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Clinical Investigation

Pain Response After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases—A Phase 2 Randomized Controlled Trial Within a Prospective Cohort

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Purpose: Pain response after conventional external beam radiation therapy (cRT) in patients with painful bone metastases is observed in 60% to 70% of patients. The aim of the VERTICAL trial was to investigate whether stereotactic body radiation therapy (SBRT) improves pain response.

Methods and Materials: This single-center, phase 2, randomized controlled trial was conducted within the PRESENT cohort, which consists of patients referred for radiation therapy of bone metastases to our tertiary center. Cohort participants with painful bone metastases who gave broad informed consent for randomization were randomly assigned to cRT or SBRT. Only patients in the intervention arm received information about the trial and were offered SBRT (1 × 18 Gy, 3 × 10 Gy, or 5 × 7 Gy), which they could accept or refuse. Patients who refused SBRT underwent standard cRT (1 × 8 Gy, 5 × 4 Gy, or 10 × 3 Gy). Patients in the control arm were not informed. Primary endpoint was pain response at 3 months after radiation therapy.

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Secondary outcomes were pain response at any point within 3 months, mean pain scores, and toxicity. Data were analyzed intention to treat (ITT) and per protocol (PP). This trial was registered with Clinicaltrials.gov, NCT02364115.

Results: Between January 29, 2015, and March 20, 2019, 110 patients were randomized. ITT analysis included 44 patients in the cRT arm and 45 patients in the SBRT arm. In the intervention arm, 12 patients (27%) declined SBRT, and 7 patients (16%) were unable to complete the SBRT treatment. In ITT, 14 of 44 patients (32%; 95% confidence interval [CI], 18%-45%) in the control arm and 18 of 45 patients (40%; 95% CI, 26%-54%) in the SBRT arm reported a pain response at 3 months ($P = .42$). In PP, these proportions were 14 of 44 (32%; 95% CI, 18%-45%) and 12 of 23 patients (46%; 95% CI, 27%-66%), respectively ($P = .55$). In ITT, a pain response within 3 months was reported by 30 of 44 control patients (82%; 95% CI, 68%-90%) and 38 of 45 patients (84%; 95% CI, 71%-92%) in the SBRT arm ($P = .12$). In PP, these proportions were 36 of 44 (82%; 95% CI, 68%-90%) and 26 of 27 patients (96%; 95% CI; 81%-100%), respectively ($P = .12$). No grade 3 or 4 toxicity was observed in either arm.

Conclusions: SBRT did not significantly improve pain response in patients with painful bone metastases. One in 4 patients preferred to undergo cRT over SBRT, and 1 in 5 patients starting SBRT was unable to complete this treatment. Because of this selective dropout, which can be attributed to the character of the intervention, the trial was underpowered to detect the prespecified difference in pain response.

Introduction

Bone metastases are a common manifestation of advanced cancer, causing pain and neurologic complaints or deficits, and they often impair overall quality of life.[1,2] Palliative radiation therapy (RT) is a proven effective and widely accepted treatment modality for metastatic bone pain.[3,4] Pain response after conventional RT (cRT) is similar in patients treated with single-fraction (8 Gy in 1 fraction) and multifraction (20-30 Gy in 5-10 fractions) RT.[1,5,6] It has been suggested that dose escalation, and more specifically dose escalation per fraction, could improve pain response in patients with metastatic bone pain.[7] Dose escalation using cRT is challenging because surrounding tissues such as the spinal cord have limited tolerance to radiation. Stereotactic body RT (SBRT) allows for accurate administration of a higher dose to the target area while sparing the surrounding tissue.

Previous studies have shown that SBRT can be administered safely to patients with bone metastases.[7,8] Recent randomized controlled trials (RCTs) comparing the proportion of patients reporting a pain response after cRT versus SBRT show inconsistent results.[9-11] Nguyen et al[9] compared single-fraction SBRT with multifraction cRT[9] and found that pain response after SBRT was superior to multifraction cRT at 2 weeks and at 3 months. The recently presented RTOG 0631 trial, however, showed no difference in pain response between single-fraction cRT (8 Gy) and single-fraction SBRT (16-18 Gy).[11]

The VERTICAL trial was designed according to the Trials within Cohorts (TwiCs) methodology with the aim to estimate whether SBRT leads to superior pain response compared with standard cRT in patients with painful bone metastases. In addition, the TwiCs design allowed us to evaluate acceptability and tolerability of SBRT in routine clinical practice.

Methods and Materials

Study design

VERTICAL was a single-center, pragmatic phase 2 RCT conducted within the PRESENT cohort.[12] The VERTICAL study followed the TwiCs design, also known as the cohort multiple RCT design.[13] All patients with bone metastases referred to the departments of radiation oncology or orthopedic surgery at our tertiary referral center are systematically invited to participate in the prospective, observational PRESENT cohort. At enrollment in PRESENT, patients give informed consent to the use of their clinical and outcome data for research purposes. Optionally, they provide additional consent to complete patient-reported outcomes (PROs) at regular intervals during follow-up. In addition, in a separate question, we ask patients for their broad consent to be randomized in (near) future RCTs conducted within the cohort. Patients are informed that randomization means that, when meeting inclusion and exclusion criteria for future trials, they will be randomized; when randomized to the intervention arm, they will be offered the experimental intervention, which they can accept or refuse. They are also informed that, when assigned to the control arm, they will not be notified about the trial and that their clinical, outcome, and PROs data might be used comparatively.[14]

Patients

For the present study, all patients eligible for the VERTICAL trial were identified within PRESENT. Inclusion criteria included histologic proof of malignancy, radiologic or histologic evidence of bone metastases, no more than 2 painful lesions requiring treatment, no compression of spinal cord/cauda equina, no or mild neurologic signs such

as (radiating) pain or numbness, Karnofsky performance status score >50 points, and pain score ≥3. Exclusion criteria included contraindications to undergo magnetic resonance imaging (MRI), metastasis from a highly radiosensitive tumor (eg, lymphoma), lesions too large for SBRT (ie, >10 cm), estimated life expectancy less than 3 months, previous cRT or SBRT on the same level, need for surgical stabilization, and severe, worsening, or progressive neurologic deficits (eg, muscle weakness). Patients were only eligible when they provided informed consent to completing PROs and when they gave broad informed consent for future randomization.

At the initiation of the study in January 2015, only patients with vertebral metastases were eligible. From November 17, 2015, onward, patients with bone metastases at any location were eligible, with the exception of the first and second cervical vertebrae because of the proximity of major neurovascular structures. All patients provided written informed consent before enrolment in PRESENT, and all patients in the intervention arm of the PRESENT study provided additional informed consent to the VERTICAL trial. Approval of the protocol was obtained from the local ethics committee.

Randomization and masking

PRESENT participants who met the inclusion criteria were randomly assigned (1:1) to receive cRT or SBRT, using block randomization with alternating block sizes. No stratification factors were used, and the random allocation sequence was masked. Following the TwiCs methodology, only patients who were randomized to the intervention arm were informed about the VERTICAL trial and were offered SBRT. Additional informed consent was obtained from patients who accepted the offer. Patients who declined the offer received standard cRT. Treatment group allocation was not masked to the investigators or the patients in the intervention arm, but the patients randomized to the control arm were not informed about the VERTICAL trial and received standard cRT.

Procedures

Patients in the cRT arm typically received 8 Gy in 1 fraction; however, a multifraction regimen of 20 Gy in 5 fractions or 30 Gy in 10 fractions could be used for patients in good clinical condition as assessed by the radiation oncologist. Single or multiple computed tomography (CT)-guided conformal fields were used for RT planning, in which the clinical target volume (CTV), which included the macroscopic tumor, received at least 80% of the prescribed dose. In 3 patients, volumetric modulated arc therapy was used to deliver the conventional dose.

No immobilization devices were used. Patients undergoing SBRT were immobilized using a vacuum cushion (BlueBAG; Elekta, Stockholm, Sweden) or a thermoplastic mask depending on localization.

A planning CT (1-mm slice thickness) was acquired and rigidly registered to a dedicated planning MRI (in treatment position), and a recent diagnostic positron emission tomography (PET) scan was coregistered if available. The radiation oncologist contoured the gross tumor volume (GTV), referred to as the boost (GTVb); the CTV, referred to as elective CTV (CTVe); and relevant organs at risk. The GTVb was defined as the macroscopic extent of the tumor on all available imaging modalities. The CTVe was generated using a 1.5-cm isotropic margin around the GTVb, excluding soft tissues (bone only); potential extraosseous disease was included in the CTVe. For spinal metastases, the whole vertebra was considered the CTVe. Both the GTVb and the CTVe were expanded with a 2-mm isotropic margin to generate planning target volume margins.[15] The planning target volume was prescribed for 18 Gy in a single fraction, 30 Gy in 3 fractions, or 35 Gy in 5 fractions using volumetric modulated arc therapy both with 3 fractions per week. A more detailed protocol for cRT and SBRT planning procedures was published earlier.[16]

From all PRESENT patients, demographic, clinical, and follow-up data and treatment characteristics were collected at baseline, before the start of RT, and until death. Because VERTICAL was executed within PRESENT, these data were available for the patients included in the VERTICAL trial. For the VERTICAL trial, data collected at baseline, 2, 4, 6, and 8 weeks and 3 months after treatment was used. Patients completed the Brief Pain Inventory combined with a form on (opioid) analgesic use. In addition, change in quality of life (QOL) was assessed using the EORTC-QLQ-C15-PAL and EORTC-QLQ-BM22. Here, only the global QOL scores of the QLQ-C15-PAL questionnaire are presented. Detailed analysis of all QOL domains of the QLQ-C15-PAL and QLQ-BM22 questionnaires will be published separately. From the opioid analgesic use, an oral morphine equivalent dose (OMED) in mg was calculated. When patients failed to return questionnaires, they were systematically reminded by a call from the research team. Patients were asked to fill out the questionnaire, and pain scores and opioid analgesic use were already noted during that call.

Outcomes

The primary endpoint of the VERTICAL trial was the proportion of patients reporting a pain response at 3 months after RT, measured with the Brief Pain Inventory and classified according to the international consensus on palliative RT.[4] Complete response was defined as a pain score of 0 on a scale from 0 to 10, without an increase in pain medication use. Partial response was a decline of at least 2 points or decline of an OMED of at least 25%, or both. Pain progression (PP) was an increase of at least 2 points without change in OMED dose, or a 1-point increase with an increase of 25% in OMED use. All other pain

responses were categorized as indeterminate response. Patients with a complete response or partial response were considered responders; patients with other outcomes were considered non−pain-responders. Patients for whom a pain score was unknown were considered non−pain-responders at that time point.

Secondary endpoints were best pain response in the first 3 months after treatment, mean pain scores, OMED use, global QOL, and toxicity in the first 3 months after treatment. Global QOL was rated on a 7-point scale ranging from "very poor" to "excellent." In accordance with the scoring manual, the scale was converted into a score ranging from 0 to 100, with higher scores indicating better QOL.[17-19] Toxicity was assessed by a physician at clinical or telephone follow-up and categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Only adverse events grade $\geq$3 were recorded because of the high number of study-unrelated adverse events, owing to the natural course of disease in patients with stage IV cancer. By applying the TwiCs design, patients' preferences to undergo SBRT could be estimated, as patients allocated to the intervention arm could accept or refuse the offer of SBRT. Patient-reported reasons for not accepting SBRT were recorded.

Statistical analysis

We assumed the proportion of patients with pain response at 3 months to be 60% after cRT versus 85% after SBRT. To achieve an 80% power and a one-sided α of 5%, 49 patients needed to be enrolled in each arm.[20,21] We assumed that 10% of the patients in the intervention arm would refuse when offered SBRT. We also assumed 100% compliance in the control arm because control patients were not informed of the SBRT intervention and underwent treatment as usual. In addition, a 10% dropout rate was anticipated in both arms, resulting in 55 patients being required for each arm.[16]

The proportions of patients reporting a pain response at 3 months (primary endpoint) were compared between the control and the intervention arms using the χ^2 test. The primary analysis was by intention to treat (ITT), excluding patients who were found to be ineligible after randomization. Patients in the intervention arm who preferred to undergo cRT when SBRT was offered, and those who did not want to undergo any treatment at all, were included in the ITT analysis.

We also conducted a per protocol (PP) analysis and included patients who completed the treatment planned according to the random allocation. In the ITT and PP analyses, patients who did not return their questionnaires were considered non−pain-responders. In addition, a third analysis, a complete case ITT analysis, was performed, in which we analyzed only patients whose response could be assessed at 3 months (alive and responding to questionnaire).

The proportions of patients reporting pain response at at least 1 of the follow-up time points up to 3 months after-treatment (secondary outcome) were compared with ITT and PP analyses using the χ^2 test.

The independent samples t test was used to compare changes in mean pain scores and OMED use between baseline and follow-up at 3 months relative to baseline by treatment arm. In addition, a linear mixed model analysis was performed to compare mean pain scores adjusted for covariates. Global QOL was analyzed using a mixed model for repeated measures, including time, treatment group, and its interaction and adjusting for baseline QOL scores. Toxicity was assessed in all enrolled patients who received at least 1 RT fraction. Data were analyzed using SPSS (IBM, Armonk, NY).[22] This trial was registered with Clinicaltrials.gov under NCT02364115.

Role of the funding source

The study was funded by internal sources. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between January 29, 2015, and March 20, 2019, 1102, patients with (painful) bone metastases were included in the PRESENT cohort at our department for RT. Of these patients, 178 patients were eligible (meeting the inclusion and exclusion criteria of VERTICAL). The majority of patients were not eligible for the VERTICAL study because 3 or more locations were treated with RT or they had oligometastatic disease, which was treated with SBRT. In addition, patients were often excluded when the metastasis was >10 cm or when there was an increased fracture risk. Of the 178 eligible patients, 42 did not want to participate in the PRESENT cohort, and they could not be included in VERTICAL. Seven patients did not provide informed consent for completing PROs, and 7 patients refused future randomization. Ten patients were not randomized because treatment in the intervention arm would not be possible within 10 days, which was considered unethical. The remaining 110 (61%) were randomized (Fig. 1).

After randomization, 11 patients in the cRT arm and 10 patients in the SBRT arm dropped out before start of treatment because they did not, or no longer did, meet the inclusion criteria. The most common reasons for dropping out were need for surgery and lack of pain, although the patient was referred because of painful metastases. As a result, 89 patients were included in the ITT analysis, 44 patients in the standard arm, and 45 patients in the experimental arm. Baseline characteristics are shown in Table 1.

After offering SBRT to the 45 patients in the intervention arm, 12 patients (27%; 95% confidence interval [CI], 15%-42%) declined the offer and opted for cRT (Fig. 1).

Eight of these patients refused SBRT because of the longer waiting time of up to 10 days until treatment. One patient had previously undergone cRT and was satisfied with the results, and 1 patient refused SBRT because of worries about the increased vertebral fracture risk after SBRT. Of the patients who refused SBRT, 10 patients underwent cRT, and 2 patients refused any treatment. Patients who refused the SBRT treatment were slightly younger, had more comorbidities, had a higher percentage of lung cancer and a lower percentage of breast cancer, and had a higher pain score than patients who accepted SBRT. They were similar in terms of sex and of location of bone metastases (Table E1).

Of the 33 patients who accepted SBRT, 7 (21%) were unable to complete the treatment, 3 of whom underwent cRT. One patient was injured between consecutive fractions because of a fall and was unable to continue SBRT; 1 patient was unable to undergo planning MRI because severe bone pain; 1 patient was in too much pain after the first SBRT fraction, did not respond to dexamethasone, and refused to undergo additional fractions; and 1 patient turned out to have 3 lesions on MRI requiring treatment. Two patients had MRI-confirmed rapid tumor or metastasis progression and underwent cRT, and 1 patient deteriorated rapidly and underwent cRT before SBRT could be started. Overall, 44 patients (100%) completed the allocated cRT, and 26 patients (58%) completed the allocated SBRT treatment. Thirteen patients (29%) randomized to the SBRT arm received cRT, and 6 patients did not undergo any treatment.

Fourteen patients died within 3 months—7 patients in the cRT arm and 7 patients in the SBRT arm. Median time to death was 44 days (interquartile range [IQR], 29-48 days) in the cRT arm and 46 days (IQR, 37-75 days) in the SBRT arm. The overall 90-day survival was 84% in both arms (Fig. E1). Despite repeated calls, questionnaire response rates were low. Thirty-five patients (39%) returned their questionnaires at all follow-up moments, and 77 patients (87%) returned at least 1 follow-up questionnaire (Table 2). The patients in the SBRT arm who did not undergo any treatment did not return any questionnaires. Of the 13 patients who underwent cRT instead of the allocated SBRT, 8 returned at least 1 questionnaire. Patients who did not return a questionnaire were considered to be non−pain-responders at the given moment in follow-up.

In the ITT analysis, 14 of 44 patients (32%; 95% CI, 18%-45%) in the cRT arm reported a pain response at 3 months compared with 18 of 45 patients (40%; 95% CI, 26%-54%) in the SBRT arm ($P = .42$). In the PP analysis, 14 of 44 patients (32%; 95% CI, 18%-45%) in the cRT arm and 12 of 26 patients (46%; 95% CI, 27%-66%) in the SBRT arm reported a pain response at 3 months ($P = .55$; Table 3).

In the subset of evaluable (alive and responding) patients (ie, complete case ITT analysis), 14 of 23 patients (61%; 95% CI, 39%-80%) in the cRT arm and 18 of 31 (58%; 95% CI, 39%-75%) in the SBRT arm reported a pain response at 3 months ($P = .84$; Table 3).

The proportion of patients reporting a pain response on at least 1 of the follow-up time points after treatment up to 3 months afterward was comparable between both treatment arms in the ITT and PP analyses: 36 of 44 patients (82%; 95% CI, 68%-90%) in the cRT arm versus 38 of 45 patients (84%; 95% CI, 71%-92%) in the SBRT arm ($P = .73$) in the ITT analysis. In the PP analysis, 36 of 44 patients (82%; 95% CI, 68%-90%) in the cRT arm versus 26 of 27 patients (96%; 95% CI, 81%-100%) in the SBRT arm reported a pain response within 3 months after treatment ($P = .12$). The percentages of patients reporting a pain response at each follow-up point were comparable (Fig. 2).

In the ITT analysis, mean pain scores at baseline were 6.2 (standard deviation [SD] = 2.0) in the cRT arm and 6.6 (SD = 1.8) in the SBRT arm (Fig. 1). At 3 months, the

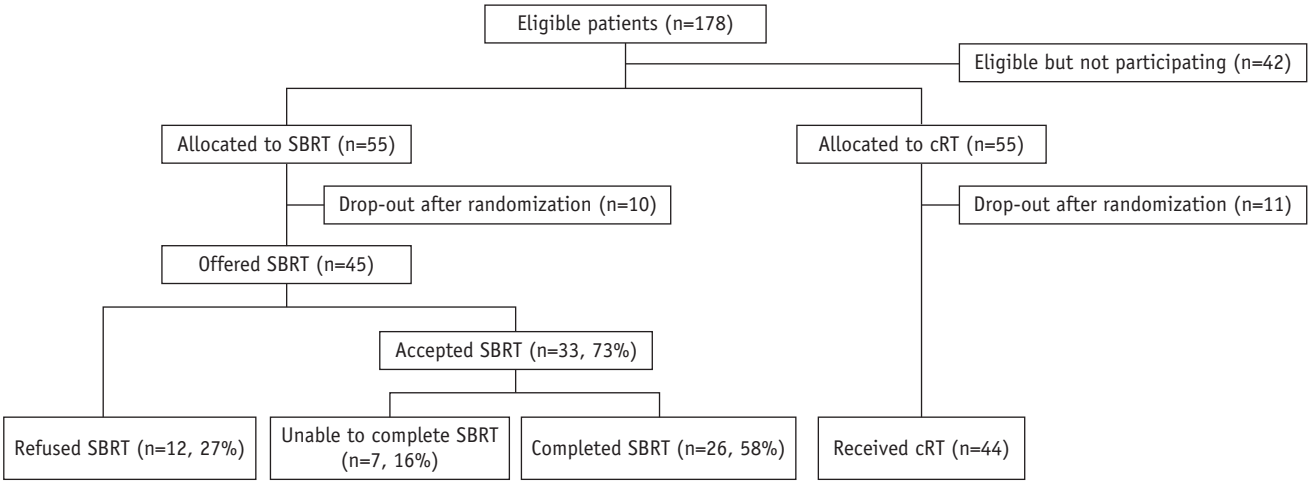

Fig. 1. Flowchart of patient enrolled in the VERTICAL trial and treatment allocation.

Table 1 Baseline characteristics of patients with painful bone metastases enrolled in the VERTICAL trial

Characteristics	Conventional radiation therapy group (N = 44)	Stereotactic body radiation therapy group N = 45
Male sex, n (%)*	31 (70)	24 (53)
Median age (IQR), y	63 (57-73)	65 (61-72)
Median Charlson comorbidity index (IQR)†	6 (6-7)	6 (6-7)
Karnofsky performance status, n (%)‡		
0-50	1 (3)	2 (6)
60-7	11 (37)	14 (40)
80-100	18 (60)	19 (42)
Primary tumor site, n (%)		
Lung	9 (21)	14 (31)
Breast	8 (18)	9 (20)
Prostate	9 (21)	11 (24)
Other§	18 (40)	11 (24)
Location bone metastases, n (%)		
Spine	22 (50)	27 (60)
Nonspine	22 (50)	18 (40)
Median pain score at baseline, NRS (IQR)	6.2 (2)	6.6 (1.8)
Pain medication at baseline, n (%)		
None	7 (16)	7 (16)
Nonopioid	15 (34)	15 (33)
Weak opioid	1 (2)	1 (2)
Strong opioid	21 (48)	22 (49)
Median oral morphine equivalent dose in mg (IQR)	60 (40-120)	60 (40-110)
Concomitant systemic treatment, n (%)	17 (39)	25 (56)
Hormone therapy	7 (16)	11 (24)
Chemotherapy	7 (16)	10 (22)
Targeted therapy	2 (4)	2 (4)
Other	1 (2)	2 (4)

Abbreviations: IQR = interquartile range; NRS = Numeric Rating Scale, ranging 0-10.

* Percentages might not add up to 100% because of rounding.

† The scale of the Charlson Comorbidity Index ranges from 0 to 40, where a higher score indicates a worse prognosis. Patients with bone metastases have a score of at least 6.

‡ The Karnofsky performance status score is assessed on a 100-point scale, with lower numbers indicating greater disability.

§ Conventional external beam radiation therapy arm: kidney (n = 5), bladder (n = 4), colon and rectum (n = 5), esophagus (n = 1), another endocrine (n = 1). Stereotactic body radiation therapy arm: bladder (n = 4), kidney (n = 3), colon and rectum (n = 1), stomach (n = 1), esophagus (n = 1), another upper digestive tract (n = 1).

mean pain score was 3.6 in the cRT arm (difference −2.5; 95% CI, −3.8 to −1.1) and 3.4 in the SBRT arm (difference −2.9; 95% CI, −4.0 to 1.9; $P = .41$; Fig. 3). In the PP analysis, the mean pain scores in the cRT remain 6.2 (SD = 2.0), because all patients allocated to the control arm underwent the standard treatment. Mean pain score in the SBRT arm at baseline was 6.3 (SD = 1.9), which dropped to 3.0 at 3 months (difference −3.0; 95% CI, −4.36 to −1.72). In a mixed-model analysis in which the treatment, interaction between treatment and time, and primary tumor were taken into account as fixed effects, no significant difference was found (Table E3). At baseline, 22 patients in both arms used opioids with a mean OMED of 83 mg (SD = 67) in the cRT arm and 95 mg (SD = 60) in the SBRT arm. At 12 weeks, 12 patients in the cRT arm and 13 in the SBRT arm used opioids, with an OMED of 83 mg (SD = 102) and 86 mg (SD = 45), respectively. No difference was found in global QOL scores between patients in the cRT and SBRT arm (Table 4; $P = .91$). No CTCAE grade 3 or 4 toxicity related to the treatment was reported in either treatment arm within 3 months after RT.

Discussion

In this cohort-embedded, randomized controlled trial following the TwiCs design, we found no differences in pain response, pain scores, and global QOL between patients receiving cRT and those (offered to be) treated with SBRT. In both arms, patients had a comparable decrease in pain and analgesic use in the 3 months after treatment. We found that a substantial proportion of patients (27%) preferred to undergo cRT instead of SBRT when given the choice. In addition, a substantial proportion of patients (21%) was unable to complete SBRT treatment, a phenomenon that was not observed in the cRT arm.

Our results are in line with the RTOG 0631 trial, in which no difference in pain response was found between the cRT (58%) and SBRT (40%) group 3 months after RT for spinal metastases.[11] In that trial, 339 patients were randomized 1:2 to cRT or SBRT, respectively.[8] In addition to similar pain response rates, our trial also showed mean pain scores similar to those in the RTOG 0631 in which, in the 3 months after RT, mean pain scores decreased from 5.88 to 2.05 in the cRT arm and from 6.06 to 3.06 in the SBRT arm. In addition, the results of Sprave et al[10] are similar to the results of the RTOG 0631 trial and our results. Sprave et al[10] performed a classic RCT with 30 patients per arm with spinal metastases receiving either 24 Gy SBRT in 1 fraction or 30 Gy multifraction cRT.[10] In the ITT analysis, no significant difference between cRT and SBRT was found in pain response after 3 months (48% vs 70%,

Table 2 Number and proportion of patients returning their questionnaire (n) of total patients at risk (N)

Treatment arm	At 2 wk	At 4 wk	At 6 wk	At 8 wk	At 3 mo
Conventional external beam radiation therapy arm, n (%)	32 (73%)	33 (77%)	27 (68%)	28 (72%)	23 (62%)
Deceased	0	1	4	5	7
Stereotactic body radiation therapy, n (%)	37 (82%)	36 (80%)	32 (76%)	33 (85%)	31 (82%)
Deceased	0	0	3	6	7

respectively; $P = .057$). Pain scores displayed a similar trend in both treatment arms. Because this trial was small and therefore underpowered, Sprave et al[10] recommended conducting larger RCTs to find clinically significant differences. A small, 3-arm, randomized phase 2 trial by Berwouts et al[23] showed that 8 Gy in a single fraction using fluorodeoxyglucose-PET−based dose painting resulted in a higher pain response (12/15; 80%) compared with 16 Gy in a single fraction using fluorodeoxyglucose-PET−based dose painting (9/15; 60%).[23] The authors explained their finding, among other reasons, by reducing the dose to normal tissues. A higher SBRT dose results in a higher dose to normal tissues, actually inducing elevation of inflammatory cytokines and possibly inducing adverse effects after SBRT.[23]

In contrast to the aforementioned studies, as well as ours, Nguyen et al found a significantly better pain response after SBRT (12-16 Gy in 1 fraction) after 2 weeks (for both ITT and PP analyses) and after 3 months (PP analysis). In this trial, the researchers compared 79 patients receiving multifraction cRT with 81 patients receiving SBRT for mainly non−spinal metastases. Pain response rates at 3 months in both arms were low compared with those found in other studies, with 21% in the cRT arm and 38% in the SBRT arm. Nguyen et al[9] mainly included patients with metastases from lung carcinoma, in contrast to the more heterogeneous study population in the RTOG 0631 trial and our trial. Moreover, the proportion of patients with lung cancer was higher in the cRT arm compared with the SBRT arm (60% and 39%). In previous models predicting pain response, patients with metastases from prostate or breast cancer had a better response than patients with lung cancer.[2,15] The low response rate and homogeneity in the Nguyen et al study could hamper extrapolation of the results to the general population with bone metastases. The joint result from these trials seems to indicate that dose escalation using SBRT does not lead to better pain response, possibly indicating a much more complex biological reaction of painful bone metastases to irradiation.

To our knowledge, this trial is the first RCT designed according to the TwiCs design in a palliative oncological setting. The TwiCs approach is different from classic RCTs, in which patients are informed about the trial and are asked 3 questions at the same time: (1) whether they are interested in participating in clinical research, (2) whether they agree to be randomized, and (3) whether they are willing to undergo an experimental intervention. In TwiCs, the first 2 questions ("Are you willing to participate in research?" and "Are you prepared to be randomized?") are asked at cohort entry, although the last question ("Are you prepared to undergo an experimental intervention?") is asked only of patients in the intervention arm (ie, only patients who can actually undergo the experimental intervention). This patient-centered, informed consent procedure is less confusing for patients than the standard informed consent procedure in a classic RCT, in which patients receive information about interventions that they might not receive. In addition, the TwiCs approach avoids disappointment of

Table 3 Patients who perceive a pain response after radiation therapy (n), according to treatment*

Analyses	At 2 wk	At 4 wk	At 6 wk	At 8 wk	At 3 mo
ITT analysis					
cRT	19/44 (43%)	19/44 (43%)	13/44 (30%)	16/44 (36%)	14/44 (32%)
SBRT	18/45 (40%)	16/45 (36%)	19/45 (42%)	17/45 (44%)	18/45 (40%)
PP analysis (patients undergoing allocated treatment)					
cRT	19/44 (43%)	19/44 (43%)	13/44 (30%)	16/44 (36%)	14/44 (32%)
SBRT	12/26 (46%)	10/26 (39%)	13/26 (50%)	11/26 (42%)	12/26 (46%)
ITT analysis of evaluable patients†					
cRT	19/32 (59%)	19/33 (58%)	13/27 (48%)	16/28 (57%)	14/23 (61%)
SBRT	18/37 (49%)	16/36 (44%)	19/32 (59%)	17/33 (52%)	18/31 (58%)

Abbreviations: cRT = conventional external beam radiation therapy; ITT = intention to treat; PP = per protocol; SBRT = stereotactic body radiation therapy.

* Presented as n/N (%). Patients are considered to have a response as pain score or analgesic use went down per the international consensus criteria.[4] In the ITT and PP analysis, patient who did not return a questionnaire or were deceased were considered nonresponders. In the ITT of analysable patients, only patients who returned a questionnaire were included.

† Number of patients reporting a pain response (n), who returned a questionnaire (N). Presented as n/N (%).

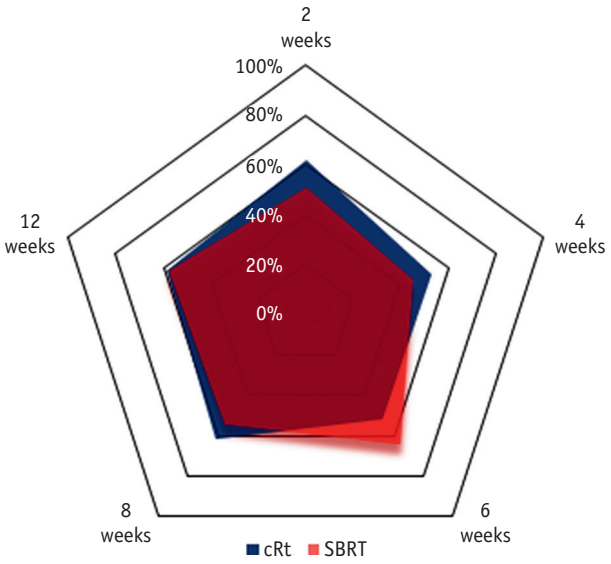

Fig. 2. Spider plot representing the proportion of patients reporting a pain response at each follow-up point. cRT (blue) and SBRT (red). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.11.060).

patients allocated to the control arm, considering only patients in the intervention arm receive information about the new intervention. As such, patients in the control arm are not prone to disappointment bias, (ie, the phenomenon observed among patients randomized to the control arm while hoping to be randomized to the intervention arm). Because patients know about the availability of a new treatment, not being able to receive the new treatment could induce disappointment and therefore result in reporting a more negative outcome.[24] Avoiding this type of bias is especially attractive in trials assessing a subjective outcome, such as pain and QOL.

TwiCs increases efficiency of recruitment.[25,26] We randomized more than 60% of the eligible patients treated for painful bone metastases at our institution during the study period. Similarly high enrollment rates were seen in other TwiCs at our institution, where 63% and 100% of the eligible patients were randomized.[26,27] In classic RCTs in the palliative setting, patient enrollment is challenging. The RTOG0631 trial, for example, took more than 9 years and 65 participating centers to enroll 339 patients (average of 0.6 patients per center per year). A Dutch multicenter classic RCT, the RACOST trial, was stopped early because of slow recruitment.[28,29] We also completed the trial within a single institution in a reasonable time frame of 4 years. As new technologies and treatment options are being developed rapidly, finishing a trial quickly is important.

Patients in the intervention arm decide whether they will accept the intervention or not; therefore, the TwiCs approach provides insightful information about the acceptability of the intervention to patients. We found that a substantial proportion of patients was not inclined to accept SBRT as a treatment: 12 patients (27%) declined to undergo SBRT, 10 of whom explicitly preferred cRT. This might be partially explained by more efficient treatment logistics of cRT; in our center; patients who undergo cRT in a single fraction can often undergo treatment on the same day as their visit to the radiation oncologist, or the day after. For the SBRT treatment, there was a waiting time of 1 to 2 weeks because of the use of a vacuum cushion and the need for an MRI scan, despite the availability of 2 dedicated MRI scanners for RT purposes at the RT department. This extra waiting time was the reason why many patients refused the intervention treatment. In addition, 1 patient had previously been treated for bone metastases with cRT; because he was satisfied with the effect of the previous cRT, he did not want to undergo SBRT.

Some differences were seen between the accepters and refusers of SBRT, specifically in primary tumor sites and the use of pain medication. Although this may be due to

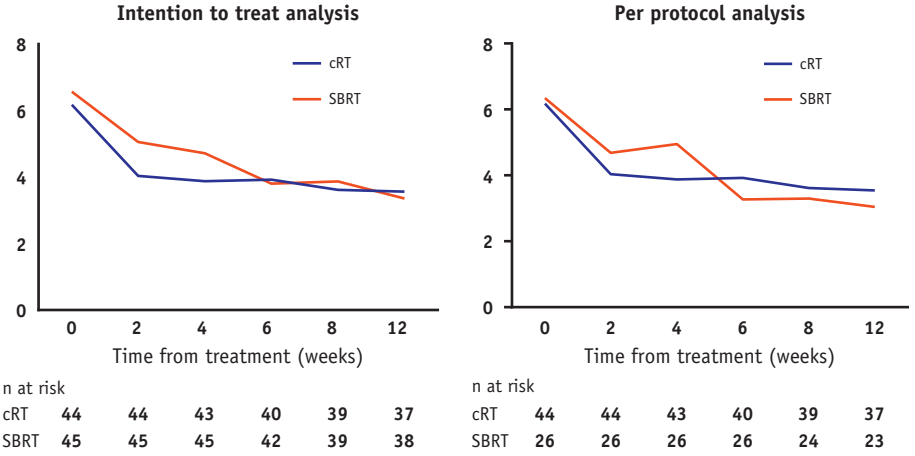

Fig. 3. Pain scores during the first 12 weeks after radiation therapy treatment. Pain was scored on a 10-point pain scale ranging from 0 (no pain) to 10 (worst imaginable pain). Pain was measured at baseline before radiation therapy treatment and after 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 3 months after radiation therapy treatment.

Table 4 Global quality of life scores of the EORTC-QLQ-C15 questionnaire*

	Baseline	At 4 wk	At 8 wk	At 3 mo
Conventional external beam radiation therapy	67 (50-67)	67 (50-83)	67 (67-83)	67 (67-83)
Stereotactic body radiation therapy	67 (50-67)	50 (50-67)	67 (50-83)	67 (50-83)

* Presented as median (interquartile range).

chance, the higher percentage of patients with lung cancer refusing SBRT treatment and more patients with breast cancer accepting could be explained by the differences in prognosis. Patients with breast cancer, who overall have a better prognosis than patients with lung cancer, could be more willing to invest in a more demanding and complex treatment. Furthermore, the percentage of patients not using any pain medication is higher among refusers, whereas their pain scores are similar to those of patients receiving lower levels of analgesia. This finding might indicate that patients had an even higher pain score without the pain medication and were therefore more likely to accept the more complex experimental treatment. In addition, 2 patients (4%) who declined SBRT did not want to receive any RT treatment, which was not seen in the cRT arm. Perhaps providing more information to patients in the intervention arm induced hesitation regarding the usefulness of both SBRT and cRT.

Our choice to design the PRESENT study according to TwiCs to create real-world evidence of the estimated effects of implementing SBRT for pain control in patients with bone metastases also had some disadvantages. Because of the dropout rate in both arms and the unexpectedly high nonacceptance rate in the SBRT arm, the trial was underpowered to detect the assumed difference in pain response between the cRT and SBRT arms. In addition, in the sample size calculation, an increase of 25% in the proportion of patients perceiving a pain response after SBRT compared with cRT was assumed. Therefore, this trial was underpowered to find smaller differences. A substantial pain difference should be present to justify adopting a new treatment, such as SBRT, which poses a considerable higher burden to the patient. Nevertheless, a smaller difference (eg, 15%) could be considered in future studies.

Despite repeated reminders, the questionnaire return rates at the different time points ranged from 71% to 78%, and only 39% of the patients returned the questionnaires at all follow-up time points. The relatively low number of returned questionnaires not only reflects the difficulty of conducting studies in vulnerable patient populations; it might also induce a response bias when, for example, mainly poor responders fail to return questionnaires. Therefore, the patients who did not return a questionnaire at a given time point were considered non−pain-responders in the ITT and PP.

A reason for patients to stop filling out questionnaires was an increase in disease burden. Other patients indicated that they did not find it necessary to complete the questionnaire because there was no change in their physical situation. Furthermore, the return rate in the control arm was lower than that in the intervention arm. This could be because control patients were unaware of being part of a clinical trial.

It has been hypothesized that the duration of response is longer after SBRT because of higher local control.[9,30] Because only 39% of the patients completed the questionnaires at all follow-up time points, we were unable to make a reliable estimate of the duration of pain response to confirm this suggestion. Furthermore, local control was not assessed in the present study. Future research could include local control as an endpoint, which could be particularly relevant for patients with a relatively high life expectancy. Despite the exclusion criterion of an estimated life expectancy of <3 months, 14 patients died within 3 months after RT. This result shows that estimating life expectancy in this patient group is difficult. Multiple prognostic models have been proposed, but none are sufficient to make a reliable estimate of the prognosis for all patients. This is a dilemma in all trials conducted with patients with bone metastases.

Finally, we depended on (follow-up) data as collected in the PRESENT cohort. In this cohort, only grade ≥ 3 adverse events are collected because of the high number of (intervention unrelated) adverse events owing to the natural course of disease in patients with stage IV cancer. Furthermore, toxicity was physician rated, not patient reported. This might have resulted in an underestimation of toxicity; however, in both RCTs from Nguyen et al[9] and Sprave et al,[10] no differences were seen in (grade 1 or 2) adverse events after cRT and SBRT.

Future research to compare the pain response after cRT and SBRT could be considered using the same TwiCs design. Classic RCTs have the disadvantage of slow accrual; this was an issue in the RACOST trial, which was suspended because of the limited patient accrual. The TwiCs design offers higher inclusion rates, but the potential dropout rate should be considered in the study design.

Conclusion

This study showed a comparable pain response after cRT or SBRT for painful bone metastases. Furthermore, when given the choice, a substantial proportion of patients preferred to receive cRT over SBRT. In addition, we found a substantial proportion of patients who were unable to complete SBRT treatment, unlike the cRT treatment. Lastly, the use of the TwiCs design is a feasible method to evaluate experimental treatments in the palliative oncology setting.

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