop bone metastases,[1] 70% of which are located in the vertebral spine.[2] Conventional external beam radiotherapy (cEBRT) is a standard component of the multidisciplinary treatment of painful vertebral metastases with and without malignant epidural spinal cord or cauda equina compression. Approximately 60% of evaluable patients with bone metastases experience overall pain relief after cEBRT, whereas complete pain response rates do not reach 13%[3] when assessed with the International Consensus on Palliative Radiotherapy Endpoints.[4] Analgesic effects are often short-lasting,[5] such that one half of patients with initial pain relief develop pain relapse within 1 year after treatment.[6] Modifying palliative radiation dose schemes did not improve the efficacy of cEBRT in achieving pain relief,[7,8] probably because radiation doses were too low to achieve durable local tumor control.

Traditional radiotherapy techniques with irradiation of the entire vertebra/e did not allow for dose escalation beyond the spinal cord tolerance to minimize the risk of radiation-induced damage of the spinal cord. Compared with cEBRT, stereotactic body radiotherapy (SBRT) provides higher precision and superior dose conformity in delivering increased radiation doses in a single fraction or a few fractions, enabling focused irradiation with doses beyond the spinal cord tolerance. Early studies on SBRT for painful vertebral metastases demonstrated durable pain relief in 80%–90% of patients, with lower retreatment rates and high local control.[9–12] Moreover, it was suggested that only the metastatic tumor within the vertebra might require higher radiation doses.[13] All these observations warranted randomized controlled trials. To our knowledge, no results of such trials were available before we initiated this randomized trial.

This randomized clinical phase 3 trial aimed to assess whether dose-intensified SBRT would improve longer term pain relief in painful, stable, or potentially unstable vertebral metastases compared with cEBRT. Herein, we report the primary and secondary outcome of the trial (ClinicalTrials.gov identifier NCT02800551).

MATERIALS AND METHODS

Study design, participants, and randomization

This was an open-label, international, multicenter, randomized, phase 3 trial, which recruited in 15 centers in Switzerland, Belgium, Germany, Italy, and Poland. Patients with vertebral metastases could be

treated with SBRT in a parallel prospective cohort if patients or clinicians refused the randomization process (for example, because of oligometastatic disease). This analysis is based on the randomized patients. The trial was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients were eligible if they were aged 18 years or older and had a histologically proven diagnosis of a solid tumor (excluding lymphoma, small cell lung cancer, multiple myeloma, and germ cell tumors), a maximum two of distinct painful vertebral metastases, a Karnofsky performance status ≥60%, and a life expectancy >1 year according to the investigator's assessment. Patients were ineligible if they had spinal instability (a spinal instability neoplastic score >12), involvement of more than three (cervical spine) or four (thoracic, lumbar, sacral spine) contiguous vertebrae, more than two treatment sites, progressive neurologic symptoms/deficits, previous radiotherapy, or previous radionuclide therapy at the treated site or surgery of the affected vertebra. Radiosensitizing agents were not allowed during radiotherapy. All patients singed an informed consent form.

Patients were randomly assigned (1:1) to either SBRT or cEBRT by the web-based data capture system secuTrial (Clinical Trials Center, University Hospital Zurich). No stratification factors were used. Neither patients nor physicians were blinded to treatment allocation.

Procedures

Conventional EBRT was delivered daily to a total dose of 20 grays (Gy) in five fractions or 30 Gy in 10 fractions to the whole affected vertebral site using a three-dimensional (3D) radiotherapy technique. The SBRT dose prescription involved two dose levels delivered simultaneously with intensity-modulated radiotherapy or volumetric-modulated arc therapy: either 48.5 Gy and 30 Gy in 10 daily fractions (with epidural involvement) to the high-dose and conventional-dose planning target volumes, respectively, or 40 Gy and 20 Gy in 5 daily fractions (without epidural involvement) to the high-dose and conventional-dose planning target volumes, respectively. Target volume definition and other SBRT treatment planning procedures can be found elsewhere.[13,14] Before trial initiation, participating centers completed the facility questionnaire, an image-guided radiotherapy questionnaire, and treatment planning of protocol-specific benchmark cases to verify that each participating center could comply with SBRT requirements. A central rapid review of the first two SBRT treatment plans from each center was performed before treatment delivery.

Clinical end points

The primary end point was patient-reported pain improvement (pain score) by two or more points on a visual analog scale (VAS) from 0 to 10[15] at the treated site 6 months after treatment; on this VAS, 0 represents no pain, and 10 represents the severest pain. The 6-month time point was chosen based on the expected durable pain relief after SBRT because of high rates of long-term local metastasis control.[9–11,16] The daily oral morphine equivalent (OMED) was analyzed in parallel to changes in the pain score.

Pain response was measured according to the International Consensus on Palliative Radiotherapy Endpoints.[4] A VAS pain score of 0 with no concomitant increase in OMED was considered to be a complete pain response. Pain progression was defined as an increase ≥2 in the pain score with stable OMED or as pain that was stable or 1 point above the baseline and a ≥25% increase in OMED. Missing pain response assessments were considered as pain progression. Each target lesion was independently assessed for pain response criteria.

Secondary end points included acute (≤3 months after treatment) and late (>3 months after treatment) adverse events graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03), overall survival defined as death from any cause, and patient-reported health-related quality-of-life (QoL). A vertebral compression fracture was defined as an imaging-determined decrease in the height of the treated vertebra, regardless of the presence of symptoms. QoL was measured using the 5-level EuroQol Group 5-dimension QoL questionnaire (EQ-5D-5L) at baseline and 1 month, 3 months, and 6 months after treatment. The EQ-5D-5L was used together with a VAS from 0 to 100 for rating overall health status (EQ-VAS). A clinical and radiologic examination of patients was performed at baseline and during follow-up or as clinically indicated. Radiologic examination included magnetic resonance imaging and/or computed tomography studies in accordance with local institutional protocol. A change in signal intensity, increased epidural disease, or enlargement of paraspinal disease on control magnetic resonance images (T1-weighted, axial, noncontrast-enhanced sequence; and T2-weighted, axial, noncontrast-enhanced sequence) or an increase in soft-tissue mass on computed tomography images were documented as radiologic progression.

Sample size and statistical analyses

We hypothesized that the proportion of treated lesions with a pain score reduction of ≥2 points according to the VAS was 70% in the SBRT group and 40% in the cEBRT group at 6 months after treatment. With 90% power at the 5% level of significance, 160 patients (80 patients in each group) would be needed in the presence of a 30% dropout rate.

We performed an intention-to-treat analysis and a per-protocol analysis. All randomized patients were included in the intention-to-treat analysis. We used descriptive statistics to report demographics and disease and treatment variables. Pain scores, complete pain responses, and pain progression rates across the two groups were assessed using the Pearson χ^2 test. QoL health profiles between the two groups at baseline and during follow-up were compared using the Wilcoxon rank-sum test. The risk ratios and

respective confidence intervals (CIs) were calculated as an effect measure along with the odds ratio as a second effect measure. We used one-way analysis of variance to test the difference between mean changes in pain scores, mean OMED intake, and mean EQ-VAS scores relative to baseline between the SBRT and control groups. The Kaplan–Meier method was used to calculate overall survival and the associated 95% CI. The difference in overall survival between the groups was compared using the log-rank. Patients were censored at the date of death or at the date of their last known follow-up, whichever came first. All tests were two-sided. A p value $< .05$ was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 19.6.4 (MedCalc Software).

RESULTS

The trial was initiated on November 8, 2016; and, on January 13, 2023, the trial was terminated because of slow accrual. In total, 214 patients were assessed for eligibility, of whom 39 did not meet the inclusion criteria (most frequently because they had no pain at baseline), 100 declined to participate in the randomized trial, and 12 were excluded for other reasons, all of whom enrolled in the non-randomized observation cohort (Figure 1).

Sixty-three patients were randomly allocated to SBRT (33 patients with 36 metastases) and to cEBRT (30 patients with 31 metastases; Figure 1). Four patients in the SBRT group and one patient in the control group did not receive allocated treatments because they no longer met inclusion criteria or they withdrew informed consent. All randomized patients were included in the intention-to-treat analysis. Fifty-eight patients received treatment and were included in the per-protocol analysis. Data analysis was completed on June 13, 2023.

The median age of all patients was 66 years (age range, 21–86 years). Patient and tumor characteristics were well balanced between the treatment groups, except sex (Tables 1 and 2). There were more men in the SBRT group than in the cEBRT group (26 [78.8%] vs. 13 [43.3%]). Non-small cell cancer (21 of 63 patients; 33.3%) and prostate cancer (11 of 63 patients; 17.5%) were the most common cancers in both groups. The mean ± standard deviation (SD) pain score at baseline was 5.6 ± 2.3 in the SBRT group and 4.6 ± 2.4 in the cEBRT group; more patients had moderate-to-severe pain (27 of 33 patients; 81.8%) in the SBRT group than in the cEBRT group (17 of 30 patients; 56.7%. In addition, more patients were on opioid medication (18 of 33 patients; 54.5%) and pretreatment opioid consumption was higher (mean ± SD OMED, 27.2 ± 31.1 mg) in the SBRT cohort compared with the cEBRT cohort (13 of 30 patients; 43.3%; mean ± SD OMED, 13.5 ± 21.4 mg; Table 1).

In the intention-to-treat analysis, the proportion of patients who had metastases with pain reduction by ≥2 points at 6 months was significantly higher in the SBRT group compared with the cEBRT group (25 of 36 patients [69.4%] vs. 13 of 31 patients [41.9%],

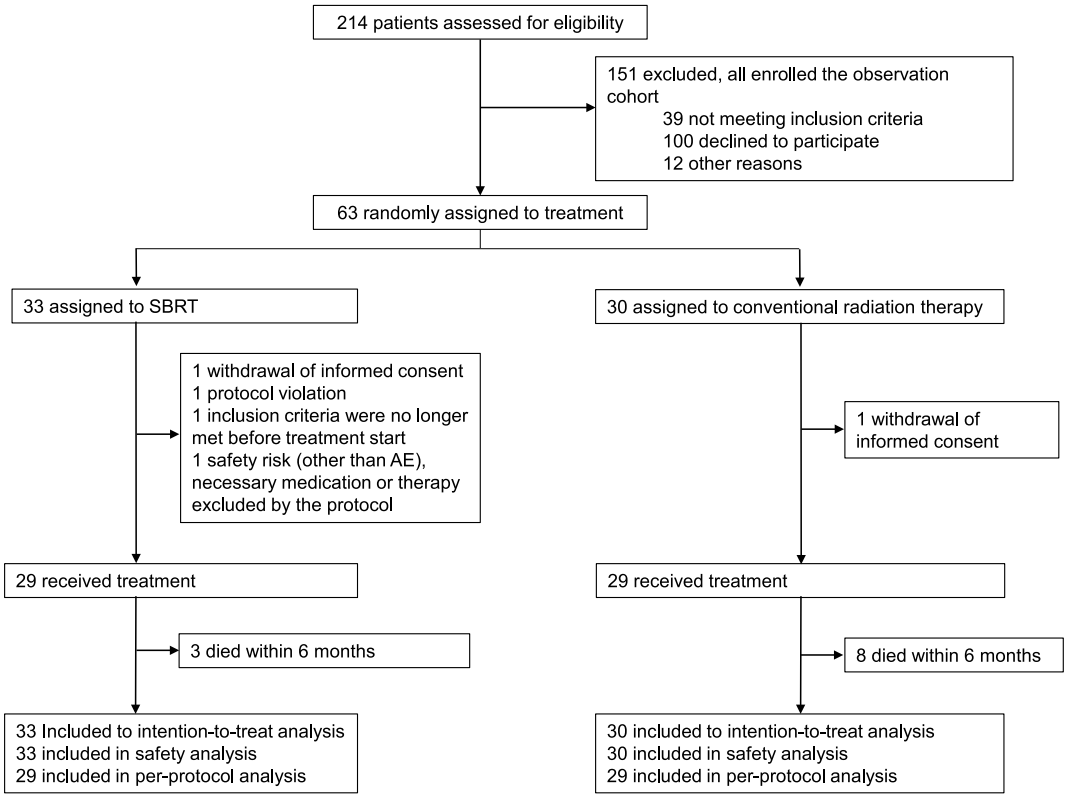

FIGURE 1 CONSORT diagram. AE indicates adverse event; CONSORT, Consolidated Standards of Reporting Trials; SBRT, stereotactic body radiotherapy.

TABLE 1 Baseline patient characteristics.

Characteristic	Patients, No. (%)	
	Stereotactic body radiotherapy, $n = 33$	Conventional external beam radiotherapy ($n = 30$)
Age: Median [range], years	67 (28–86)	65 (21-86)
Sex		
Men	26 (78.8)	13 (43.3)
Women	7 (21.2)	17 (56.7)
Karnofsky performance status		
90–100	21 (63.6)	16 (53.3)
70–80	10 (30.3)	13 (43.3)
60	2 (6.1)	1 (3.3)
Primary tumor site		
Lung	10 (30.3)	11 (36.7)
Prostate	6 (18.2)	5 (16.7)
Breast	4 (12.1)	5 (16.7)
Head and neck	4 (12.1)	1 (3.3)
Colorectal	1 (3.0)	2 (6.7)
Skin melanoma	2 (6.1)	-
Kidney	2 (6.1)	-
Liver	1 (3.0)	-
Sarcoma	1 (3.0)	1 (3.3)
Other	2 (6.1)	5 (16.7)
Histology		
Adenocarcinoma	20 (60.6)	19 (63.3)
Squamous cell carcinoma	2 (6.1)	3 (10)
Renal cell	2 (6.1)	-
Malignant melanoma	2 (6.1)	3 (10)
Sarcoma	1 (3.0)	1 (3.3)
Other	5 (15.2)	4 (13.3)
Presence of visceral metastases	16 (48.5)	16 (53.3)
Presence of additional bone metastases	27 (81.8)	28 (93.3)
Oligometastatic disease status: Maximum, five metastases	15 (45.5)	10 (33)
Daily oral morphine equivalent: Mean ± standard deviation, mg	27.2 ± 31.1	13.5 (21.4)

TABLE 2 Baseline metastatic tumor characteristics.

Characteristic	Metastases, No. (%)	
	Stereotactic body radiotherapy, $n = 36$	Conventional external beam radiotherapy, $n = 31$
Site of treated metastasis		
Cervical	2 (5.6)	3 (9.7)
Cervicothoracic	1 (2.8)	1 (3.2)
Thoracic	18 (50.0)	9 (29.0)
Thoracolumbar	1 (2.8)	—
Lumbar	11 (30.6)	15 (48.4)
Lumbosacral	1 (2.8)	3 (9.7)
Sacral	2 (5.6)	—
Metastasis type		
Osteolytic	26 (72.2)	19 (61.3)
Osteoblastic	1 (2.8)	3 (9.7)
Mixed	9 (25.0)	9 (29.0)
Maximum pain score at baseline		
≤4	9 (25.0)	14 (45.2)
5–7	20 (55.6)	14 (45.2)
8–10	7 (19.4)	3 (9.7)
Spinal instability neoplastic score		
Stable: 0–6	14 (38.9)	13 (41.9)
Potentially unstable: 7–12	22 (61.1)	18 (58.1)
Epidural spinal cord compression score		
Grade 0	24 (66.7)	18 (58.1)
Grade 1a	2 (5.6)	5 (16.1)
Grade 1b	2 (5.6)	5 (16.1)
Grade 1c	3 (8.3)	2 (6.5)
Grade 2	5 (13.9)	1 (3.2)
Paraspinal component	17 (47.2)	10 (32.3)
GTV: Mean ± SD, cm^3	30.4 ± 29.5	36.8 ± 49.2

Abbreviations: GTV, gross tumor volume; SD, standard deviation.

respectively; two-sided $p = .02$), resulting in a relative risk of 1.7 (95% CI, 1.04–2.64) and an odd ratio of 3.1 (95% CI, 1.2–8.6; Table 3). The average ± SD reduction in pain score at the treated site relative to baseline was numerically larger but not significantly different in the SBRT group compared with the control group at 6 months (−3.4 ± 4.0 vs. −2.2 ± 2.7, respectively; $p = .24$). Opioid medication intake relative to baseline decreased in the SBRT group (from 27.2 ± 31.1 to 22.1 ± 41.5 mg), whereas it increased in the cEBRT group (from 13.5 ± 21.4 to 18.6 ± 40.0 mg), but the difference between the groups was nonsignificant ($p = .76$). At 6 months, the proportion of patients who had a complete pain response did not differ between the SBRT and cEBRT groups (8 of 36 patients [22.2%] vs. 9 of 31 patients [29.0%], respectively, $p = .53$; Table 3). The 6-month proportion of patients who had pain progression was twice less in the SBRT group (eight of 36 patients; 22.2%) compared with

TABLE 3 Treatment outcome after stereotactic body radiotherapy and conventional external beam radiotherapy in the intention-to-treat and per-protocol treatment groups.

	No. of treated metastases (%)		
Treatment group	**Stereotactic body radiotherapy**	**Conventional external radiotherapy**	***p***
Intention-to-treat group			
1-month assessment			
Pain score reduction ≥2 on VAS	23 of 36 (63.9)	17 of 31 (54.8)	.45
Change in pain score: Mean ± SD	−3.2 ± 3.1	−2.1 ± 2.97	.17
Change in OMED intake: Mean ± SD, mg	−4.9 ± 41.3	−3.1 ± 27.5	.83
Complete pain response	9 (25.0)	6 (19.4)	.58
Progressive pain	8 (22.2)	8 (25.8)	.74
3-month assessment			
Pain score reduction ≥2 on VAS	19 of 36 (52.8)	13 of 31 (41.9)	.38
Change in pain score: Mean ± SD	−3.4 ± 3.3	−2.6 ± 2.4	.38
Change in OMED intake: Mean ± SD, mg	−16.8 ± 35.5	2.2 ± 29.3	.05
Complete pain response	7 (19.4)	5 (16.1)	.73
Progressive pain	11 (30.6)	11 (35.5)	.67
6-month assessment			
Pain score reduction ≥2 on VAS	25 of 36 (69.4)	13 of 31 (41.9)	.02
Change in pain score: Mean ± SD	−3.4 ± 4.0	−2.2 ± 2.7	.24
Change in OMED intake: Mean ± SD, mg	1.1 ± 47.0	9.5 ± 42.7	.69
Complete pain response	8 (22.2)	9 (29.0)	.53
Progressive pain	8 (22.2)	13 (41.9)	.09
Per-protocol group			
1-month assessment			
Pain score reduction ≥2 on VAS	23 of 32 (71.9)	17 of 30 (48.4)	.21
Change in pain score: Mean ± SD	−3.1 ± 3.1	−2.0 ± 2.9	.21
Change in OMED intake: Mean ± SD, mg	−4.9 ± 41.3	−3.1 ± 27.5	.83
Complete pain response	9 (28.1)	6 (20.0)	.46
Progressive pain	4 (12.5)	7 (23.3)	.27
3-month assessment			
Pain score reduction ≥2 on VAS	19 of 32 (59.4)	13 of 30 (43.3)	.21
Change in pain score: Mean ± SD	−3.3 ± 3.4	−2.5 ± 2.4	.43
Change in OMED intake: Mean ± SD, mg	−16.8 ± 35.5	2.2 ± 29.3	.05
Complete pain response	7 (21.9)	5 (16.7)	.61
Progressive pain	7 (21.9)	10 (33.3)	.32
6-month assessment			
Pain score reduction ≥2 on VAS	25 of 32 (78.1)	13 of 30 (43.3)	.005
Change in pain score: Mean ± SD	−3.4 ± 4.0	−2.1 ± 2.7	.29
Change in OMED intake: Mean ± SD, mg	1.1 ± 47.0	9.5 ± 42.7	.69
Complete pain response	8 (25.0)	9 (30.0)	.66
Progressive pain	4 (12.5)	12 (40.0)	.01

Abbreviations: OMED, daily oral morphine equivalent; SD, standard deviation; VAS, visual analog scale.

that in the cEBRT group (13 of 31 patients; 41.9%; $p = .09$). There was no difference in pain improvement or changes in pain scores and pain responses between the groups at 1 month and 3 months (Table 3).

In the per-protocol analysis, the proportion of patients who had metastases with pain reduction by ≥2 was significantly higher in the SBRT group than in the cEBRT group at 6 months (25 of 32 patients [78.1%] vs. 13 of 30 patients [43.3%]; two-sided $p = .005$; Table 3). Changes in 6-month opioid medication intake did not differ between the groups. The proportion of patients who had a complete pain response in the SBRT group was 25.0% (eight of 32 patients) and 30.0% (nine of 30 patients) in the cEBRT group ($p = .66$).

The median follow-up time of all patients was 10 months (interquartile range, 5–15 months). Three of 33 patients (9.1%) in the SBRT group and eight of 30 patients (26.7%) in the cEBRT group died within 6 months of randomization, all from cancer progression. The actuarial estimates of overall survival at 12 months was 62.1% (95% CI, 45.1%–79.1%) after SBRT and 60.0% (95% CI, 41.3%–78.7%) after cEBRT (hazard ratio, 1.1; 95% CI, 0.52–2.31; $p = .79$). At the time of analysis, radiologic progression at the treated site was observed in one of 32 evaluable lesions (3.1%) after SBRT and in two of 25 evaluable lesions (8.0%) after cEBRT ($p = .42$).

No grade 4–5 adverse events related to treatment were reported in either arm. Neither radiation-induced myelopathy nor plexopathy were reported during follow-up. The proportion of patients who had vertebral compression fracture was 19.4% after SBRT versus 13.3% after cEBRT ($p = .47$). No differences in treatment-induced adverse events were reported between the groups (see Tables S1 and S2).

Twenty-two of 33 patients (66.7%) in the SBRT group and 15 of 30 patients (50.0%) in the cEBRT group completed the EQ-5D-5L QoL questionnaire at baseline and at the 6-month follow-up. Health profiles for each dimension were stable or slightly improved by 6 months, and differences were not significant between the groups (Table 4). The EQ VAS score improved from a mean ± SD of 61.2 ± 20.5 at baseline to 64.3 ± 14.7 at 6 months in the SBRT group versus 61.3 ± 19.7 and 63.9 ± 22.7 in the cEBRT group, respectively ($p = .94$; Table 5).

DISCUSSION

In this randomized phase 3 trial, dose-intensified SBRT for vertebral metastases significantly increased pain improvement by ≥2 points on the VAS compared with cEBRT at 6 months; thus the primary end point was met. This was not driven by differences in daily opioid medication between treatment groups: numerically, opioid medication decreased in the SBRT group and increased in the cEBRT group, with differences that were not significant. In addition, the proportion of patients who had pain progression was almost twice as high after cEBRT compared with that after SBRT, supporting the hypothesis that the superiority of SBRT is explained by more durable local metastasis control and re-stabilization as a mechanism of pain relief. Both treatments were well tolerated without any grade 4–5 treatment-related adverse events during treatment or follow-up.

Conflicting results of randomized clinical trials on the role of SBRT for pain relief and pain response in bone metastases and systematic reviews with meta-analyses of those trials[17,18] make a comparison of results challenging. Of seven published randomized clinical trials, only three were exclusively addressing verterbral metastases,[19–21] and all were measuring the primary end point early, at 3 months. The largest NRG Oncology/Radiation Therapy Oncology Group randomized phase 2/3 trial (RTOG 0631) reported a nonsignificant 6-month mean ± SD change from baseline in pain scores of −3.1 ± 3.5 in the single-fraction SBRT group versus −3.9 ± 2.6 in the cEBRT group using a numerical rating pain score.[21] This overall magnitude of pain relief is comparable to our results. In contrast, a randomized explorative trial by Sprave et al.[19] with 55 patients reported significantly increased mean pain score changes on the VAS from 0 to 100 after single-fraction SBRT (−25.0) compared with cEBRT (−11.4) at 6 months.[19] A randomized phase 2/3 trial by Sahgal et al. with 229 patients[20] and the trial by Sprave et al.[19] demonstrated superior complete pain responses at 6 months after SBRT 37 of 114 patients [32%] and 10 of 30 patients [33%], respectively. However, we did not observe any difference between SBRT and cEBRT in proportions of complete pain responses. Of note, in our trial, the 6-month complete pain response after cEBRT of 29% was higher than that in the trials by Sahgal et al. (16%)[20] and Sprave et al. (10%).[19] We treated patients in the control group consistently with the 3D conformal radiotherapy technique used by Sprave et al.,[19] whereas Sahgal et al. used both 2D and 3D conformal radiotherapy techniques.[20] Overall, three of four randomized trials, including ours, reported the superiority of SBRT over cEBRT with respect to longer term outcomes at 6 months postradiotherapy. In addition, all trials, including ours, confirmed the safety of SBRT, which was not associated with an increased risk of vertebral compression fracture nor with any event of radiation-induced myelopathy, although longer follow-up is warranted for drawing firm conclusions about adverse events.

Several factors might contribute to the differences in results of the randomized trials, including the definition of the primary end points (pain score improvement by ≥2 or 3 points), the inclusion criteria (number of consecutive vertebral bodies and treated sites, performance status, primary tumor histology, systemic treatment), baseline pain score, target volume definition, radiation doses and fractionation [single or multiple fractions], and radiotherapy techniques).[22,23]

The smaller than planned number of randomized patients underpowered this trial. Despite the multi-institutional and international efforts, one half of the registered patients and/or clinicians declined participation in the randomized trial and preferred SBRT. There was also an unforeseeable delay in patients' accrual because of the coronavirus disease 2019 pandemic. The pandemic had a negative effect on patients' willingness to participate or to continue participating in the trial and on the engagement of medical teams to enroll patients in the study. Given the small sample size, we did not

TABLE 4 The percentage of patients who reported five levels of health on the EuroQol Group five-dimensional health-related quality-of-life questionnaire before treatment and at 1 month, 3 months, and 6 months after treatment.[a]

	Baseline, %		1 month, %		3 months, %		6 months, %	
EQ-D5 dimension	**SBRT**	**cEBRT**	**SBRT**	**cEBRT**	**SBRT**	**cEBRT**	**SBRT**	**cEBRT**
Mobility								
Level 1	43.4	45.8	40.9	40.0	55.3	52.6	44.4	40.0
Level 2	15.1	12.5	31.8	30.0	18.4	21.1	25.0	20.0
Level 3	34.0	33.3	20.5	15.0	18.4	21.1	27.8	40.0
Level 4	7.5	8.3	4.5	10.0	7.9	5.3	2.8	0.0
Level 5	0.0	0.0	2.3	5.0	0.0	0.0	0.0	0.0
p	.94		.77		.93		.67	
Self-care								
Level 1	70.0	69.2	72.0	70.0	85.0	68.4	72.7	60.0
Level 2	23.3	23.1	28.0	15.0	5.0	26.3	18.2	33.3
Level 3	3.3	7.7	0.0	15.0	10.0	5.3	9.1	6.7
Level 4	3.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Level 5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p	.95		.66		.30		.50	
Usual activities								
Level 1	40.0	23.1	36.0	30.0 (RT)	45.0	42.1	22.7	40.0
Level 2	30.0	46.2	32.0	30.0	25.0	36.8	45.5	26.7
Level 3	23.3	15.4	20.0	30.0	20.0	15.8	31.8	26.7
Level 4	3.3	7.7	8.0	5.0	10.0	5.3	0.0	6.7
Level 5	3.3	7.7	4.0	5.0	0.0	0.0	0.0	0.0
p	.32		.64		.85		.65	
Pain/discomfort								
Level 1	6.7	7.7	16.0	5.0	20.0	21.1	13.6	20.0
Level 2	16.7	15.4	52.0	60.0	50.0	42.1	45.5	33.3
Level 3	40.0	53.8	24.0	30.0	15.0	36.8	27.3	40.0
Level 4	33.3	23.1	8.0	5.0	15.0	0.0	13.6	6.7
Level 5	3.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p	.44		.58		.96		.90	
Anxiety/depression								
Level 1	53.3	42.3	72.0	55.0	60.0	63.2	59.1	53.3
Level 2	40.0	34.6	16.0	30.0	30.0	36.8	27.3	26.7
Level 3	6.7	23.1	12.0	15.0	10.0	0.0	13.6	20.0
Level 4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Level 5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p	.21		.29		.67		.66	

Abbreviations: cEBRT, conventional external beam radiotherapy; EQ-5D, the EuroQol Group 5-dimensional quality-of-life questionnaire; SBRT, stereotactic body radiotherapy.

[a]On the EQ-5D questionnaire, 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems.

TABLE 5 Mean ± standard deviation self-reported overall health status score on the visual analog scale from 1 to 100.[a]

	Stereotactic body radiotherapy	Conventional external beam radiotherapy	*p*
Baseline	61.2 ± 20.5	61.3 ± 19.7	.89
1 month	68.8 ± 18.4	59.3 ± 25.1	.15
3 months	70.3 ± 15.8	70.1 ± 18.5	.98
6 months	64.3 ± 14.7	63.9 ± 22.7	.94

[a]On this scale, 100 indicates the best health you can imagine, and 1 indicates the worst health you can imagine.

attempt an analysis of factors relevant for a prognosis of pain outcomes. Low compliance of the limited number of patients in reporting QoL might have undermined the positive effects of SBRT on QoL.

CONCLUSIONS

For patients who have cancer with painful verterbal metastases, dose-intensified SBRT improved pain scores more effectively than cEBRT at 6 months without increasing toxicity. These findings warrant further investigations on optimizing patient selection, radiation dose, and fractionation.

AUTHOR CONTRIBUTIONS

Matthias Guckenberger: Conceptualization, formal analysis, funding acquisition, investigation, project administration, supervision, writing–original draft preparation, and writing–review and editing. **Charlotte Billiet**: Investigation and writing–review and editing. **Daniel Schnell**: Investigation and writing–review and editing. **Ciro Franzese**: Investigation and writing–review and editing. **Mateusz Spałek**: Investigation and writing–review and editing. **Susanne Rogers**: Investigation and writing–review and editing. **Jean-Jacques Stelmes**: Investigation and writing–review and editing. **Daniel M. Aebersold**: Conceptualization, funding acquisition, investigation, and writing–review and editing. **Hossein Hemmatazad**: Investigation and writing–review and editing. **Frank Zimmermann**: Conceptualization, funding acquisition, investigation, and writing–review and editing. **Jörg Zimmer**: Investigation and writing–review and editing. **Thomas Zilli**: Investigation and writing–review and editing. **Alessio Bruni**: Investigation and writing–review and editing. **Brigitta G. Baumert**: Investigation and writing–review and editing. **Franziska Nägler**: Investigation and writing–review and editing. **Philipp Gut**: Investigation and writing–review and editing. **Robert Förster**: Conceptualization, investigation, and writing–review and editing. **Indira Madani**: Conceptualization, data curation, formal analysis, writing–original draft preparation, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Mateusz Spałek reports honoraria from Stryker and NovaSpine outside the submitted work. Daniel M. Aebersold reports personal/consulting fees from Insel Gruppe AG outside the submitted work. Alessio Bruni reports grants/contracts from AstraZeneca and F. Hoffmann-La Roche AG; and travel support from AstraZeneca outside the submitted work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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