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CLINICAL INVESTIGATION

Quality of Life After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases

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Purpose: Painful bone metastases hamper quality of life (QoL). The aim of this prespecified secondary analysis of the PRESENT trial was to compare change in global QoL, physical functioning, emotional functioning, functional interference, and psychosocial aspects after conventional radiation therapy (cRT) versus stereotactic body RT (SBRT).

Methods and Materials: A total of 110 patients were enrolled in the phase 2 randomized controlled VERTICAL trial (NCT02364115) following the "trials within cohorts" design and randomized 1:1 to cRT or SBRT. Patient-reported global QoL, physical functioning, emotional functioning, functional interference, and psychosocial aspects were assessed by the European Organization for Research and Treatment of Cancer QoL Questionnaire (QLQ) Core 15 Palliative Care and QLQ Bone Metastases 22 modules. Changes in QoL domains over time were compared between patients treated with cRT and SBRT using intention-to-treat (ITT) and per-protocol (PP) linear mixed model analysis adjusting for baseline scores. Proportions of patients in the cRT versus SBRT arm reporting a clinically relevant change in QoL within 3 months were compared using a χ^2 test.

Results: QoL scores had improved over time and were comparable between groups for all domains in both the ITT and PP analyses, except for functional interference and psychological aspects in the ITT. Functional interference scores had improved more after 12 weeks in the cRT arm than in the SBRT arm (25.5 vs 14.1 points, respectively; effect size [ES] = 0.49, P = .04). Psychosocial aspects scores had improved more after 8 weeks in the cRT arm than in the SBRT arm (12.2 vs 7.3; ES = 0.56, P = .04). No clinically relevant differences between groups at 12 weeks in terms of global QoL, physical functioning, emotional functioning, functional interference, and psychosocial aspects were observed.

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

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Conclusions: Palliative RT improves QoL. Both SBRT and cRT have a comparable effect on patient-reported QoL outcomes in patients with painful bone metastases. Functional interference and psychological aspects scores improved more in patients treated with cRT versus patients offered SBRT.

Introduction

Bone metastases are a common manifestation of advanced cancer, causing pain, neurologic complaints, (impending) fractures, hypercalcemia, and deterioration of overall quality of life (QoL).[1-5] Conventional radiation therapy (cRT), consisting of schedules such as 1 × 8 Gy or 10 × 3 Gy, is the standard local treatment for painful bone metastases. The intent of this palliative intervention is to reduce pain and improve QoL.[3,6] Previous studies have shown that patients with a pain response after RT experienced a better overall QoL compared with patients without a pain response.[7]

Recently, results from the phase 2 randomized trial VERTICAL were published, comparing pain response after stereotactic body RT (SBRT) or cRT in patients with painful bone metastases.[8,9] The rationale behind the VERTICAL trial was that dose escalation using SBRT would lead to an improved pain response as a result of the delivery of a higher (tumoricidal) dose per fraction.[9]

In the primary analysis of the VERTICAL trial, no clinically significant difference in pain response was found between cRT and SBRT (32% and 40% of the patients, respectively).[8] Despite swift pain relief being a very important outcome, other patient-reported outcomes (PROs), such as global QoL, physical functioning, and emotional functioning, are relevant to patients in the palliative phase of their disease. These outcomes are subjective and multidimensional constructs and may therefore depend on more factors than pain alone, including limitations in physical and daily functioning, expectations of RT effectiveness at initiation of the treatment, and perception of treatment effectiveness after treatment.[10-12] When expectations are met after RT, patients are more likely to be satisfied with the treatment outcome and may perceive their posttreatment functioning and QoL as more favorable.[13] Such subjective outcomes could be affected by the study design, such as retrospective designs or classic randomized trials where patients know to which arm they are randomized. Among other things, this was the reason that this secondary analysis was performed within the VERTICAL trial, which followed the "trials within cohorts" (TwiCs) design.

So far, only one randomized controlled trial (RCT) evaluated the change in QoL in patients treated with cRT compared with SBRT for painful bone metastases, and this trial did not show superiority of QoL in the SBRT arm, as no differences were found between the groups.[10] Here, we present the results of a prespecified secondary analysis of the VERTICAL trial, where we compared the change in various domains of QoL in patients with painful bone metastases treated with cRT compared with those treated with SBRT.

Methods and Materials

Study design

The VERTICAL trial was designed to compare pain response and PROs among patients treated with cRT or SBRT for painful bone metastases (NCT02364115). VERTICAL followed the TwiCs design and was embedded in the PRrospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort.[14,15] In the context of PRESENT, all patients with bone metastases, referred to the Radiation Oncology Department of our tertiary referral hospital, were systematically asked to (1) give informed consent for use of their routine clinical data for research purposes, (2) consent to fill out QoL questionnaires and PROs, and (3) provide broad consent for possible future randomization into trials.[16]

Patients

Patients participating in PRESENT who gave broad consent for future randomization and meeting the in- and exclusion criteria for the VERTICAL trial were identified.[9] Inclusion criteria included radiologic and/or histologic evidence of bone metastases, no more than 2 painful lesions requiring radiation treatment, no or mild neurologic signs such as (radiating) pain or numbness, Karnofsky Performance Status scale of 50 points or higher, and pain score of 3 or higher on a numerical rating scale ranging from 0 (no pain) to 10 (worst pain). 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 symptoms. Eligible patients were randomized in a 1:1 ratio to the cRT or SBRT arm using block randomization with alternating block size. After randomization, in line with the TwiCs design, only patients allocated to the SBRT arm were informed about the VERTICAL trial and were offered to undergo SBRT.[16] Informed consent to undergo SBRT was obtained from patients accepting this offer. Patients who refused SBRT were planned for standard treatment (cRT) and remained in the intervention arm for analyses. Patients randomized to the cRT (control) arm were not informed about the VERTICAL trial and received standard cRT. Ethical approval for both the VERTICAL trial and PRESENT was obtained from the institutional review board of the UMC Utrecht, the Netherlands.

Treatment procedures

A detailed protocol for cRT and SBRT planning was published earlier.[9] In the cRT arm, patients received 1 × 8 Gy, 5 × 4 Gy, or 10 × 3 Gy. In the SBRT arm, patients received 1 × 18 Gy, 3 × 10 Gy, or 5 × 7 Gy.

Data collection

Within PRESENT, demographic and clinical data were collected prospectively at baseline (before start of RT), at 2, 4, 6, and 8 weeks; 3 and 6 months; and then every 6 months after treatment until death. Patient comorbidities were summarized using the Charlson Comorbidity Index.[17] Pain scores and PROs were measured in the PRESENT cohort using European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ) Core 15 Palliative Care (C15-PAL) and EORTC QLQ Bone Metastases 22 (BM22) modules.[11,18,19] In addition, toxicity and adverse events were physician assessed at clinical or telephone follow-up. Adverse events were graded following the Common Terminology Criteria for Adverse Events, version 4.0; only adverse events ≥grade 3 were recorded because in the study population of patients with stage IV disease, the amount of study-unrelated (low-grade) adverse events is high.[8]

Outcome measures

The C15-PAL questionnaire consists of 15 questions representing 9 domains: global QoL, 2 functional scales (physical functioning and emotional functioning), and 6 symptom scales (nausea, loss of appetite, dyspnea, constipation, sleeping difficulties, and fatigue).[11] The BM22 questionnaire consists of 22 questions representing 4 domains: painful sites, pain characteristic, functional interference, and psychosocial aspects.[18] For both the C15-PAL and BM22 questionnaire, patients rated their response on a 4-point Likert scale. The Global QoL domain was rated using a 7-point Likert scale. Scale scores were linearly transformed to a 0 to 100 scale for the functional and symptom domains.[18] A higher score on the global QoL and functional scales indicates better QoL and functioning, whereas lower scores on the symptom scales indicate less symptoms.[11] Higher scores on functional interference and psychosocial aspects domains are more favorable.[18] Patients were considered to have a clinically relevant improvement or deterioration when they had an increase or decrease, respectively, of 10 points on a 100-points scale compared with the baseline score.[19] For the present study, we focused on global QoL and physical and emotional functioning of the C15-PAL and the functional interference and psychosocial aspects domains of the BM22. Global QoL is a single-question domain, depicting the overall QoL. Physical functioning is a 3-question domain to measure the ability to perform essential physical activities such as self-care. Emotional functioning is a 2-question domain about patients' feeling of being depressed or tense. Functional interference is an 8-question domain, measuring the influence of (painful) bone metastases on physical activity, sleep, sitting, and lying down. The psychosocial aspects domain is described by 6 questions, measuring hope and worries about the disease, social isolation, and social isolation due to the disease.[20]

Statistical analysis

The current study is a predefined secondary analysis of the VERTICAL trial, and no sample-size calculation was performed for the current outcome.[8,9] For the primary analysis, 55 patients had to be included in each treatment arm to find a 25% difference in overall pain response with an α of 5% and a 10% drop-out.

A linear mixed model (LMM) for repeated measurements was used to evaluate the change in QoL scores between the 2 treatment arms. The scores at follow-up were compared with the baseline scores.

A random intercept for each patient was used to account for between-patient variation, and an autoregressive covariance structure was applied. Missing outcome data were assumed to be missing at random; the LMM accounts for such missing data.[21-23] Random slopes did not improve the model and were not included. The models included treatment arm and the interaction between treatment and time as an ordinal variable and the baseline scores and the interaction between treatment arm and time. The LMM analysis was presented as means for each domain on each time point for both cRT and SBRT and the mean difference with a 95% confidence interval (95% CI) between the treatment arms. The standardized effect size (ES) was calculated by dividing the mean between group difference at each time point by the pooled standard deviation at baseline.[24] In addition, an ES was calculated for the full model, using the mean difference between the 2 treatment arms without the time as stratification. An ES of ≤0.2 was considered as no difference, 0.2 to 0.5 was considered a small difference, 0.5 to 0.8 was considered a moderate difference, and an ES of >0.8 was considered a substantial difference in the reported scores.[25]

Proportions of patients with clinically relevant improvement or deterioration, that is, a change of at least 10 points on a 100-point scale, were compared between the treatment arms at each time point using the χ^2 test.[26] In addition, proportions of patients reporting a clinically relevant improvement at any time point within 12 weeks were compared. Here, patients who did not return a questionnaire were conservatively considered as having no improvement at that time point.

Statistical analyses were performed as intention to treat (ITT) and per protocol (PP). In the ITT analysis, all patients were included except for the patients who were not eligible after randomization. In the PP analysis, only patients who completed the treatment according to the random allocation were included. P values ≤ .05 were considered statistically significant.

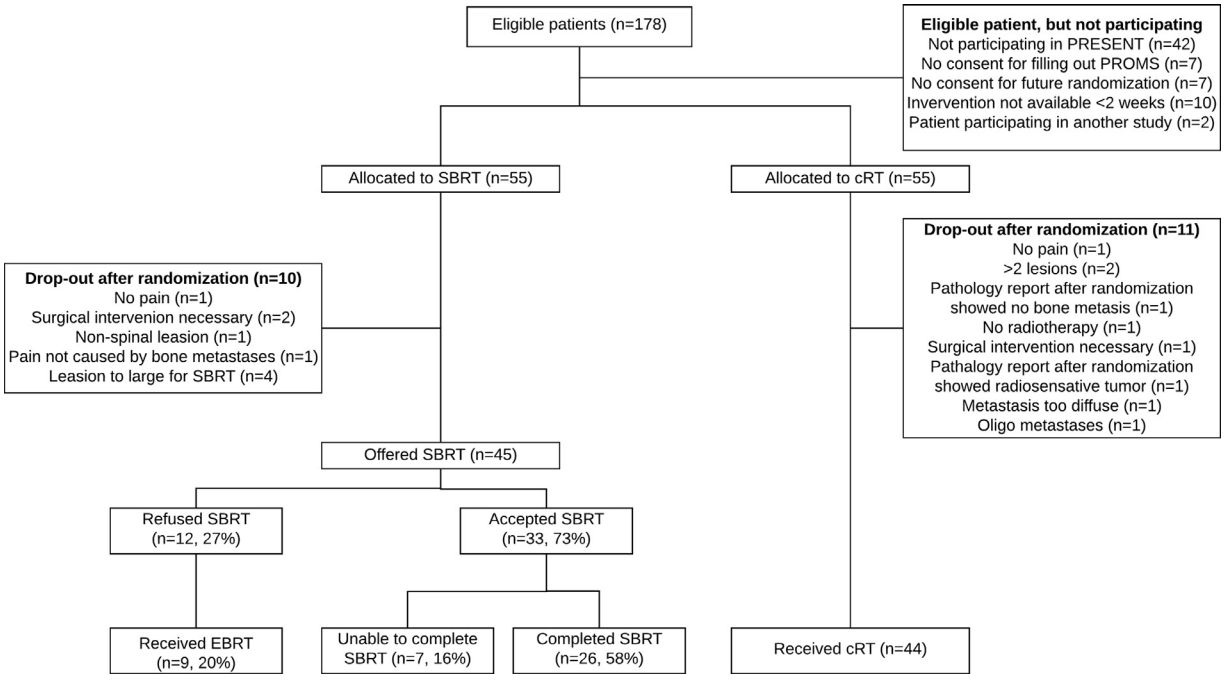

Fig. 1. Flowchart of patients enrolled in the VERTICAL trial and treatment allocation.

Results

Between January 2015 and March 2019, 110 patients were randomized. After randomization, 11 patients in the cRT arm and 10 patients in the SBRT arm were excluded, as they did not, or no longer, meet the inclusion criteria (Fig. 1). The most common reasons were lack of pain, new need for surgery, or additional MRI showing the lesion to be too large for SBRT. A total of 89 patients were included in the ITT analysis, 44 patients in the cRT arm and 45 in the SBRT arm. The majority of patients were male (n = 55, 62%), and the most common primary tumors were lung and prostate (26% and 22%, respectively; Table 1).[8]

After randomization, 12 of the 45 patients (27%) who were offered SBRT refused and chose to undergo cRT or no treatment (Fig. 1). The major reason to not undergo SBRT was the longer waiting time for treatment compared with cRT. Furthermore, 7 patients (16%) were unable to fully undergo SBRT due to various reasons, for example, increase in pain after 1 SBRT fraction or rapid deterioration between fractions. Subsequently, all 44 patients in the cRT and 26 patients in the SBRT arm were analyzed in the PP analysis. In the cRT arm, 21 patients (48%) received 1 × 8 Gy, 6 patients (14%) received 5 × 4 Gy, and 17 patients (39%) received 10 × 3 Gy. In the SBRT arm, 6 patients (23%) received 1 × 18 Gy, 11 patients (42%) received 3 × 10 Gy, and 9 patients (35%) received 5 × 7 Gy.

The proportion of patients returning a questionnaire varied over time from 49% in week 12 to 78% at baseline (Table E1). The return rate in the cRT arm was not statistically different at any follow-up time point compared with the SBRT arm (P = .81 at baseline, P = .06 at 12 weeks; Table E1). During the reminder telephone calls, patients indicated that they did not return their questionnaires for a variety of reasons: some indicated a lack of energy to fill out the questionnaires as a result of disease progression, whereas others reported that the treatment had a positive effect, and they therefore no longer saw a reason to return the questionnaires.

In the LMM analysis, no interaction was found between treatment and time and each separate follow-up point. Therefore, an overall score ES was calculated as well to compare the course of the QoL scores between the treatment arms (Tables 2 and 3). Compared with baseline scores, a positive change in QoL scores at some point during the 12 weeks after treatment was observed in all domains in both the ITT and PP analyses, specifically in the psychosocial aspects and functional interference domains (Tables 2 and 3 and Figs. 2 and 3). Figures 2 and 3 show a difference in course of QoL scores between the treatment arms. However, these visible differences did not translate into significant overall differences in the LMM analyses for the course of the QoL scores.

In the ITT LMM analysis, there was a significant difference at 12 weeks of 10.6 points (95% CI −21.0 to −0.3; ES = 0.62) between the cRT and the SBRT arm in functional interference in favor of cRT (Table 2). Between baseline and 12 weeks after treatment, functional interference scores improved from 55.0 (95% CI 49.6-64.1) to 80.5 (95% CI 72.8-88.2) and from 55.8 (95% CI 48.7-62.9) to 69.9 (95% CI 63.2-76.5) in, respectively, the cRT and SBRT arms (Table 2). There was a comparable, but nonsignificant, course of function interference scores. In the PP LMM analysis, no significant differences were found between the treatment arms.

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

	Conventional radiation therapy group, n = 44	Stereotactic body radiation therapy group,n = 45
Sex, no. (%)		
Male	31 (70)	24 (53)
Age in years, median (IQR)	63 (57-73)	65 (61-72)
Charlson Comorbidity Index, median (IQR)*	6 (6-7)	6 (6-7)
Karnofsky Performance Status, no. (%)†		
≤50	1 (3)	2 (7)
60-70	11 (37)	14 (40)
80-100	18 (60)	19 (42)
Missing	14 (32)	10 (22)
Primary tumor site, no. (%)		
Lung	9 (21)	14 (31)
Breast	8 (18)	9 (20)
Prostate	9 (21)	11 (24)
Other‡	18 (40)	11 (24)
Location bone metastases, no. (%)		
Spine	22 (50)	27 (60)
Nonspine	22 (50)	18 (40)
Shoulder	2 (9)	3 (16)
Rib	5 (23)	3 (16)
Pelvis or hip	12 (55)	9 (50)
Other	3 (14)	3 (16)
Pain score (NRS) at baseline, mean (SD)	6.2 (2.0)	6.6 (1.8)
Pain medication at baseline, no. (%)		
None	7 (16)	7 (16)
Nonopioid	15 (34)	15 (33)
Strong opioid	22 (50)	23 (51)
Oral morphine equivalent dose, median (IQR)	60 (40-120)	60 (40-110)
Concomitant systemic treatment	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 from 0 to 10; SD = standard deviation.

* The scale of the Charlson Comorbidity Index ranges from 0 to 40; 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 radiation therapy arm: kidney (n = 5), bladder (n = 4), colon and rectum (n = 5), esophagus (n = 1), and another endocrine (n = 1); stereotactic body radiation therapy arm: kidney (n = 3), bladder (n = 4), colon and rectum (n = 1), esophagus (n = 1), stomach (n = 1), and another upper digestive tract (n = 1).

Percentages may not add up to 100% as a result of rounding.

In the ITT analysis, a (small) majority of patients in both arms reported a clinically relevant improvement in the global QoL (55% and 56% in the cRT and SBRT arm, respectively) and emotional functioning (55% and 64% in the cRT and SBRT arm, respectively) domains at 1 or more time points within 12 weeks after treatment (Tables 3 and

Table 2 Linear mixed model intention-to-treat analysis for all QoL domains of the EORTC QLQ-C15 and BM22 questionnaires, comparing QoL between patients treated with cRT or SBRT

Domain	Group	Baseline	Week 4				Week 8				Week 12				During 12 weeks
		Mean*	Mean*	MD†	95% CI†	ES‡	Mean*	MD†	95% CI†	ES‡	Mean*	MD†	95% CI†	ES‡	ES‡
C15															
Global QoL	cRT	57.8	63.9				67.7				64.9				
	SBRT	58.6	59.1	−4.8	−16.2 to 6.5	0.25	64.4	−8.7	−20.2 to 2.9	0.44	63.1	−1.8	−13.8 to 10.2	0.09	0.27
Physical functioning	cRT	58.6	63.3				62.8				67.4				
	SBRT	59.4	59.7	−3.6	−13.6 to 6.4	0.14	52.8	−10.0	−22.1 to 2.0	0.39	58.8	−8.6	−19.3 to 2.1	0.34	0.24
Emotional functioning	cRT	73.8	72.7				86.0				80.3				
	SBRT	65.5	78.2	5.5	−6.1 to 17.0	0.26	72.8	−12.2	−24.1 to −0.3	0.56‡	72.5	−7.8	−19.9 to 4.2	0.36	0.23
BM22															
Functional interference	cRT	55.0	67.3				74.9				80.5				
	SBRT	55.8	66.0	−1.2	−10.8 to 8.4	0.05	66.1	−8.8	−18.5 to 0.9	0.40	69.9	−10.6	−21.0 to −0.3	0.49‡	0.28
Psychosocial aspects	cRT	55.4	57.4				59.0				57.3				
	SBRT	53.0	55.8	−1.6	−9.5 to 6.3	0.09	57.0	−2.0	−10.0 to 6.0	0.11	57.8	0.6	−7.9 to 9.0	0.03	0.07

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; CI = confidence interval; cRT = conventional radiation therapy; ES = effect size; MD = mean difference; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.

* Mean scores for the QoL domains of the EORTC QLC-C15 Palliative Care (EORTC QLQ-C15-PAL) and EORTC QLQ-BM22. Scores range from 0 to 100. Higher scores indicate better QoL.

† Mean difference in scores between the cRT arm and SBRT arm with 95% CI.

‡ Statistically significant difference between cRT and SBRT. A P value < .05 is considered statistically significant. The ES represents the difference between the cRT arm and SBRT arm in QoL scores.

Table 3 Linear mixed model per-protocol analysis for all QoL domains of the EORTC QLQ-C15 and BM22 questionnaires, comparing QoL between patients treated with cRT or SBRT

Domain	Group	Baseline	Week 4				Week 8				Week 12				During 12 weeks
		Mean*	Mean*	MD†	95% CI†	ES‡	Mean*	MD†	95% CI†	ES‡	Mean*	MD†	95% CI†	ES‡	ES‡
C15															
Global QoL	cRT	57.8	64.3				68.1				65.2				
	SBRT	59.8	60.8	−3.5	−15.9 to 8.9	0.18	63.6	−4.4	−16.9 to 8.1	0.23	65.5	0.2	−12.4 to 12.9	0.01	0.13
Physical functioning	cRT	58.6	63.8				63.1				67.5				
	SBRT	62.4	59.6	−4.2	−15.5 to 7.2	0.16	59.3	−3.8	−17.1 to 9.4	0.15	60.4	−7.2	−18.8 to 4.5	0.28	0.19
Emotional functioning	cRT	73.8	73.2				86.4				80.7				
	SBRT	63.7	77.4	4.2	−8.5 to 16.9	0.19	75.3	−11.1	−24.0 to 1.8	0.50	73.6	−7.2	−20.0 to 5.8	0.32	0.22
BM22															
Functional interference	cRT	55.0	67.6				75.2				80.7				
	SBRT	58.3	65.0	−2.6	−13.0 to 7.9	0.12	69.0	−5.2	−15.6 to 5.2	0.26	72.9	−7.9	−18.6 to 2.8	0.39	0.22
Psychosocial aspects	cRT	55.4	56.6				58.1				56.1				
	SBRT	49.2	55.4	−1.1	−9.5 to 7.3	0.06	58.5	0.4	−8.1 to 8.9	0.02	59.7	3.6	−4.9 to 12.2	0.20	0.05

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; CI = confidence interval; cRT = conventional radiation therapy; ES = effect size; MD = mean difference; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.

* Mean scores for the QoL domains of the EORTC QLC-C15 Palliative Care (EORTC QLQ-C15-PAL) and EORTC QLQ-BM22. Scores range from 0 to 100. Higher scores indicate better QoL.

† Mean difference in scores between the cRT arm and SBRT arm with 95% CI.

‡ Statistically significant difference between cRT and SBRT. A P value <0.05 is considered statistically significant. The effect size represents the difference between the cRT-arm and SBRT-arm in QoL scores.

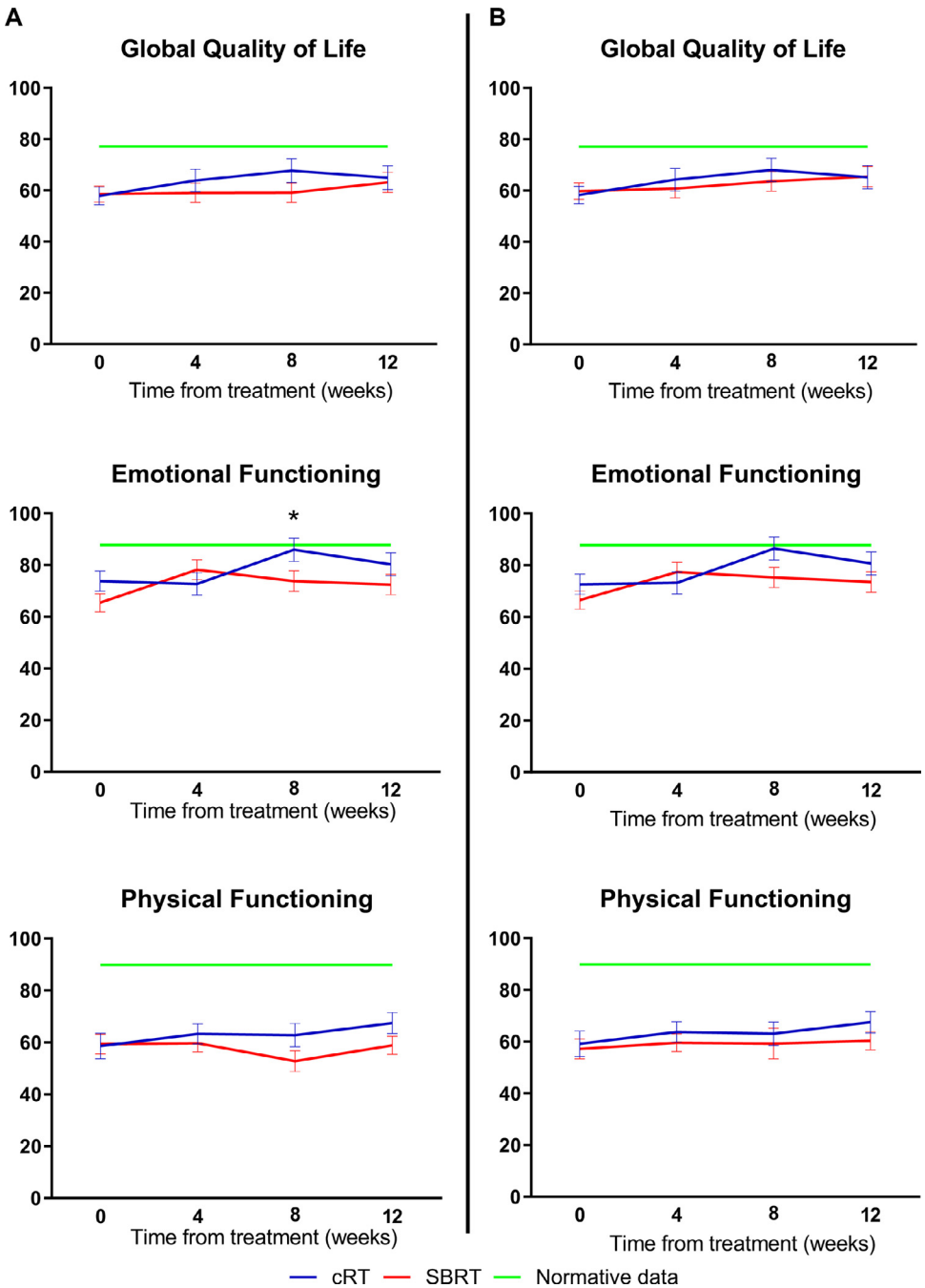

Fig. 2. Quality of life domains of the C15-PAL questionnaires in the ITT mixed model analysis. (A) In the ITT analysis, all patients were included except for the patients who we found not eligible after randomization. (B) In the PP analysis, only patients who completed the treatment according to the random allocation were included. A higher score depicts an improved quality of life. Normative data show the mean score of the general, cancer-free population. *Significant difference. *Abbreviations:* C15-PAL = Quality of Life Questionnaire Core 15 Palliative Care; ITT = intention to treat; PP = per protocol.

5). Nevertheless, the proportion of patients with a clinically relevant improvement was not significantly different between treatment arms within 12 weeks after RT (Tables 4 and 5). In the PP analysis, the proportion of patients with a clinically significant difference in the cRT arm remained unchanged compared with the ITT analysis (Tables 4 and 5). However, in the SBRT arm, a higher proportion of patients had clinically significant improvement for several domains (Tables 4 and 5). However, differences in proportions of patients with a clinically relevant difference between the cRT arm and SBRT arm were not statistically significant in the PP analysis either.

In both the ITT and PP analyses, a minority of the patients had a clinically relevant deterioration in QoL domains in each arm (Table E2). In the PP analysis, the difference in proportion of patients with a clinically relevant

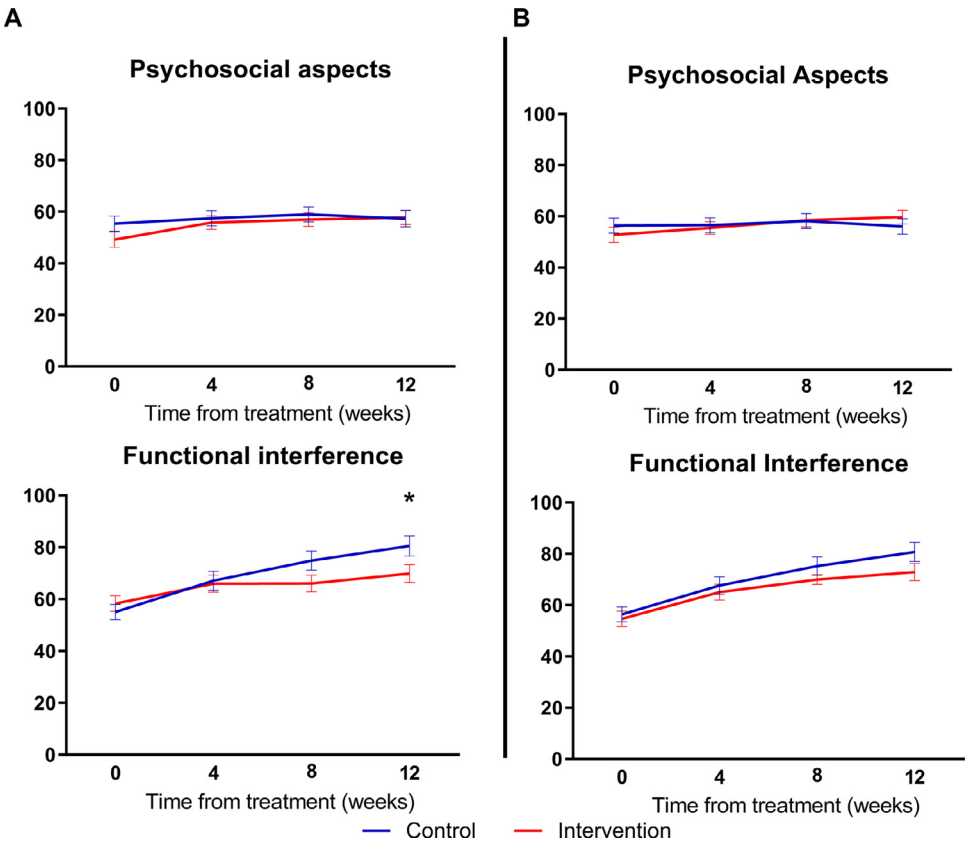

Fig. 3. Quality of life domains of the BM22 questionnaires in the ITT mixed model analysis. (A) In the ITT analysis, all patients were included except for the patients who we found not eligible after randomization. (B) In the PP analysis, only patients who completed the treatment according to the random allocation were included. A higher score depicts an improved quality of life. *Significant difference. *Abbreviations:* BM22 = QLQ Bone Metastases 22; ITT = intention to treat; PP = per protocol.

improvement between the 2 groups changed in favor of the SBRT arm but remained nonsignificant. The proportion of patients with clinically relevant deterioration was comparable between the 2 treatment arms. As reported previously in the primary analysis, no treatment-related Common Terminology Criteria for Adverse Events, grades 3 or 4 adverse events, within 3 months after treatment were reported in either treatment arm.[8]

Discussion

Our study shows that there was no difference in change in QoL between treatment with cRT or SBRT for painful bone metastases. Nonetheless, QoL improved in the majority of patients at some point in the 3 months after treatment. Patients receiving cRT reported larger improvements in terms of functional interference of pain with daily functioning and psychosocial aspects compared with patients receiving SBRT. The absence of superior QoL scores among patients in the SBRT arm was not unexpected. The primary analysis of the VERTICAL trial showed no differences between cRT and SBRT in terms of pain response (32% and 40% of the patients, respectively). As pain is considered to be one of the main elements in QoL, we also did not expect a significant difference in QoL between the cRT arm and SBRT arm.[8,27]

Our results are in line with the results of the secondary analysis of Sprave et al.[10] In their exploratory trial comparing SBRT and cRT, 55 patients were randomized to either 1 × 24 Gy SBRT or 10 × 3 Gy cRT. In their study, QoL was measured using the EORTC QLQ BM22 and EORTC QLQ FA13 (fatigue) questionnaires directly after RT, and 3 and 6 months after RT. They showed an improvement in all QoL domains but no significant difference between the cRT arm and SBRT arm. To our knowledge, the trial performed by Sprave et al[28] is the only trial directly comparing QoL between cRT and SBRT in patients with bone metastases, albeit with a somewhat protracted 10-fraction cRT schedule. In addition to the QoL domains, a secondary analysis was performed on bone mineral density and vertebral compression fractures (VCFs).[29] In this secondary analysis, Sprave et al[29] found an increase of VCF in patients treated with SBRT compared with cRT. This could influence the pain and QoL response in patients treated with SBRT with a VCF. Other trials have reported the results of cRT versus SBRT on pain response, but no results on the QoL have yet been published.[30-32] Furthermore, the ROBOMET trial (A

Table 4 Number of patients in the intention-to-treat analysis reporting a clinically relevant improvement in selected QoL domains of the EORTC QLQ-C15 and BM22 questionnaires

	Group	Week 4	Week 8	Week 12	Within 12 weeks	*P* value*
Cumulative deaths	cRT	1	5	7	7	
	SBRT	0	6	7	7	
Domains						
C15		n/N (%)†	n/N (%)†	n/N (%)†	n/N (%)†	
Global QoL	cRT	16/43 (37)	17/39 (44)	17/37 (46)	24/44 (55)	
	SBRT	19/45 (42)	17/39 (38)	21/38 (55)	25/45 (56)	.12
Physical functioning	cRT	16/43 (37)	7/39 (18)	7/37 (19)	18/44 (41)	
	SBRT	16/45 (36)	6/39 (13)	10/38 (26)	20/45 (44)	.83
Emotional functioning	cRT	15/43 (35)	19/39 (49)	13/37 (35)	24/44 (55)	
	SBRT	23/45 (51)	18/39 (40)	17/38 (44)	29/45 (64)	.52
BM22						
Functioning interference	cRT	3/43 (7)	3/39 (7)	2/37 (5)	4/44 (9)	
	SBRT	4/45 (9)	3/39 (7)	0/38 (0)	5/45 (11)	1.00
Psychosocial aspects	cRT	4/43 (9)	2/39 (5)	4/37 (11)	8/44 (18)	
	SBRT	7/45 (16)	3/39 (7)	3/38 (8)	9/45 (20)	1.00

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; cRT = conventional radiation therapy; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.

* *P* value is based on the difference of the proportion of patients with a clinically significant response between cRT and SBRT within 12 weeks after RT.

† Number of patients with a clinically relevant increase (n), defined as an increase of at least 10 points on a 100-point scale, compared with baseline score among the total number of patients alive at each point in follow-up (N) in the intention-to-treat analysis.

Trial to Improve Quality of Life With Stereotactic Body Radiotherapy for Patients With Painful Bone Metastases; clinical trial NCT03831243; recruiting until 2023) and the PREST trial (Reduction of Pain Symptoms With Stereotactic Radiotherapy on Bone Metastases; clinical trial NCT03597984; awaiting commencement) aim to compare QoL between cRT and SBRT in patients with painful bone metastases.[33,34]

Because of drop-out after randomization, both ITT and PP analyses were performed. In the ITT analysis, all patients who were found ineligible after randomization were excluded. For the PP analysis, only patients who completed the allocated treatment were included, leaving out another 19 SBRT patients. We found more often a clinically relevant improvement after SBRT in the PP analyses. In these analyses, the patients willing to wait and able to undergo the entire SBRT treatment remained, and it is likely that these patients were in a better clinical condition than the patients dropping out. As a result of the selection as a result of drop-out after randomization, patients included in the PP were presumably in a better general condition than the patients who could not complete the treatment (Table E3). It could be expected that this selection could change the outcome of the analysis in favor of the SBRT arm in which the selection took place. Nonetheless, in the PP analysis, no major significant differences between the groups were found.

Although most QoL domains showed a comparable trend for both the cRT and SBRT arms, there was a significant difference between the cRT arm and SBRT arm in the change in functional interference scores at 12 weeks in favor of the cRT arm. Functional interference of pain with daily functioning reflects a patient's ability to do lie down, sit, and complete moderate activities. Although SBRT needs more preparatory time, including additional MRI, stabilization in vacuum mattress, and more treatment time on linear particle accelerators, this probably does not reflect in the functional interference domain in the short term. The time to observe an effect of SBRT might be delayed, which might explain why we only see a difference at 12 weeks' follow-up.

The VERTICAL study is the first trial following the TwiCs design in the palliative setting. Previous studies following the TwiCs design showed that the representativeness of patients is higher in trials using the TwiCs design compared with a classic RCT.[35,36] For the VERTICAL trial, patients participating in the PRESENT cohort who were eligible to undergo SBRT were selected and randomized without any additional selection. In the PRESENT cohort, all patients were asked to participate in the cohort and whether they wanted to participate in future studies on experimental

Table 5 Number of patients in the per-protocol analysis reporting a clinically relevant improvement in selected QoL domains of the EORTC QLQ-C15 and BM22 questionnaires

	Group	Week 4	Week 8	Week 12	Within 12 weeks	*P* value*
Cumulative deaths	cRT	1	5	7	7	
	SBRT	0	2	3	3	
Domains						
C15		n/N (%)†	n/N (%)†	n/N (%)†	n/N (%)†	
Global QoL	cRT	16/43 (37)	17/39 (44)	17/37 (46)	24/44 (55)	
	SBRT	14/26 (54)	13/24 (54)	15/23 (65)	17/23 (74)	.16
Physical functioning	cRT	16/43 (37)	7/39 (18)	7/37 (19)	18/44 (41)	
	SBRT	10/26 (39)	6/24 (25)	7/23 (30)	13/23 (57)	.62
Emotional functioning	cRT	15/43 (35)	19/39 (49)	13/37 (35)	24/44 (55)	
	SBRT	14/26 (54)	14/24 (58)	12/23 (52)	18/23 (78)	.31
BM22						
Functioning interference	cRT	3/43 (7)	3/39 (7)	2/37 (5)	4/44 (9)	
	SBRT	3/26 (12)	1/24 (4)	0/23 (0)	3/23 (13)	1.00
Psychosocial aspects	cRT	4/43 (9)	2/39 (5)	4/37 (11)	8/44 (18)	
	SBRT	4/26 (15)	1/24 (4)	2/23 (9)	5/23 (22)	1.00

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; cRT = conventional radiation therapy; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.

* *P* value is based on the difference of the proportion of patients with a clinically significant response between cRT and SBRT within 12 weeks after RT.

† Number of patients with a clinically relevant increase (n), defined as an increase of at least 10 points on a 100-point scale, compared with baseline score among the total number of patients alive at each point in follow-up (N) in the intention-to-treat analysis.

interventions.[8] Therefore, the results of the VERTICAL trial are more generalizable to the real-world population of patients eligible for treatment with SBRT for painful bone metastases compared with patients in classic RCTs comparing SBRT and cRT.[37,38] However, this is negatively influenced by the drop-out after randomization in this trial.

Another advantage of the TwiCs design is that it may prevent disappointment bias by not informing (and potentially disappointing) patients allocated to the control arm. In a classic RCT, patients are informed about an innovative treatment that could induce hope for better results. Because of the knowledge of being allocated to the control arm, patients could rate their outcomes more negatively.[39] Therefore, the TwiCs design could be especially relevant in trials with subjective outcomes such as pain and QoL. The opposite, however, may have happened as well: patients in VERTICAL who were offered SBRT may have had overly optimistic expectations.[12] When the high expectations were not met, disappointment could have been reflected in the self-reported QoL scores. In the cRT arm, where patients were not informed about the trial, the effect of this disappointment bias was limited or nonexistent.[39] This could influence the QoL scores positively in the cRT and negatively in the SBRT arm. This negative influence on the outcomes in the SBRT arm could be reinforced by the increased burden of the treatment. Nonetheless, as pain and QoL are subjective scores, they could also be positively influenced by the idea of receiving a new and innovative treatment.

The VERTICAL trial was primarily powered to detect a difference in pain response. Because of the unexpected high number of patients in the intervention arm refusing to undergo SBRT and the high number of patients unable to complete SBRT, the primary analysis was underpowered to detect a difference in pain. As such, the current study was not powered to detect clinically relevant differences in the QoL domains. Nonetheless, proportions of patients with a clinically relevant improvement did not differ between the 2 groups. Because of the drop-out after randomization, a PP analysis was performed in addition to the ITT to examine the true effect of SBRT versus cRT. Owing to the additional analysis and thus the induced multiple comparison, an additional study could be performed with an increased number of patients to adjust for the drop-out.

In addition, the number of returned questionnaires in both arms was less than expected, despite follow-up calls to remind patients, which could have influenced the results. For some patients, their disease progressed over time, leaving them unable to return questionnaires. Other patients informed the researcher the pain from the metastases and QoL improved, and therefore, they stopped filling out the questionnaires. Notably, and probably due to the design, the

proportion of patients returning questionnaires was lower in the cRT arm. The awareness of being part of a clinical trial —more often the case for patients in the SBRT arm—might have positively affected the return rate of questionnaires. In the figures, a difference is seen in the trend of the QoL scores between the treatment arms. Nonetheless, this difference is limited in the LMM analysis. The difference could be too small to be detected in this trial due to the drop-out and limited return of questionnaires.

Lastly, this study only evaluated PROs in the first 12 weeks after RT, whereas the duration of the effect of RT might differ between cRT and SBRT, where the effect of SBRT could last longer.[10] Therefore, future studies should study the effects on the longer term as well.

Conclusions

In this secondary analysis of the VERTICAL trial, we found that both cRT and SBRT had a comparable positive effect on all QoL domains in patients irradiated for painful bone metastases. Improvement in functional interference and psychological aspects was slightly greater in the cRT arm.

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