Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial

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Summary

Background Although repeat radiation treatment has been shown to palliate pain in patients with bone metastases from multiple primary origin sites, data for the best possible dose fractionation schedules are lacking. We aimed to assess two dose fractionation schedules in patients with painful bone metastases needing repeat radiation therapy.

Methods We did a multicentre, non-blinded, randomised, controlled trial in nine countries worldwide. We enrolled patients 18 years or older who had radiologically confirmed, painful (ie, pain measured as ≥2 points using the Brief Pain Inventory) bone metastases, had received previous radiation therapy, and were taking a stable dose and schedule of pain-relieving drugs (if prescribed). Patients were randomly assigned (1:1) to receive either 8 Gy in a single fraction or 20 Gy in multiple fractions by a central computer-generated allocation sequence using dynamic minimisation to conceal assignment, stratified by previous radiation fraction schedule, response to initial radiation, and treatment centre. Patients, caregivers, and investigators were not masked to treatment allocation. The primary endpoint was overall pain response at 2 months, which was defined as the sum of complete and partial pain responses to treatment, assessed using both Brief Pain Inventory scores and changes in analgesic consumption. Analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00080912.

Findings Between Jan 7, 2004, and May 24, 2012, we randomly assigned 425 patients to each treatment group. 19 (4%) patients in the 8 Gy group and 12 (3%) in the 20 Gy group were found to be ineligible after randomisation, and 140 (33%) and 132 (31%) patients, respectively, were not assessable at 2 months and were counted as missing data in the intention-to-treat analysis. In the intention-to-treat population, 118 (28%) patients allocated to 8 Gy treatment and 135 (32%) allocated to 20 Gy treatment had an overall pain response to treatment (p=0·21; response difference of 4·00% [upper limit of the 95% CI 9·2, less than the prespecified non-inferiority margin of 10%]). In the per-protocol population, 116 (45%) of 258 patients and 134 (51%) of 263 patients, respectively, had an overall pain response to treatment (p=0·17; response difference 6·00% [upper limit of the 95% CI 13·2, greater than the prespecified non-inferiority margin of 10%]). The most frequently reported acute radiation-related toxicities at 14 days were lack of appetite (201 [56%] of 358 assessable patients who received 8 Gy *vs* 229 [66%] of 349 assessable patients who received 20 Gy; p=0·011) and diarrhoea (81 [23%] of 357 *vs* 108 [31%] of 349; p=0·018). Pathological fractures occurred in 30 (7%) of 425 patients assigned to 8 Gy and 20 (5%) of 425 assigned to 20 Gy (odds ratio [OR] 1·54, 95% CI 0·85–2·75; p=0·15), and spinal cord or cauda equina compressions were reported in seven (2%) of 425 versus two (<1%) of 425, respectively (OR 3·54, 95% CI 0·73–17·15; p=0·094).

Interpretation In patients with painful bone metastases requiring repeat radiation therapy, treatment with 8 Gy in a single fraction seems to be non-inferior and less toxic than 20 Gy in multiple fractions; however, as findings were not robust in a per-protocol analysis, trade-offs between efficacy and toxicity might exist.

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Introduction

Radiation therapy can effectively palliate pain in patients with bone metastases.[1,2] Improvements in systemic and supportive therapies have increased the life expectancy of these patients, who can have recurrence of pain at sites of previous radiation treatment. Repeat radiation treatment might be an option to palliate pain in patients who have had no pain relief after previously receiving radiation therapy, as well as for those who have had partial improvement in pain and who might receive additional benefit from repeat treatment, or in those whose pain has recurred after an initial satisfactory response.[3] Data from seven single-group cohort studies showed that 306 (58%) of 527 patients (95% CI 0·49–0·67) obtained a beneficial response with repeat radiation therapy.[4] However, to our knowledge, no randomised controlled trials have assessed radiation dose fractionation schedules in patients with bone metastases requiring treatment.

We aimed to compare the pain-relieving efficacy of two frequently administered radiation re-treatment

doses[3–6]—8 Gy administered in a single fraction or 20 Gy given in multiple fractions—in patients with pain from bone metastases who had received previous radiation therapy.

Methods

Study design and participants

Our trial was a multicentre, non-blinded, randomised controlled, non-inferiority trial conceived, undertaken, and analysed by the NCIC Clinical Trials Group (CTG). Patients were accrued from centres based in Canada by the NCIC CTG, and in eight other countries by the Trans Tasman Radiation Oncology Group (Australia and New Zealand), the Radiation Therapy Oncology Group (RTOG; USA, Israel, and Switzerland), the UK National Cancer Research Network, and networks based in the Netherlands and France. All participating centres received approval from their local research ethics boards, and written informed consent was obtained from all patients. Data were held and analysed by the NCIC CTG, and the group's independent data safety monitoring committee reviewed details of trial conduct at confidential 6-monthly meetings. The study protocol including a summary of amendments is available online.

Eligible patients were aged 18 years or older with a proven diagnosis of cancer and pain corresponding to sites of radiologically confirmed bone metastases that had previously received radiation. The re-treatment area could not be larger than the initial treatment area as stated in the study protocol, and the initial radiation treatment field had to be reproducible for re-irradiation. Severity of pain needed to be at least 2 out of 10 according to the Brief Pain Inventory,[7] and patients receiving prescribed analgesics had to be on a stable dose and schedule, including as-needed doses. The interval between the last fraction of initial radiation and the date of randomisation had to be at least 4 weeks. Patients were ineligible if they had clinical or radiological evidence of spinal cord compression, a pathological fracture, or an impending fracture that needed to be fixed surgically. Other exclusion criteria were having treatment areas associated with previous palliative surgery, having a Karnofsky performance status of less than 50, or receiving systematic radiotherapy or half-body irradiation within 30 days before the beginning of randomisation.

Eligibility criteria also accounted for specifics of previous radiation therapy and normal tissue tolerance. Patients were eligible only if the treatment site involved: an extremity or rib, and previous therapy was with 6, 7, or 8 Gy in a single fraction, 18 Gy in four fractions, 20 Gy in five fractions, 24 Gy in six fractions, 27 Gy in eight fractions, or 30 Gy in ten fractions; the spine or pelvis, and previous therapy was with 6, 7, or 8 Gy in a single fraction, 18 Gy in four fractions, or 20 Gy in five fractions; and the acetabulum, hip, or proximal femur, and previous treatment was with 24 Gy in six fractions, 27 Gy in eight fractions, or 30 Gy in ten fractions, provided that the medial field border did not cross midline. Patients receiving treatment to the spine or any part of the pelvis that encompassed the small or large intestine or the rectum were ineligible if their previous treatment was with 24 Gy in six fractions, 27 Gy in eight fractions, or 30 Gy in ten fractions.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either 8 Gy in a single fraction or 20 Gy in multiple fractions by a computer-generated allocation sequence based at the NCIC CTG central office in Kingston, ON, Canada. Randomisation requests were sent to the offices of the participating groups by staff at the treating centre. Staff at the participating group entered relevant data into the web-based interface of the computer program that did the randomisation and then communicated the treatment allocation provided by the computer program back to the treating centre. Involvement of the staff entering the data in other aspects of the trial varied by participating group, but was mainly administrative. Dynamic minimisation[8] was used to conceal assignment of participants, and assignment was stratified by previous radiation fraction schedule, response to initial radiation, and treatment centre. Patients, caregivers, and investigators were not masked to treatment allocation.

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For the **study protocol** see http://www.ctg.queensu.ca/public/publications/SC20_public/SC20_Protocol-Amend5-2009AUG07_Public-secured.pdf

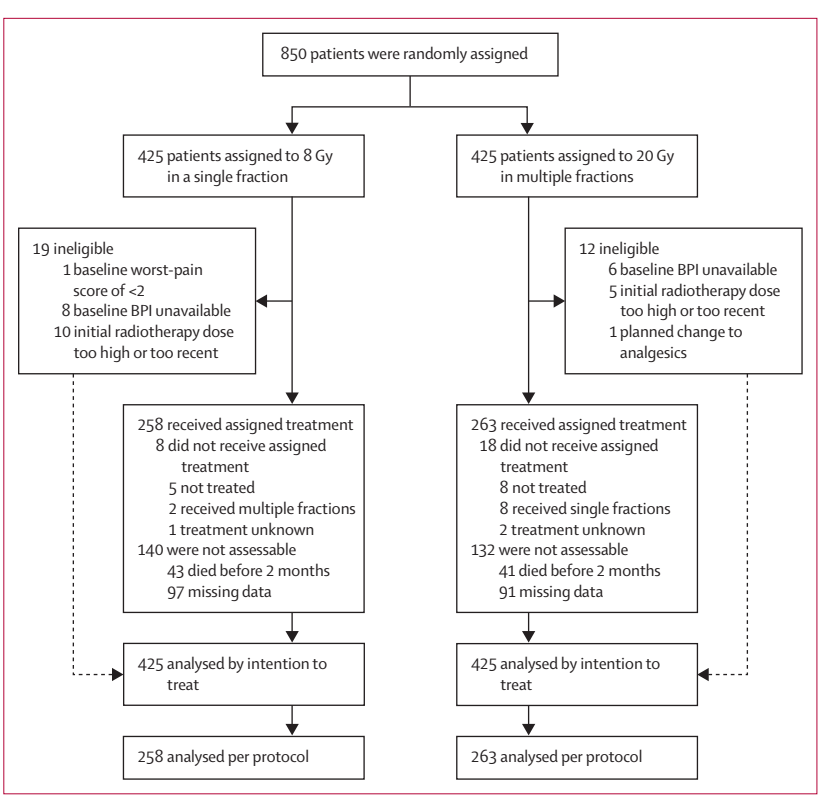

Figure 1: **Trial profile**
BPI=Brief Pain Inventory score.

Procedures

Patients randomly assigned to receive 20 Gy were to receive treatment in five fractions, unless the target field was the spine or whole pelvis, and previous radiation therapy consisted of 18 Gy in four fractions or 20 Gy in five fractions, in which case they were to receive 20 Gy in eight fractions. Patients assigned to receive 8 Gy received treatment in a single fraction. The study allowed both two-dimensional and three-dimensional planning at the discretion of the treating radiation oncologist, because this was planned as a pragmatic trial. A prophylactic antiemetic was recommended for patients receiving radiation to fields that included the epigastrium, lumbar spine, or pelvis.[9] Bone-modifying agents and systemic therapy were allowed at the discretion of the treating physicians. Their effects on the outcomes will be reported in another paper.

See Online for appendix

	8 Gy/single fraction (N=425)	20 Gy/multiple fractions (N=425)
Age, years	64·6 (17·4)	65·3 (17·1)
Sex		
Men	243 (57%)	256 (60%)
Women	181 (43%)	167 (39%)
Missing	1 (<1%)	2 (<1%)
Primary cancer site		
Prostate	113 (27%)	116 (27%)
Breast	117 (28%)	106 (25%)
Lung	94 (22%)	96 (23%)
Kidney	17 (4%)	24 (6%)
Colon	22 (5%)	15 (4%)
Oesophagus	11 (3%)	10 (2%)
Rectum	6 (1%)	9 (2%)
Other	34 (8%)	43 (10%)
Unknown	11 (3%)	6 (1%)
Karnofsky performance status		
50–60	96 (23%)	85 (20%)
70–80	226 (53%)	240 (56%)
90–100	98 (23%)	91 (21%)
Missing or unknown	5 (1%)	9 (2%)
Worst-pain score at baseline		
Missing, uninterpretable, or ineligible	16 (4%)	13 (3%)
2–4	48 (11%)	54 (13%)
5–6	104 (24%)	96 (23%)
7–10	257 (60%)	262 (62%)
Sites of painful bone lesion		
Pelvis or hips	154 (36%)	153 (36%)
Lumbo-sacral spine	71 (17%)	83 (20%)
Superficial bones	58 (14%)	45 (11%)
Upper limbs	37 (9%)	48 (11%)
Thoracic spine	45 (11%)	38 (9%)
Other	60 (14%)	58 (14%)
Response to initial radiation		
No response	71 (17%)	71 (17%)
Response	354 (83%)	354 (83%)
Initial radiation treatment fraction schedule		
Multiple	145 (34%)	146 (34%)
Single	280 (66%)	279 (66%)
Time from date of last fraction of initial radiation to randomisation of re-treatment, days	113·0 (174·0)	106·0 (180·0)
Dose of daily oral morphine equivalent at baseline, mg	47·5 (160·0)	40·0 (110·0)

Data are mean (SD) or number (%).

***Table 1*: Baseline characteristics of randomly assigned patients**

We used international consensus endpoints to assess pain severity and analgesic consumption.[10,11] Pain severity was scored with the Brief Pain Inventory, which includes an 11-point scale to assess pain. For this trial, the questionnaire at baseline asked patients to rate their pain by circling the number (from zero to ten) that best described their pain at its worst in the previous 3 days, and at follow-up visits asked patients to rate their pain by circling the number that best described their pain at its worst during the previous 3 days in the area treated by radiation. The questionnaire also included an 11-point scale that asked how pain had interfered with general activity, mood, walking ability, normal work, relations with other people, sleeping, and enjoyment of life. Analgesic consumption was converted into a daily oral morphine equivalent according to a schema (appendix).

The primary endpoint was overall response to treatment in terms of pain relief, defined as the sum of complete and partial responses at 2 months after commencement of radiation treatment. A complete response was defined as a Brief Pain Inventory worst-pain score of zero with no associated increase in daily oral morphine equivalent. A partial response was defined as pain that persisted after treatment, either with a worst-pain score reduction of 2 or more and no increase in daily oral morphine equivalent consumption, or no increase in pain and a reduction in daily oral morphine equivalent consumption of at least 25%. Pain progression was defined as an increase in a worst-pain score of 2 or more without reduced daily oral morphine equivalent consumption or as no change in worst-pain score and an increase in daily oral morphine equivalent consumption of at least 25%.[11] Responses were obtained by patient self-reported questionnaires in clinic, by mail, or by telephone follow-up. The Brief Pain Inventory and recording of daily oral morphine equivalent were completed 7 and 14 days after start of radiation therapy, monthly for 6 months, and at 9 months and 12 months after radiation therapy.

Secondary endpoints were freedom from pain progression, as defined above, in all patients that had an overall pain response at 2 months,[11] reduction in functional interference of daily activities due to pain as assessed by part of the Brief Pain Inventory, assessment of health-related quality of life, incidence of acute radiation-related side-effects, and incidence of in-field pathological fractures and spinal cord compression. Patient-reported health-related quality of life was assessed using the European Organisation for Research

and Treatment of Cancer Quality-of-Life Questionnaire (QLQ)-C30[12] in patients randomised by the NCIC CTG, RTOG, and the network from the Netherlands. Quality of life was not assessed in patients recruited in the other countries (Australia, France, New Zealand, and the UK). Health-related quality of life was assessed at baseline, and then monthly for 6 months. Adverse events were assessed in patients who received their allocated treatment and completed an acute toxicity questionnaire 7 and 14 days after the start of treatment (outlined in our protocol). In the questionnaire, patients were asked to rate the extent to which they experienced five adverse events (anorexia, nausea, vomiting, diarrhoea, and skin reddening) using a 4-point rating scale (1=not at all; 2=a little; 3=quite a bit; 4=very much), and to state whether they took medication to treat three of these events (nausea, vomiting, and diarrhoea). The haematological toxicity with local external beam radiotherapy is usually mild, so our study did not require any blood tests. Presence of pathological fracture and spinal cord compression or cauda equina syndrome occurring within the field of protocol treatment were established by individual treating physicians and were analysed in the intention-to-treat population. Overall survival was measured from the date of randomisation until the date of death from any cause.

Statistical analysis

A retrospective analysis done by Mithal and colleagues[5] identified that 57 (20%) of 280 individual treatment sites were re-treated in 105 patients, of which overall pain response was reported for 87% of the sites. We calculated the sample size of our study by assuming that at least 70% of patients would achieve an overall pain response; 260 patients were required in each group to have 80% power to exclude 60% or fewer of patients achieving an overall response with single fraction therapy with a one-sided α of 0·05. On the assumption that 20% of patients would not be assessable for response at 2 months, we needed to enrol 650 patients.

We analysed the proportion of overall, complete, and partial pain responses of the two different radiotherapy fractionation groups using a Cochran-Mantel-Haezel test,[13] and calculated the one-sided upper 95% confidence limit of the difference between the groups. We defined a non-inferiority margin of 10%; thus, if the upper boundary of the 95% confidence limit for the difference in overall response in patients assigned to receive 8 Gy in a single fraction was no more than 10% less than the overall response in those assigned to receive 20 Gy in multiple fractions, we would regard treatment with 8 Gy to be non-inferior to 20 Gy.[14] The primary analysis was by intention to treat, with missing data treated as a separate category in this analysis.

We calculated the mean and SD of the Brief Pain Inventory and QLQ-C30 scores at baseline, and each follow-up. We used the Wilcoxon rank-sum test[15] to compare changes in each assessment from baseline by treatment group. Improvement or deterioration by 2 points or more on the Brief Pain Inventory score led to classification as improved or worsened, respectively.[16] Similarly, increases or decreases of 10 points or more on the QLQ-C30 score were classified as improved or worsened quality of life.[17] Other changes were classified as stable. We did a χ^2 test to compare the distribution of these three categories between the two treatment groups.

In view of the non-inferiority hypothesis, we also did a per-protocol analysis, which excluded patients who were found to be ineligible after randomisation, failed to receive allocated therapy, or whose response to treatment was not assessable at 2 months. Based on per-protocol analyses, we used logistic regression[18] to assess the relation between overall pain response to repeat radiation therapy and the variables used to stratify randomisation. Overall pain responses by randomised assignment were also assessed in these subgroups. An interim analysis to ensure that the single-fraction group was not inferior was to be done when 260 patients could be assessed for the primary endpoint (ie, response to treatment 2 months after repeat radiation). The stopping boundary for inferiority of single fraction treatment was a p value of 0·005 or less. All analyses were based on SAS Software, version 9.2.

Recruitment of patients began on Jan 7, 2004, and an interim analysis was done on Feb 10, 2009, when the response status at 2 months was assessable for 343 patients. The data safety monitoring committee observed that the proportion of patients achieving an overall pain response at 2 months was less than the projected rate of 70%, and that more than 20% of patients were not assessable for response at 2 months, and thus recommended expansion of the sample size to 850 patients.

This study is registered with ClinicalTrials.gov, number NCT00080912.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, or data interpretation, and

	Intention-to-treat analysis		Per-protocol analysis	
	8 Gy/single fraction (N=425)	20 Gy/multiple fractions (N =425)	8 Gy/single fraction (N=258)	20 Gy/multiple fractions (N=263)
Overall response	118 (28%)	135 (32%)	116 (45%)	134 (51%)
Complete response	36 (8%)	30 (7%)	35 (14%)	29 (11%)
Partial response	82 (19%)	105 (25%)	81 (31%)	105 (40%)
Not assessable	162 (38%)	160 (38%)	0	0
Not defined*	92 (22%)	91 (21%)	91 (35%)	91 (35%)
No change	7 (2%)	7 (2%)	7 (3%)	7 (3%)
Pain progression	46 (11%)	32 (8%)	44 (17%)	31 (12%)

Data are number (%). *Response assessments that could not be classified as complete response, partial response, no change, or pain progression.

***Table 2*: Response to treatment according to Brief Pain Inventory score and daily oral morphine equivalent at 2 months in the intention-to-treat and per-protocol populations**

writing of the report. The corresponding author had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

Between Jan 7, 2004, and May 24, 2012, we randomly assigned 850 patients to a treatment group (425 to each group) from 92 centres worldwide (appendix). Some patients were discovered to be ineligible after randomisation; reasons for ineligibility are listed in the trial profile (figure 1). Characteristics at baseline were balanced between the two treatment groups (table 1). The most common previous prescription in both treatment groups was single-fraction treatment. Reasons for repeat radiation therapy were: no response to the initial radiation (73 [17%] in the 8 Gy group *vs* 72 [17%] in the 20 Gy group), hopes for further pain relief after partial improvement (39 [9%] *vs* 46 [11%]), recurrent pain after an initial response (310 [73%] *vs* 304 [72%]), and unknown (three [1%] *vs* three [1%]).

258 (61%) patients in the 8 Gy group and 263 (62%) in the 20 Gy group were assessable for pain-relief response at 2 months (table 2). In the intention-to-treat analysis, 118 (28%) of 425 patients in the 8 Gy/single fraction group and 135 (32%) of 425 patients in the 20 Gy/multiple fractions group had an overall pain response at 2 months (p=0·21; response difference 4·00%, upper limit of the 95% CI 9·2), meeting the prespecified non-inferiority margin. In the per-protocol population, pain response was assessable for 258 (61%) of 425 patients in the 8 Gy group and 263 (62%) of 425 patients in the 20 Gy group. 116 (45%) patients in the 8 Gy group and 134 (51%) in the 20 Gy group achieved an overall pain response at 2 months, with a response difference of 6·00% (p=0·17, upper limit of the 95% CI 13·2), exceeding the predefined non-inferiority margin (table 2). Freedom from pain progression was similar between groups (hazard ratio [HR] for 20 Gy *vs* 8 Gy was 1·07, 95% CI 0·56–2·07; table 2). No difference in pain response was noted between groups when the per-protocol population was analysed by interval from initial radiotherapy to randomisation (>3 months *vs* ≤3 months; data not shown; p=0·18).

In patients who completed the sections of the Brief Pain Inventory that assessed how pain interfered with daily activities, there were no significant differences between treatment groups in the proportion of patients with improved, stable, or worse scores at 2 months compared with baseline for any of the seven domains assessed (table 3).

In patients who completed the QLQ-C30 at baseline and 2 months, no significant differences in global quality of life were noted between treatment groups (79 [34%] of 230 improved and 73 [32%] of 230 were worse in the 8 Gy group *vs* 83 [35%] of 234 improved and 69 [29%] of 234 were worse in the 20 Gy group; p=0·87), and no significant differences between treatment groups were noted for the change in the pain domain (table 4). Patients assigned to the 20 Gy group were significantly less fatigued than those in the 8 Gy group according to the QLQ-C30 results (p=0·030; table 4); no other significant differences were detected in the other 12 assessed domains (table 4).

7 days after receiving therapy, patients who received 20 Gy treatment reported more skin reddening (ie, a little, quite a bit, or very much) than patients who received 8 Gy (68 [22%] of 308 assessable patients who received 20 Gy *vs* 49 [16%] of 312 assessable patients who received 8 Gy; p=0·033), and, 14 days after receiving therapy, more frequent and increased lack of appetite (229 [66%] of 349 *vs* 201 [56%] of 358; p=0·011), vomiting (82 [23%] of 349 *vs* 47 [13%] of 357; p=0·0010), diarrhoea (108 [31%] of 349 *vs* 81 [23%] of 357; p=0·018), and skin reddening (75 [24%] of 308 *vs* 44 [14%] of 305; p=0·0020). Only one patient had a serious adverse event (admission to hospital with coronary thrombosis [grade 4 cardiac ischaemia or infarction]) 166 days after receiving 8 Gy in a single fraction as study treatment. This event was assessed as being possibly related to study treatment because the patient's heart was in the

	8 Gy/single fraction							20 Gy/multiple fractions							p value*
	Baseline		2 months		Change in score at 2 months			Baseline		2 months		Change in score at 2 months			
	n	Score	n	Score change	Improved	Stable	Worse	n	Score	n	Score change	Improved	Stable	Worse	
General activity	390	5·9 (2·8)	254	−1·3 (3·5)	126 (35%)	61 (17%)	176 (48%)	390	5·9 (2·8)	261	−1·7 (3·5)	111 (31%)	67 (19%)	181 (50%)	0·53
Mood	389	4·5 (2·9)	256	−1·2 (3·6)	136 (37%)	66 (18%)	161 (44%)	392	4·5 (2·9)	257	−1·3 (3·6)	134 (37%)	70 (19%)	157 (43%)	0·92
Walking ability	384	5·7 (3·2)	252	−1·2 (3·4)	102 (28%)	76 (21%)	180 (50%)	394	5·4 (3·2)	261	−1·0 (3·4)	121 (33%)	72 (20%)	169 (47%)	0·36
Normal work	385	6·3 (3·0)	252	−1·1 (3·8)	118 (33%)	80 (22%)	162 (45%)	390	6·3 (3·0)	257	−1·5 (3·8)	111 (31%)	79 (22%)	168 (47%)	0·85
Relation with other people	391	3·3 (3·0)	258	−0·4 (3·2)	142 (39%)	98 (27%)	125 (34%)	391	3·4 (3·0)	257	−0·9 (3·2)	142 (39%)	89 (25%)	130 (36%)	0·78
Sleeping	390	4·2 (3·2)	258	−1·2 (3·5)	119 (33%)	72 (20%)	174 (48%)	393	4·4 (3·2)	260	−1·6 (3·5)	112 (31%)	82 (23%)	168 (46%)	0·62
Enjoyment of life	390	5·4 (3·3)	256	−0·9 (3·8)	115 (32%)	78 (21%)	172 (47%)	391	5·3 (3·3)	253	−1·2 (3·8)	118 (33%)	75 (21%)	167 (46%)	0·93

Data are mean (SD) or number (%). *p value is comparing the difference between the proportions of patients with improved, stable, or worse scores between treatment groups.

***Table 3*: Change in score between baseline and 2 months in patients who completed the functional interference sections of the Brief Pain Inventory**

	8 Gy/single fraction			20 Gy/multiple fractions			p value
	Improved	Stable	Worse	Improved	Stable	Worse	
Global	79 (34%)	78 (34%)	73 (32%)	83 (35%)	82 (35%)	69 (29%)	0·87
Pain	155 (68%)	24 (10%)	50 (22%)	161 (68%)	31 (13%)	45 (19%)	0.57
Role	114 (49%)	42 (18%)	78 (33%)	126 (53%)	42 (18%)	72 (30%)	0·68
Fatigue	107 (46%)	36 (15%)	90 (39%)	126 (53%)	19 (8%)	93 (39%)	0·030
Sleep	106 (46%)	81 (35%)	45 (19%)	99 (42%)	87 (37%)	52 (22%)	0·64
Social	101 (44%)	50 (22%)	81 (35%)	106 (45%)	52 (22%)	80 (34%)	0·96
Cognitive	98 (42%)	62 (27%)	73 (31%)	96 (40%)	66 (28%)	78 (33%)	0·90
Emotional	94 (41%)	84 (37%)	52 (23%)	83 (35%)	95 (40%)	58 (25%)	0·45
Physical	84 (36%)	81 (35%)	69 (29%)	90 (38%)	75 (31%)	75 (31%)	0·74
Constipation	82 (35%)	99 (42%)	52 (22%)	84 (35%)	91 (38%)	62 (26%)	0·55
Nausea	72 (31%)	101 (44%)	59 (25%)	61 (26%)	111 (47%)	66 (28%)	0·43
Appetite	65 (28%)	90 (39%)	78 (33%)	70 (29%)	91 (38%)	77 (32%)	0·93
Dyspnea	57 (24%)	110 (47%)	67 (29%)	61 (25%)	112 (47%)	67 (28%)	0·96
Financial	35 (15%)	155 (67%)	42 (18%)	37 (16%)	155 (65%)	46 (19%)	0·92
Diarrhoea	31 (13%)	154 (66%)	47 (20%)	26 (11%)	144 (61%)	68 (29%)	0·10

Data are number (%). The number of patients who completed each domain of the questionnaire differed within and between treatment groups. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C30.

Table 4: **Change in health-related quality of life between baseline and 2 months in patients who completed the QLQ-C30 questionnaire**

exit beam. No treatment-related deaths were reported. In the intention-to-treat population, in-field pathological fractures occurred in 30 (7%) of 425 patients assigned to 8 Gy treatment and 20 (5%) of 425 patients assigned to 20 Gy treatment (odds ratio [OR] 1·54, 95% CI 0·85–2·75; p=0·15). Spinal cord or cauda equina compressions were reported in seven (2%) of 425 patients assigned to 8 Gy and two (<1%) of 425 assigned to 20 Gy (OR 3·54, 95% CI 0·73–17·15; p=0·094). No cases of radiation myelitis were reported.

Logistic regression modelling using the per-protocol analysis showed that pain response to previous radiation (p=0·18), and previous radiation fractionation schedule (p=0·44), were not associated with overall pain response at 2 months, with adjustment for treatment allocation. No differences in pain response were reported within the subsets grouped according to overall pain response to previous radiation therapy ($p_{interaction}$=0·48) or previous radiation treatment fractionation schedule ($p_{interaction}$=0·39; table 5).

After a median follow-up of 12·2 months (95% CI 12·1–12·3) in both treatment groups, 227 (53%) of 425 patients assigned to 8 Gy had died compared with 220 (52%) of 425 patients assigned to 20 Gy (median survival was 9·3 months [7·8–10·5] *vs* 9·7 months [8·5–10·8]; HR 0·96, 95% CI 0·8–1·2; p=0·66; figure 2).

	Received per-protocol therapy (N=521)	Obtained an overall pain response to protocol therapy (N=250)
Response to initial radiation treatment	441 (85%)	210 (48%)
8 Gy in single fraction	218 (42%)	96 (44%)
20 Gy in multiple fractions	223 (43%)	114 (51%)
No response to initial radiation treatment	80 (15%)	40 (50%)
8 Gy in single fraction	40 (8%)	20 (50%)
20 Gy in multiple fractions	40 (8%)	20 (50%)
Initially received single-fraction therapy	345 (66%)	168 (49%)
8 Gy in single fraction	171 (33%)	76 (44%)
20 Gy in multiple fractions	174 (33%)	92 (53%)
Initially received multiple-fraction therapy	176 (34%)	82 (47%)
8 Gy in single fraction	87 (17%)	40 (46%)
20 Gy in multiple fractions	89 (17%)	42 (47%)

Response to initial radiation was established by the treating physician at the time of randomisation on the basis of each patient's history (ie, whether they did or did not report having pain improvement after initial radiation).

Table 5: **Response evaluation by stratification factor variable**

Discussion

In this trial we assessed dose–response and efficacy of repeat radiation to palliate pain associated with bone metastases from various primary origins, and found that, in the intention-to-treat population, 8 Gy in a single fraction was non-inferior to 20 Gy in multiple fractions. However, findings were not robust in a per-protocol analysis, and therefore trade-offs between efficacy and toxicity might exist. To our knowledge, our trial is the first randomised controlled trial to assess the appropriate schedule of repeat radiotherapy to palliate pain from bone metastases (panel), and our results provide key information that has implications for practice policies and future research.

First, our analyses show that repeat radiation therapy is beneficial to these patients, irrespective of schedule. Three variables support this conclusion, including the per-protocol analysis of the primary endpoint, which

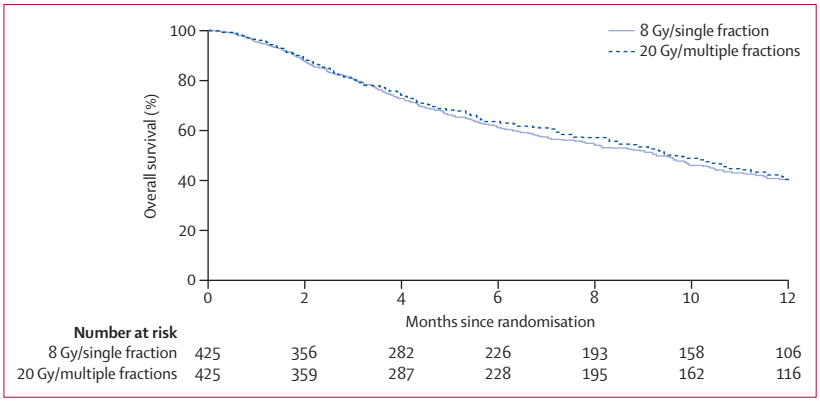

Figure 2: **Kaplan-Meier curves of overall survival in the intention-to-treat population**

Panel: Research in context

Systematic review

No systematic review was undertaken when planning this trial. However, a previous search with the terms "retreatment", "re-irradiation", and "bone metastases" found several retrospective and prospective case series on re-treatment, and their results were summarised in our study protocol. Generally, the scientific literature supports the effectiveness of re-irradiation, but the optimal dose-fractionation schedule was unknown.

Interpretation

In patients with painful bone metastases needing repeat radiation therapy, treatment with 8 Gy in a single fraction seems to be non-inferior and less toxic than 20 Gy in multiple fractions, with a pain response rate in keeping with that reported in a systematic review by Huisman and colleagues.[4] Because our findings were not confirmed in our per-protocol analysis, trade-offs between efficacy and toxicity might exist between the two fractionation schedules.

showed that 250 (48%) of all patients who received their assigned treatment had reduced pain at the site of repeat radiation or reduced need for opioid analgesia. We noted this benefit both in patients who responded to previous radiation, and in those who did not respond to initial treatment. Additionally, we noted improved quality-of-life pain scores in 316 (68%) of 466 patients for whom we had data.

Second, our results suggest that treatment with 8 Gy given in a single fraction is non-inferior to treatment with 20 Gy administered in multiple fractions. This conclusion is based on meeting the prespecified non-inferiority criteria according to an intention-to-treat analysis, and very similar scores between the two treatment groups when assessing functional interference associated with pain as assessed by the Brief Pain Inventory, and global function and pain as assessed by EORTC QLQ-C30. Thus these data could be taken to support policy to provide treatment with 8 Gy delivered in a single fraction, as opposed to treatment with 20 Gy in multiple fractions. However, this conclusion needs careful interpretation because, although the per-protocol analysis showed a difference in overall pain response of only 6% between groups, the high proportion of patients who were not assessable restricted the statistical power of the study, and the associated upper boundary of the 95% CI (13·2%) exceeded the prestated margin of 10%, thus failing to confirm results of the intention-to-treat analysis. Furthermore, we cannot exclude the possibility that a significant difference between treatment groups might exist for compression of the spinal cord or cauda equina, and pathological fractures in the radiated field, but the incidences of both were very small. The provision of treatment with 8 Gy in a single fraction is also supported by our finding that this treatment is associated with fewer adverse events than 20 Gy in multiple fractions. Finally, due to the realistic assumption that this population of patients will have important treatment limitations due to metastatic cancer, it is likely they would find a single treatment more convenient.

The major limitations of our trial include the lack of concurrence between the intention-to-treat and per-protocol analyses, which we believe is due to the difficulties in the assessment of pain as an endpoint. Issues include a desire to achieve durable pain control while recognising the poor outlook of some patients because of the burden of metastatic cancer. In our trial, 98 (12%) patients died before the 2 month assessment. Additionally, there is a need to separate the role of providing optimal analgesic medication from the need for radiation therapy. The international consensus endpoints were designed for this purpose; responses are based on reductions of both pain and need for analgesic medication, in view of the potential for these analgesics to have untoward effects.[19] Unfortunately, assessments of these endpoints are often affected by compliance-related issues, because patients often do not return to the radiation therapy health-care provider system for assessment, and thus these endpoints need to be assessed remotely according to patient-reported outcomes. We had difficulties with missing data, often because of imprecise documentation of analgesic use by patients, which could explain the difference between the expected and observed response rates, and might have compromised our ability to show robust results in the per-protocol analysis.

Overall, we conclude that repeat radiation treatment seems to be beneficial for patients with symptomatic bone metastases, and that a single treatment with 8 Gy might be preferable to treatment with 20 Gy in multiple fractions. These conclusions are based on the results of our intention-to-treat analysis, and the fact that quality of life and interference in daily activities associated with pain were very similar between the two treatment groups. However, as our per-protocol analysis did not show 8 Gy in a single fraction to be non-inferior, it is possible that a small proportion of patients might gain more benefit from multiple fraction treatment, but this schedule should be considered in view of the potential costs of greater acute toxicity, and probably greater inconvenience to patients.

Contributors

CFW, YMvdL, RMM, DR, BEC, MDB, JSYW, PH, WFH, RKSW, and EC were responsible for the study design. CJAT-T, YMvdL, DR, AN, JSYW, PH, WFD, EC, SB, RKSW, and BO accrued patients at the participating centres. CJAT-T, YMvdL, DR, BEC, AN, JSYW, PH, WFD, EC, SB, RKSW, and BO assisted in data collection. Data analysis was completed by YMvdL, RMM, BEC, MDB, PH, WFH, RKSW, and EC. CFW, YMvdL, RMM, DR, BEC, MDB, JSYW, PH, WFH, RKSW, and EC interpreted the data. The major manuscript writing was completed by RMM, DR, BEC, MDB, RKSW, and EC. All authors assisted in manuscript review and appraisal.

Conflicts of interest

We declare that we have no conflicts of interest.

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